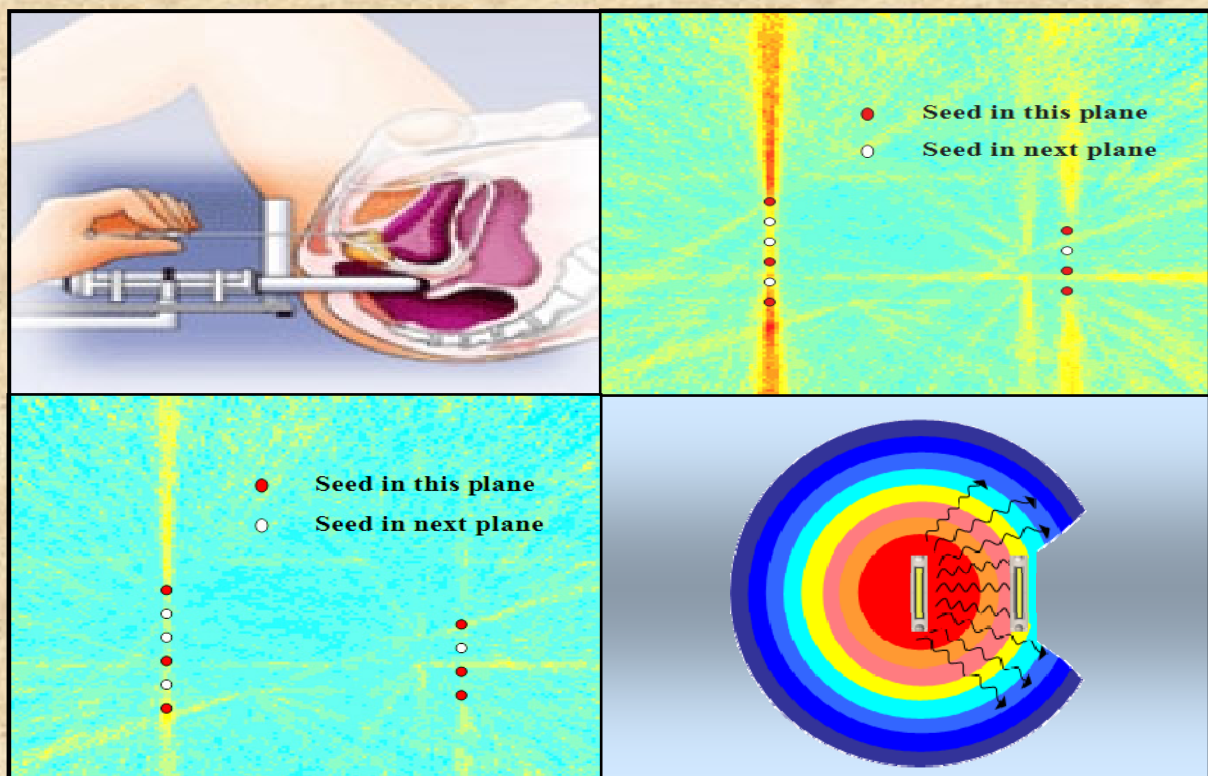




UNIVERSITE CATHOLIQUE DE LOUVAIN
Faculté de médecine
Pôle d'Imagerie Moléculaire, Radiothérapie et Oncologie

Permanent brachytherapy challenges and solutions: New plastic radioactive seeds and interseed effect correction for online prostate treatment dosimetry

Fadi Abboud



Thèse présentée en vue de l'obtention du grade de
Docteur en Sciences Biomédicales et Pharmaceutiques

Promoteur : Prof. Stefaan Vynckier
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2011

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Table of contents

Table of contents	i
Acknowledgment	vii
Abstract	ix
Résumé	xi
List of abbreviations	xiii
Chapter 1: Introduction	
1. Overview of cancer	3
1.1 Prostate cancer	3
1.2 Treatment techniques of prostate cancer	5
1.2.1 Observation — "Watchful Waiting"	5
1.2.2 Radical prostatectomy	5
1.2.3 Hormonal therapy	6
1.2.4 Chemotherapy	6
1.2.5 Radiotherapy	6
1.2.5.1 External beam radiotherapy	8
1.2.5.2 High dose rate (HDR)	8
1.2.5.3 Interstitial implants	8
1.3 Guidelines on primary treatment of prostate cancer	11
2. Radiation dosimetry	14
2.1 Source dosimetry used for permanent prostate brachytherapy	15
2.1.1 Update of AAPM Task Group No. 43 Report	15
2.1.1.1 General two dimension formalism	15
2.1.1.2 General one dimension formalism	15
2.1.2 Measurements	16
2.1.3 Monte Carlo simulation	17
2.2 Permanent prostate brachytherapy dosimetry	19
2.3 Sources of errors in permanent prostate brachytherapy dosimetry	21
3. Objectives of the thesis	22
4. Additional studies	22
5. References	23

Chapter 2: Publication 1

An experimental palladium-103 seed (OptiSeed^{exp}) in a biocompatible polymer without a gold marker: Characterization of dosimetric parameters including the interseed effect

	30
I. Introduction	30
II. Materials and Methods	31
II.A. Dose calculations using the TG-43U1 protocol	31
II.B. Source of Pd ¹⁰³ (OptiSeed ^{exp})	31
II.C. Measurements in solid water phantom	32
II.D. Monte Carlo calculations	32
II.E. Interseed effects	32
III. Results	34
III.A. Radial dose function	34
III.B. Anisotropy function	35
III.C. Dose rate constant Λ	35
III.D. Seed shadowing (Interseed attenuation)	36
IV. Discussion and Conclusion	37

Correspondence

<i>Comment on “An experimental palladium-103 seed (OptiSeed^{exp}) in a biocompatible polymer without a gold marker: Characterization of dosimetric parameters including the interseed effect”</i>	40
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Correspondence

<i>Response to “Comment on ‘An experimental palladium-103 seed (OptiSeed^{exp}) in a biocompatible polymer without a gold marker: Characterization of dosimetric parameters including the interseed effect’ ”</i>	41
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Chapter 3: Publication 2

Experimental and theoretical dosimetry of a new polymer encapsulated iodine-125 source—SmartSeed: Dosimetric impact of fluorescence x

	42
I. Introduction	42
II. Materials and Methods	43
II.A. Radioactive seed (SmartSeed)	43
II.B. TLD dosimetric measurements	43
II.C. Solid water phantoms (WT1)	43

Table of contents

II.D. Monte Carlo simulation (MCNP5)_____	44
II.D.1. Monte Carlo simulation (MCNP5)—Air-kerma strength S_K _____	44
II.D.2. Monte Carlo simulation (MCNP5)—Solid water_____	44
II.D.3. Monte Carlo simulation (MCNP5)—Dose distribution in water_____	45
II.E. Dosimetry formalism of brachytherapy sources: TG-43U1 protocol _____	45
III. Results _____	45
III.A. TLD vs MCNP-dose distribution in solid water_____	45
III.B. MCNP5 TG-43U1 parameters (in liquid water)_____	46
III.B.1. MCNP5 dose rate constant in water Λ _____	46
III.B.2. MCNP5 radial dose function $g(r)$ _____	46
III.B.3. MCNP5 1D and 2D anisotropy functions_____	47
III.C. Impact of fluorescence x rays on air-kerma strength S_K (MCNP5) _____	47
III.D. Uncertainty analysis_____	49
IV. Discussion and Conclusion _____	49
Chapter 4: Submitted patent	
SYSTEM AND METHOD FOR DETERMINING RADIATION DOSE DISTRIBUTION _____	
	51
1. Introduction_____	52
2. Materials and Methods_____	52
3. Results and discussion_____	54
4. Conclusion_____	56
Chapter 5: Publication 3	
Fast Monte Carlo treatment planning for prostate brachytherapy: a comparison with VariSeed _____	
	57
1. Introduction_____	57
2. Materials and Methods_____	57
2.1 VariSeed program (VARIAN)_____	57
2.2 Monte Carlo (MC) simulation (MCNP5)_____	57
3. Results and discussion_____	58
4. Conclusion_____	59

Chapter 6: Article prepared for submission

FAST MONTE CARLO TREATMENT PLANNING SYSTEM FOR PROSTATE BRACHYTHERAPY: A COMPARISON WITH VARISEED	61
1. Introduction	62
2. Materials and Methods	63
2.1 TG43U1 Protocol	63
2.1.1 General two dimension formalism	63
2.1.2 General one dimension formalism	63
2.2 VariSeed program	64
2.3 Monte Carlo simulation (MCNP5)	64
2.4 Monte Carlo methods	65
2.4.1 MCOSST (Monte Carlo One-Seed Superposition Technique)	65
2.4.2 FMCT (Full Monte Carlo Technique)	65
2.4.3 MCOSST (Monte Carlo One-Seed Superposition Interseed Technique)	65
3. Results	66
3.1 Symmetra source model validation (I25S06)	66
3.2 Comparison between VariSeed & MCOSST	66
3.3 Comparison between MCOSST & FMCT	66
3.4 Comparison of DVH; influence of the use of the 1D & 2D anisotropy functions (TG43U1 protocol)	69
4. Discussion	72
5. Conclusion	73

Chapter 7: Publication 4

Is 1D anisotropy function recommended by TG-43U1 protocol good enough for clinical brachytherapy dosimetry?	76
1. Purpose	76
2. Materials and Methods	76
3. Results and discussion	76
4. Conclusion	78

Chapter 8: Publication 5

Evaluation of the Dose Distribution Gradient in the Close Vicinity of Brachytherapy Seeds Using Electron Paramagnetic Resonance Imaging

1. Introduction	69
2. Materials and Methods	80
- Phantoms	80
- Irradiation	80
- EPR Imaging	80
- MC simulation	80
- Resolution—ESF Determination	81
3. Results	81
4. Discussion	82

Chapter 9: Publication 6

Experimental determination of the radial dose distribution in high gradient regions from a low dose rate iridium-192 wire sources using EPR imaging

I. Introduction	86
II. Materials and Methods	87
A. EPRI dosimetry	87
B. Gafchromic film dosimetry	87
C. Monte Carlo calculations	87
III. Results	88
IV. Discussion	88
V. Conclusion	89

Chapter 10: Publication 7

Experimental determination of the radial dose distribution in high gradient regions around ¹⁹²Ir wires: Comparison of electron paramagnetic resonance imaging, films, and Monte Carlo simulations

I. Introduction	90
II. Materials and Methods	91
II.A. Iridium wire sources	91
II.B. Phantoms	91
II.C. EPR Imaging	92
II.C.1. Deconvolution: Image reconstruction	92

II.D. EPRI resolution: Determination of the edge spread function_____	92
II.E. Gafchromic film dosimetry_____	92
II.F. Monte Carlo calculations_____	93
III. Results_____	93
IV. Discussion_____	94
V. Conclusion_____	95
Chapter 11: Discussion_____	98
1. Dosimetry study of a new iodine-125 and palladium-103 brachytherapy seeds_____	98
2. Accuracy of dose calculation based on TG-43U1 algorithm_____	102
2.1 Errors due to using 1D & 2D approximation_____	103
2.2 Errors due to interseed effect_____	107
3. Uncertainty analysis_____	109
4. Future of EPRI (a collaboration study)_____	112
Chapter 12: Conclusion_____	115
References_____	116
INDEX	
SYSTEM AND METHOD FOR DETERMINING RADIATION DOSE	
DISTRIBUTION_____	128
- TECHNICAL FIELD_____	128
- DESCRIPTION OF RELATED ART_____	128
- SUMMARY OF THE INVENTION_____	129
- BRIEF DESCRIPTION OF THE DRAWINGS_____	132
- DETAILED DESCRIPTION OF THE INVENTION_____	133
- Claims_____	144
- Abstract_____	148
- Figures_____	149

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*I dedicate this thesis to
my family, my wife, Karoline, and my beloved daughter Elena
for their constant support and unconditional love.
I love you all dearly.*

Abstract

The overall subject of this work was the dosimetric study of new, low energy photon sealed sources made of polymer for clinical brachytherapy application. A key goal was to resolve the problem of inaccuracies in real-time dosimetry that occur as a result of self-shielding by seeds (interseed effect), which is neglected by current treatment planning systems (TPS).

Permanent brachytherapy implantation has become a popular treatment option in the management of early stage prostate cancer. Adjuvant stereotactic permanent seed breast implants, similar to those used in the treatment of prostate cancer, have also been developed, with encouraging results. With this mode of therapy, a high radiation dose can be delivered locally to the tumor with rapid dose fall-off in the surrounding normal tissue. Two known isotopes are commonly used: Iodine-125 (mean energy of 27 keV) and Palladium-103 (mean energy of 21 keV). At these low energies, dosimetric characteristics are very dependent on the internal design of the seed; hence, a thorough dosimetric study of any new source design is essential. Most marketed seeds have a metallic shell (titanium), which, however, causes artifacts that can disturb follow-up imaging. This problem prompted companies to develop plastic seeds to reduce these artifacts. The first part of the present work, therefore, describes a dosimetric study of two new seed models produced by the IBt-Bebig group, made with a biocompatible polymeric shell rather than titanium. Measurements with thermoluminescent detectors and Monte Carlo calculations using MCNP codes versions 4C and 5, were performed to determine the dosimetric characteristics of the seeds based on the AAPM Task Group No. 43 Updated (TG-43U1) recommendations.

One of the major concerns in radiation treatment is the accuracy of calculated and delivered doses and their distributions relative to the prescribed dose. Currently, dose calculations for patient treatment in brachytherapy are based on the TG-43U1 protocol, which uses line or point source approximation, and assumes homogeneous medium dosimetry and negligible interseed effect because of the complexity of including these factors in the calculations; however, these assumptions do not accurately reflect the dose distribution for brachytherapy using low-energy photon emitters. The interseed effect is defined as the attenuation effect of one seed on the irradiation field of another implanted seed. The complexity of this effect involves many variables, e.g., seed construction, seed positions, distances between seeds and the density of implanted seeds per volume (seed/cm³). Many studies have shown non-negligible perturbations in the dose distributions of ¹²⁵I and ¹⁰³Pd coplanar aligned seeds when the interseed attenuation effect is ignored. Therefore, the Monte Carlo TPS is necessary to correct for these differences, and is a more accurate calculation method than TG-43U1 for implant dosimetry. However, general-purpose Monte Carlo codes have prohibitively long computing times, taking about 24h per calculation for one patient depending on computer performance, so this method cannot be used for real-time dosimetry. The second part of this thesis presents a more rapid Monte Carlo dose calculation engine, which has been developed using the MCNP5 code and takes into account the interseed effect.

In general, seed dosimetric characteristics are determined using Monte Carlo (MC) simulations. However, such calculations can give different results depending on the MC calculation codes used. These codes can differ in their basic data or in the approximations made in the underlying physics. Experimentally, dosimetry can be performed using thermoluminescent dosimeters (TLDs). However, it is still a challenge to obtain data with high spatial resolution because of the large dose gradient and the very low dose rate (LDR). In this context, there is a need to develop new experimental methods that allow estimation of the

dose deposited in the proximity of brachytherapy seeds. The third part of this work concentrates on attempts to develop a new dosimetry method, based on the reconstruction of dose using electron paramagnetic resonance (EPR) imaging (EPRI).

Résumé

Le thème général de ce travail est l'étude dosimétrique des nouvelles sources, émettrices des photons de basse énergie, scellées en polymère, pour une application clinique de brachythérapie. Un objectif clé est de résoudre le problème des inexactitudes dosimétriques en temps réel due à l'atténuation créée par les grains (ou effet interseed), qui est négligée par les systèmes actuels de planification de traitement (TPS).

La brachythérapie par implants permanents est devenue une option de traitement populaire pour la prise en charge du cancer de prostate au stade précoce. Des traitements adjuvants par implants permanents stéréotaxique ont également été développés dans le cancer du sein avec des résultats encourageants. Avec ce mode de traitement, une forte dose de rayonnement peut être localement délivrée à la tumeur en épargnant les tissus normaux avoisinant. Deux isotopes connus sont couramment utilisés: l'iode-125 (d'une énergie moyenne de 27 keV) et du palladium-103 (d'une énergie moyenne de 21 keV). À ces basses énergies, les caractéristiques dosimétriques sont très dépendantes de la structure interne du grain, de sorte qu'une étude dosimétrique approfondie de toute nouvelle source est essentielle. La plupart des grains commercialisés ont une capsule métallique (titane) qui provoque des artefacts dans l'image, pouvant perturber le suivi monographique des patients. Ce problème a incité les entreprises à développer des grains en plastique pour réduire ces artefacts.

La première partie du présent travail décrit une étude dosimétrique de deux nouveaux modèles de grains produits par le groupe IBt Bebig. Leur capsule est constituée de polymère biocompatible, plutôt que de titane. Des mesures à l'aide de détecteurs thermoluminescents et des calculs de Monte Carlo utilisant le code MCNP (version 4C et 5) ont été effectués pour déterminer les caractéristiques dosimétriques des grains, sur base des recommandations du Groupe de Travail révisé n ° 43 AAPM (TG-43U1).

Une des préoccupations majeures dans le traitement de radiothérapie est la précision des doses calculées et délivrées, et leur distribution en regard de la dose prescrite. Actuellement, les calculs de dose pour les patients traités par brachythérapie sont basés sur le protocole TG-43U1, qui utilise l'approximation de la source linéaire ou ponctuelle, et qui présuppose que le milieu dosimétrique est homogène et l'effet interseed négligeable, en raison de la difficulté d'apprendre en compte ces facteurs dans le calcul. Ce présupposé ne reflète pas la distribution réelle de dose pour la brachythérapie utilisant des émetteurs de photons de basse énergie. L'effet interseed est défini comme l'effet d'atténuation d'un grain sur le champ d'irradiation d'un autre grain implanté. La complexité de cet effet est due aux nombreuses variables telles par exemple, la structure du grain, la position des grains, la distance entre les grains et la densité des grains implantés par volume (grain/cm³). De nombreuses études ont montré des perturbations non négligeables de distribution de la dose par des grains coplanaires alignés d'iode-125 ou de palladium-103, lorsque l'effet d'atténuation (interseed) est ignoré. D'où l'utilité du TPS Monte Carlo pour corriger ces différences, celui-ci étant une méthode de calcul plus précise que TG-43U1 pour le calcul dosimétrique des implants. Toutefois, les codes Monte-Carlo exigent un temps de calcul d'une lenteur prohibitive, fonction de la performance de l'ordinateur qui prend environ 24h par calcul pour un patient. Cette méthode ne peut donc pas être utilisée pour la dosimétrie en temps réel.

La deuxième partie de cette thèse présente un moteur de calcul de dose plus rapide basé sur la méthode Monte Carlo, développé en utilisant le code MCNP5 et prenant en compte l'effet de l'interseed.

En général, les caractéristiques dosimétriques de grains sont déterminées en utilisant les

simulations Monte Carlo (MC). Ces calculs peuvent donner des résultats différents selon les codes utilisés, lesquels codes peuvent différer dans leurs données de base ou dans les approximations physiques sous-jacentes. Expérimentalement, la dosimétrie peut être réalisée à l'aide de dosimètres thermoluminescents (TLD). Cependant, il reste difficile d'obtenir des données d'une haute résolution spatiale, en raison du fort gradient de dose et du faible débit de dose (LDR). Il est dès lors nécessaire de développer de nouvelles méthodes expérimentales qui permettent l'estimation de la dose déposée à proximité des grains de brachythérapie. La troisième partie de ce travail se concentre sur les tentatives de développer une nouvelle méthode dosimétrique, basée sur la reconstruction de la dose en utilisant l'imagerie par résonance paramagnétique électronique (EPRI).

GLOSSARY OF SYMBOLS AND TERMS

1D	: One-Dimensional.
2D	: Two-Dimensional.
3D	: Three-Dimensional.
3D-CRT	: Three-dimensional Conformal RadioTherapy.
AAPM	: American Association of Physicists in Medicine.
ADCL	: Accredited Dosimetry Calibration Laboratory.
β	: Angle subtended by $P(r, \theta)$ and the two ends of the active length. As used in the line source approximation, β has units of radians.
CaP	: Cancer of the Prostate.
CT	: Computerized Tomography.
CTV	: Clinical Target Volume.
δ	: Energy cutoff parameter used for air-kerma rate evaluation, which is 5 keV for TG-43U1 protocol.
D_x	: Dose that covers X percent of the volume for the selected target structure.
D_{max}	: The maximum dose received by the selected target structure.
D_{min}	: The minimum dose received by the selected target structure.
D_{mean}	: The average dose received by the selected target structure.
DNA	: DeoxyriboNucleic Acid.
DRE	: Digital Rectal Exam.
DVH	: Dose Volume Histogram.
EGS	: Electron Gamma Shower.
EPR	: Electron Paramagnetic Resonance.
EPRI	: Electron Paramagnetic Resonance Imaging.
ETV	: Evaluation Target Volume.
EU	: European Union.
$\phi_{an}(r)$	: The one-dimensional anisotropy function. At any radial distance r , $\phi_{an}(r)$ is the ratio of dose rate averaged over 4π steradian integrated solid-angle to the dose rate at the same distance r on the transverse plane. Dimensionless units.
$F(r, \theta)$	: 2D anisotropy function describing the ratio of dose rate at radius r and angle θ around the source, relative to the dose rate at $r_0 = 1$ cm and $\theta_0 = 90^\circ$ when removing geometry function effects. Dimensionless units.
FAC	: Ritz parallel-plate Free-Air Chamber developed by Loftus of NIST.

FMCT	: Full Monte Carlo Technique.
FMCS	: Full Monte Carlo Simulation.
$g(r)$	: Radial dose function describing the dose rate at distance r from the source relative to the dose rate at $r_0=1$ cm. Dimensionless units.
$g_L(r)$	: Radial dose function, determined under the assumption that the source can be represented as a line segment. Dimensionless units.
$g_P(r)$	: Radial dose function, determined under the assumption that the source can be represented as a point. Dimensionless units.
HDR	: High Dose Rate.
IMRT	: Intensity Modulated RadioTherapy.
ISEDRES	: InterSeed Effect on the Dose Rate of the First Seed.
ISSETDR	: InterSeed Effect on the Total Dose Rate.
Λ	: Dose-rate constant in water, with units of $\mu\text{Gy h}^{-1} \text{U}^{-1}$. Λ is defined as the dose rate at $P(r_0, \theta_0)$ per unit S_K .
$\text{CON}\Lambda$	: Notation indicating that the reported value of Λ is the consensus value determined by the AAPM from published data, with units of $\text{cGy h}^{-1} \text{U}^{-1}$.
$\text{EXP}\Lambda$	: Notation indicating that the reported value of Λ was determined by experimental measurement.
$\text{MC}\Lambda$	: Notation indicating that the reported value of Λ was determined using Monte Carlo calculations.
L	: Active length of the source (length of the radioactive portion of the source) with units of cm.
L_{eff}	: Effective active length of the source, with unit cm.
LDR	: Low Dose Rate.
LIBD	: Low-energy Interstitial Brachytherapy Dosimetry subcommittee of the AAPM Radiation Therapy Committee.
LiF	: Lithium Fluoride.
LiFo	: Lithium Format.
LW	: Line-width.
MC	: Monte Carlo.
MCNP	: Monte Carlo N Particle code.
MCOSSIT	: Monte Carlo One Seed Superposition Interseed Technique.
MCOSSST	: Monte Carlo One Seed Superposition Technique.
MCPI	: Monte Carlo dose calculation for prostate implant.

Glossary of symbols and terms

MPD	: Matched Peripheral Dose.
MRI	: Magnetic Resonance Imaging.
NCS	: Nederlandse Commissie voor Stralingsdosimetrie.
NHT	: Neoadjuvant Hormonal Therapy.
NIST	: National Institute of Standards and Technology.
$P(r, \theta)$	: Point-of-interest, positioned at distance r and angle θ from the geometric center of the radionuclide distribution.
PET	: Positron Emission Tomography.
PSA	: Prostate Specific Antigen.
PTRAN	: P roton T ransport Monte Carlo code.
PTV	: Planning Target Volume.
r	: The distance from the source center to $P(r, \theta)$, with units of cm.
r_0	: The reference distance, which is 1 cm for this protocol
S_K	: Air kerma strength.
θ	: The polar angle between the longitudinal axis of the source and the ray from the active source center to the calculation point, $P(r, \theta)$.
θ_0	: The reference polar angle, which is 90° or $\pi/2$ radians.
TG-43	: AAPM Task Group No. 43.
TG-43U1	: AAPM Task Group No. 43 Updated.
TLD	: ThermoLuminescent Dosimeter, generally composed of LiF.
TNM	: Tumor Node Metastasis.
TPS	: Treatment Planning System.
TRUS	: TransRectal UltraSound.
TURP	: Trans-Urethral Resection of the Prostate.
U	: The unit of air-kerma strength, equivalent to $\mu\text{Gy m}^{-2} \text{h}^{-1}$ or $\text{cGy cm}^{-2} \text{h}^{-1}$.
US	: Ultrasound.
USA	: United States American.
V_x	: The percent of the structure volume which is receiving the dose or a higher dose X.
WAFAC	: The wide-angle free-air chamber presently used at NIST to determine the air-kerma strength of a low-energy photon-emitting brachytherapy source.
WT1	: solid water phantom
WW	: Watchful Waiting.

Chapter 1

Introduction

Brachytherapy is the placement of radioactive sources in close proximity to any tumor. High doses of radiation are present in the vicinity of a radioactive material, and a rapid drop in dose occurs with increasing distance from the source due to the high attenuation of the low energy radiation. A key feature of brachytherapy is that the irradiation only affects a localized area around the radiation sources and exposure to radiation of healthy tissues further away from the sources is therefore reduced. Brachytherapy is characterized by {(Gerbaulet 1996),(Henschke 1963), (ICRU 58 1997), (ICRU 38 1985), (Joslin 1994) and (Stitt 1997)} the positioning of the radionuclides (interstitial brachytherapy where radioactive sources are inside the tumor or contact brachytherapy where they are close to the tumor), the duration of the irradiation (permanent or temporary implant) and the dose rate (low, medium and high dose rate) {(ICRU 58 1997), (ICRU 38 1985)}.

The history of brachytherapy began in Paris, in 1896, when Henri Becquerel described invisible radiations emitted by uranium. Two years later, Marie Curie and her husband, Pierre Curie, extracted a new radioactive substance, which they named radium. {(Dutreix 1998),(Gerbaulet 1999)} In 1901, Danlos and Bloc irradiated lupus at the St. Louis hospital in Paris and Abbe (1905) performed radium implants in the USA. Four years later, Finze started treating patients with radium in England. (Mazeron 1999) In 1913, two small pavilions were opened in Paris, one was reserved for Madame Curie and the other was assigned to Claudius Regaud for medical and biological research. After World War I different schools of brachytherapy were created and progressively the bases of brachytherapy were established. (Pierquin 1987) The Stockholm and Paris methods for intracavitary radiation were described between 1914 and 1919. Paterson, with Herbert Parker and John Meredith developed a didactic system of brachytherapy, which was published as the Manchester System as early as 1934. {(Paterson 1938) (Meredith 1967)} In the same year, Marie Curie's daughter and her husband Frederic Joliot discovered artificial radioactivity, which opened the possibility of a new era of brachytherapy.

First attempts to develop new sources after World War II were pursued by William Myers in USA,. He introduced a cobalt-60 needles in 1948 that fell out of use later on. Ulrich Henschke standardized an afterloading system utilizing plastic tubes and gold-198 seeds in 1953. Later on, Henschke and Basil Hilaris developed a school based on the afterloading principle with caesium-137 and iridium-192. During 1965 and 1966, Pierquin and Dutreix have determined the rules for a new implantation system, which they named the Paris System. (Bartelink 1988).

Implantation techniques for prostate cancer have evolved from intraurethral insertion of a temporary source in the early decades of last century, to permanent interstitial implantation using a retropubic approach. Iodine-125 seed permanent implantation was performed by free-hand placement of seeds in an open surgical procedure via the retropubic approach (Whitmore 1972). Dosimetric planning was limited to the use of nomographs following intraoperative measurement of the size of the prostate gland (Anderson 1976, 1993). The total activity to be implanted was determined using the average dimensions of the prostate. Postimplant dosimetry was analyzed in terms of the matched peripheral dose (MPD), defined as the isodose surface that would cover a spatial volume numerically equal to the volume of the prostate inferred from the ellipsoidal approximation (Hilaris 1988). Overall, the open surgical technique suffered from substantial uncertainties in dosimetric planning, implant execution and dose evaluation.

The technique has been improved greatly through the years due to the introduction of contemporary techniques for prostate brachytherapy relying on three-dimensional (3D) image-based treatment planning and real-time visualization of needle insertion and/or seed deposition. Seed implantation is performed under template guidance via a transperineal approach in a percutaneous procedure typically performed in an outpatient surgical setting.

Holm *et al.*(1983) first described the use of transrectal ultrasound (TRUS) for precise guidance of transperineal seed insertion in 1983. The technique was further popularized by Blasko, Grimm, Ragde and co-workers,(Blasko 1987, 1993) (Grimm 1994.) and has evolved into the most popular modality for prostate seed implantation to date. Characteristic of the technique is the use of TRUS for preoperative dosimetric planning and intraoperative visualization of needle placement. A somewhat different technique, developed by Wallner *et al.* in 1991 and 1994, uses computerized tomography (CT) to identify the target volume for treatment planning; intraoperative needle placement is verified under fluoroscopy using the urethra as the primary landmark. Compared to the open surgical technique, these contemporary techniques place considerable emphasis on 3D conformal dosimetric planning and precise placement of the planned seed configuration in the patient.

Today the vast majority of permanent implants are done using either ^{125}I (27 keV) or ^{103}Pd (21 keV) low energy sources. At this energy level, tissue absorption becomes an important factor due to the photoelectric effect. This is an advantage for the ease of radioprotection. On the other hand, it is a disadvantage because an extreme precision of sources positions is needed to avoid areas of underdosage (cold spots) and tumor sparing (Nath 1989) due to the limited penetration of the low-energy radiation.

The dosimetry of sources used in interstitial brachytherapy has been the subject of considerable research in recent years. A number of articles have appeared introducing revised calibration standards, source strength specification quantities, and dose calculation formalisms. With all these reports appearing in the literature, the medical physics community is faced with a confusing situation regarding the selection of dosimetry data. Therefore, the Radiation Therapy Committee of the American Association of Physicists in Medicine (AAPM) in 1988 formed the Task Group No. 43 (Nath 1995) to review the recent publications on the dosimetry of interstitial brachytherapy sources and recommend a dosimetry protocol, which would include formalism for dose calculations and data set for the values of dosimetry parameters.

Since significant advances have taken place in the field of permanent source implantation and brachytherapy dosimetry during time, TG-43 was updated in 2004 by Rivard *et al.* to include all new sources and eliminate minor inconsistencies.

TG-43U1 protocol has resulted in significant improvements in the standardization of both dose-calculation methodologies as well as dose rate distributions used for clinical implementation of brachytherapy. Moreover, it gave a mathematical tool to have a fast and more precise calculation of dose distribution for real-time dosimetry. However, there are still some questions open, particularly the tissue heterogeneity effect and the attenuation effect performed by one seed on the irradiation field of the other seeds that is called the interseed effect. TG-43U1 dose not take these two effects into account because of the difficulties to represent them by mathematical functions. The emergence of Monte Carlo method may offer a solution.

The efficacy of the Monte Carlo simulation technique in radiation dosimetry of brachytherapy has been demonstrated over the past several years (Ye 2003). The accuracy of Monte Carlo calculation makes it a good candidate to use for brachytherapy treatment planning system (TPS). However, the major problem with general-purpose Monte Carlo codes is the prohibitive computing time. It takes, in average, about 24h per calculation for one patient so it can't be used for real-time dosimetry.

An accelerated Monte Carlo engine was developed by Chibani *et al.* in 2005 in order to calculate dose distribution for prostate brachytherapy. It takes one minute per calculation which is not fast enough to use for real-time dosimetry. It can be used, however for postimplant dosimetry. This accelerated MC engine is capable to take into account the interseed and the heterogeneity effects from scan images. The presence of artifacts in CT

images due to the titanium seed shells makes heterogeneity correction difficult and disturbs the determination of seeds position. This prompted companies to produce new sources made in polymer to decrease as much as possible these artifacts. The dosimetry of these new seeds will be the first part of this thesis.

Correction for tissue heterogeneity is not easy to include in real-time dosimetry because ultrasound (US) imaging does not give any information about prostate composition. Therefore, the other dosimetric deficiency rest to solve for real-time dosimetry is the interseed effect. A fast Monte Carlo dose calculation engine, taking into account the interseed effect, has been developed for this goal, using the MCNP5 code. It will be the second part of this work.

1. Overview of cancer

Cancer is a class of diseases in which a group of cells display uncontrolled growth (division beyond the normal limits), invasion (intrusion on and destruction of adjacent tissues), and sometimes metastasis (spread to other locations in the body via lymph or blood). These three malignant properties of cancers differentiate them from benign tumors, which are self-limited, and do not invade or metastasize.

Cancers are caused by abnormalities in the genetic material of the transformed cells (Kinzler 2002). These abnormalities may be due to the effects of carcinogens, such as tobacco smoke, radiation, chemicals, or infectious agents. Other cancer-promoting genetic abnormalities may randomly occur through errors in DNA replication, or are inherited, and thus present in all cells from birth.

Cancers are classified by their tissue of origin, their size and extension, and the cell type present in the tumor. Examples of general categories include:

- **Carcinoma:** Malignant tumors derived from epithelial cells. This group represents the most common cancers, including the common forms of breast, prostate, lung and colon cancer.
- **Sarcoma:** Malignant tumors derived from connective tissue, or mesenchymal cells.
- **Lymphoma and leukemia:** Malignancies derived from hematopoietic (blood-forming) cells
- **Germ cell tumor:** Tumors derived from germinal cells (testicle and ovary).

1.1 Prostate cancer

The prostate is a gland of the male reproductive system. It produces and stores seminal fluid, a milky fluid that nourishes sperm. This fluid is released to form part of semen. The prostate is about the size of a walnut. It is located below the bladder and in front of the rectum. It surrounds the upper part of the urethra, the tube that empties urine from the bladder.

Cancer of the prostate (CaP) is considered as one of the principal medical problems facing the male population. In Europe, an estimated 2.6 million new cases of cancer are diagnosed each year. Prostate cancer constitutes about 11% of all male cancers in Europe (Bray 2002), and accounts for 9% of all cancer deaths among men within the European Union (EU) (Black 1997). In most countries, irrespective of whether prostate cancer is common or not in the country/region, a slight increase in prostate cancer mortality has been seen in most, but not all, countries since 1985 (Quinn 2002). It is a malignant tumor that consists of cells from the prostate gland. The tumor usually grows slowly and remains confined to the gland for many years. During this time, the tumor produces little or no symptoms or outward signs

(abnormalities on physical examination). As the cancer advances, however, it can spread beyond the prostate into the surrounding tissues (local spread). Moreover, the cancer also can metastasize (spread even farther) throughout other areas of the body, such as the bones, lungs, and liver. Symptoms and signs, therefore, are more often associated with advanced prostate cancer.

The causes of prostate cancer are not well understood. Studies have found that the following risk factors are associated with prostate cancer:

- **Age:** The older you are, the greater the risk.
- **Family history of prostate cancer:** A man's risk for developing prostate cancer is higher if his father or brother has had the disease.
- **Race:** This disease is much more common in African American men than in American men. It is less common in Asian and American Indian men.
- **Diet and dietary factors:** Some evidence suggests that a diet high in animal fat may increase the risk of prostate cancer and a diet high in fruits and vegetables may decrease the risk. Studies are in progress to learn whether men can reduce their risk of prostate cancer by taking certain dietary supplements.

In the beginning, prostate cancer patients may not have any symptoms. When the cancer grows, the tumor becomes larger and presses against nearby organs such as the urethra, interfering with the flow of urine. that translates into increased frequency in urination, difficult and painful urination or blood in the urine. Later on, the cancer may spread to nearby lymph nodes, bones or other organs.

There are many ways to diagnose prostate cancer; the most common methods are:

a. Digital rectal exam (DRE)

During the examination, the doctor inserts a gloved, lubricated finger into the patient's rectum to determine if the prostate feels irregular or abnormally firm. This procedure takes less than a minute and causes minimal discomfort.

b. Prostate specific antigen (PSA) level

PSA is produced by both normal and cancer cells in the prostate gland. In the early stage of prostate cancer, PSA level usually rises. The blood level of PSA can also reflect the stage of the cancer (see Table 1) (Sobin 2002). Most men have PSA levels under 4 ng/ml. A high value or rapid increase in PSA readings requires further tests. Once prostate cancer is diagnosed, the PSA can also be used to follow the progress of the cancer.

c. Transrectal ultrasound (TRUS) and Biopsy

During this procedure, the doctor places a small echography into the patient's rectum so that an image of the prostate can be created on a video screen. If prostate cancer is suspected, the doctor takes biopsies through a thin needle for examination under the microscope. A biopsy is the most reliable method for the diagnosis of prostate cancer. If the result of the biopsy is positive, meaning cancer is found, the pathologist will grade the cancer according to how closely the cancer cells resemble normal cells. The most commonly used prostate cancer grading system is called the Gleason score, which ranges from 2 to 10. The higher the score, the faster the cancer is likely to grow and spread.

Prostate cancer staging indicates how widespread the cancer is. Results from the digital rectal exam, PSA level, Gleason score and other tests are used as part of the staging process. The most commonly used staging system is called the TNM System (Table 1) (Sobin

2002). It describes the extent of the primary tumor and whether the cancer has spread to nearby lymph nodes, or other distant organs or bones. The TNM stages for prostate cancer are I (1), II (2), III (3) and IV (4). The lower the number, the less the cancer has spread.

Depending on the stage of the cancer, the age and health condition of the patient, treatment options may vary. When choosing between these options, the doctor and patient must discuss the benefits and risks of each treatment. The different treatments proposed are: observation, prostatectomy, hormonal therapy, chemotherapy and radiotherapy (external radiotherapy and brachytherapy that concerned us in this work).

1.2 Treatment techniques of prostate cancer

According to statistics collected in the early 1990s, approximately 30 percent of prostate cancer patients in the United States were treated with surgery, 30 percent were treated with radiation and 20 percent elected watchful waiting. Most of the remaining 20 percent were treated with a combination of therapies. In Europe, by contrast, watchful waiting was the standard treatment for asymptomatic prostate cancer.

1.2.1 Observation — "Watchful Waiting"

The term watchful waiting (WW) is used to describe a treatment strategy that includes an active standpoint to postpone treatment until it is required. This does not only mean that treatments, such as palliative or hormonal, are withdrawn until symptomatic progression occurs (local or systemic). In rare, selected cases, this approach may also include younger patients with localized disease for whom potentially curative treatments are withheld until an indication of tumor activity occurs (i.e. rising serum PSA level, deteriorating histopathological factors on repeat biopsy). Patients who are offered WW must be followed-up carefully. It is worth mentioning that a patient's anxiety is also a symptom that might warrant active treatment.

1.2.2 Radical prostatectomy

The surgical treatment of prostate cancer consists of radical prostatectomy, meaning the removal of the entire prostate gland between urethra and bladder, with resection of both seminal vesicles. The procedure is routinely performed either retropubically or using a transperineal approach, although some centers have gained experience with laparoscopic radical prostatectomy {(Lein 2006),(Rassweiler 2006)}.

Over the last 5-7 years several European centres have acquired considerable experience with laparoscopic radical prostatectomy (Rozet 2005). More recently, the robotic-assisted laparoscopic radical prostatectomy has been developed. Functional and short-term oncological outcomes seem comparable with the open technique in high-volume centres. However, long-term oncological outcomes are still unavailable.

Radical prostatovesiculectomy was first applied at the beginning of the 20th century by Young (Young 1905). He used a perineal approach, while Memmelaar and Millin performed retropubic radical prostatectomy for the first time (Memmelaar 1949). In 1982, Walsh and Donker described the anatomy of the dorsal venous complex and the neurovascular bundles. This resulted in a significant reduction of the blood loss and improved continence and potency rates (Walsh 1982).

Currently, radical prostatectomy is the only treatment for localized prostate cancer that has shown a cancerspecific survival benefit when compared to conservative management in a prospective, randomized trial (Bill-Axelson 2005).

Surgical expertise has decreased the complication rates and improved cancer cure (Potosky 1999). In the hands of an experienced urological surgeon, the procedure is associated with minimal intra-operative and postoperative morbidity {(Lepor 2001),(Maffezzini 2003)}. The retropubic approach is more commonly performed, as it enables simultaneous pelvic lymph node assessment to be carried out – an advantage over the perineal approach.

It has been suggested that perineal radical prostatectomy might result in positive surgical margins more often than the retropubic approach (Boccon-Gibod 1998), but this has not been confirmed (Weldon 1995). It is likely that laparoscopic prostatectomy and perineal prostatectomy have lower morbidity than the retropubic operation, but randomized studies are as yet unavailable.

In men with localized prostate cancer and a life expectancy of 10 years or more, the goal of a radical prostatectomy by any approach must be eradication of the disease (Huland 1997). In fact, there is no rigid age limit for radical prostatectomy and a patient should not be denied this procedure on the grounds of age alone (Corral 1994). However, it is worth pointing out that increasing comorbidity with increasing age substantially decreases the actual risk of dying from localized prostate cancer in men over the age of 70 years (Albertsen 1998).

1.2.3 Hormonal therapy

In 1941, Huggins and Hodges assessed the favorable effect of surgical castration and estrogen administration on the progression of metastatic prostate cancer, demonstrating for the first time the responsiveness of prostate cancer to androgen deprivation (Huggins 2002 & 1941).

Since their pivotal studies, androgen-suppressing strategies have become the mainstay for the management of advanced prostate cancer. In recent years, however, there has been an evolution towards increasing hormonal treatment of younger men with earlier (i.e. non-metastatic) stages of disease or recurrent disease after definitive treatment, either as the primary single-agent therapy or as a part of a multimodality approach (McLeod 2003).

Even if hormonal treatment effectively palliates the symptoms of advanced disease, there is no conclusive evidence at present that it can extend life.

1.2.4 Chemotherapy

Chemotherapy is a treatment to destroy cancer cells using cytotoxic drugs. There are more than 50 chemotherapy drugs available that can be used in a variety of ways according to the type of cancer, how advanced it is and a person's general health. It is beyond the scope of this work to detail all the possible chemotherapy drugs.

1.2.5 Radiotherapy

Radiotherapy treats cancer by using ionization radiation to destroy cancer cells, while doing as little harm as possible to normal cells. Radiotherapy for cancer of the prostate is usually given from an external machine (external beam radiotherapy), but for some men with early prostate cancer it can be given by inserting small radioactive seeds into the tumor (brachytherapy).

Table 1. Tumor Node Metastasis (TNM) classification of prostate cancer (Sobin 2002)

Primary Tumor, Clinical (T)									
TX	Primary tumor cannot be assessed								
T0	No evidence of primary tumor								
T1	Clinically inapparent tumor not palpable or visible by imaging								
	T1a	Tumor incidental histologic finding in 5% or less of tissue resected							
	T1b	Tumor incidental histologic finding in more than 5% of tissue resected							
	T1c	Tumor identified by needle biopsy (<i>e.g., because of elevated PSA</i>)							
T2	Tumor confined with prostate*								
	T2a	Tumour involves one half of one lobe or less							
	T2b	Tumour involves more than half of one lobe, but not both lobes							
	T2c	Tumor involves both lobes							
T3	Tumor extends through prostate capsule**								
	T3a	Extracapsular extension (<i>unilateral or bilateral</i>)							
	T3b	Tumor invades seminal vesicle(s)							
T4	Tumor is fixed or invades adjacent structures other than the seminal vesicles: bladder neck, external sphincter, rectum, levator muscles and/or pelvic wall								
Regional Lymph Nodes (N) ***									
NX	Regional lymph nodes cannot be assessed								
N0	No regional lymph node metastasis								
N1	Metastasis in regional lymph node or nodes								
Distant Metastasis (M) ****									
MX	Presence of distant metastasis cannot be assessed								
M0	No distant metastasis								
M1	Distant metastasis								
	M1a	Non-regional lymph node(s)							
	M1b	Bone(s)							
	M1c	Other site(s)							
Histopathologic Grade (G)									
GX	Grade cannot be assessed								
G1	Well-differentiated (<i>slight anaplasia</i>)								
G2	Moderately differentiated (<i>moderate anaplasia</i>)								
G3-4	Poorly undifferentiated or undifferentiated (<i>marked anaplasia</i>)								
Stage Grouping									
Stage I	T1a	N0	M0	G1	Stage III	T3	N0	M0	Any G
Stage II	T1a	N0	M0	G2, G3-4	Stage IV	T4	N0	M0	Any G
	T1b	N0	M0	Any G		Any T	N1	M0	Any G
	T1c	N0	M0	Any G		Any T	Any N	M1	Any G
	T1	N0	M0	Any G					
	T2	N0	M0	Any G					
*	Tumor found in one or both lobes by needle biopsy, but not palpable or reliably visible by imaging, is classified as T1c								
**	Invasion into the prostatic apex or into (<i>but not beyond</i>) the prostatic capsule is not classified as T3, but as T2.								
***	Metastasis no larger than 0.2 cm can be designated pN1mi.								
****	When more than one site of metastasis is present, the most advanced category is used.								

* Tumor found in one or both lobes by needle biopsy, but not palpable or reliably visible by imaging, is classified as T1c

** Invasion into the prostatic apex or into (*but not beyond*) the prostatic capsule is not classified as T3, but as T2.

*** Metastasis no larger than 0.2 cm can be designated pN1mi.

**** When more than one site of metastasis is present, the most advanced category is used.

1.2.5.1 External beam radiotherapy:

Anatomical data, acquired by scanning the patient in a treatment position, are transferred to the 3D treatment planning system where the clinical target volume is contoured, and safety margin is added to account for interfraction positioning variability. The real-time verification of the irradiation beams is done by portal imaging, comparing the treated and simulated fields. Deviations are corrected when displacement is more than 5 mm (or less depending on the treatment technique). Three-dimensional conformal radiotherapy (3D-CRT) is a high-precision technique that improves local control through dose escalation, without increasing the risk of morbidity. The typical doses are 50 Gy to the pelvic nodes, 54 to 56 Gy to the seminal vesicles if they are involved and 70 to 80 Gy to the prostate. The use of intensity modulated radiotherapy (IMRT) is possible with linear accelerators equipped with the latest multileaf collimators and specific software. The movement of the leaves during the course of the irradiation allows for the adaptation of the dose to be delivered within the treatment field and provides concave isodose curves. IMRT enables radiation oncologists to increase homogeneously the doses up to 80 Gy within the target volume, while respecting the threshold doses in organs at risk.

1.2.5.2 High dose rate (HDR):

HDR temporary brachytherapy involves inserting thin plastic catheters into the prostate gland, and then giving a series of radiation treatments through these catheters. The catheters are then easily pulled out, and no radioactive material is left in the prostate gland. A computer-controlled machine (afterloader) pushes a single highly radioactive iridium seed into the catheters one by one. The radiation dose in different regions of the prostate is controlled by the computer driven afterloader, by varying the dwell times of the successive source positions. The catheters are then easily pulled out, and no radioactive material is left in the prostate gland. This ability to modify the dose after the needles are placed is one of the main advantages of temporary brachytherapy over permanent seed implants.

1.2.5.3 Interstitial implants:

In recent years the use of permanent interstitial implants for treating prostate cancer has increased. The reason for this is improvements in diagnosis at the early stage of the disease as well as refinements in the brachytherapy technique. Permanent implants with iodine-125 or palladium-103 are used in the treatment of early stage prostate cancer as the sole modality or in combination with external beam radiation therapy. The target volume for implantation in either case is the prostate gland itself, with minimal margins allowed to account for uncertainty of prostate localization. The modern technique of implantation, which began in the 1980s, consists of transperineal approach in which iodine-125 or palladium-103 seeds are inserted into the prostate gland under the guidance of transrectal ultrasonography and through a perineal template (Figure 1).

When using permanent interstitial implants, the dose distribution depends on the accuracy of the source positioning with respect to the treatment plan. Post-implant analysis describes how the actual dose distribution conforms to the desired dose. There are organized steps in prostate brachytherapy that ensures the efficiency and accuracy of the process. These steps include the volume study, the treatment planning stage, the implant procedure, and the post-operative analysis.

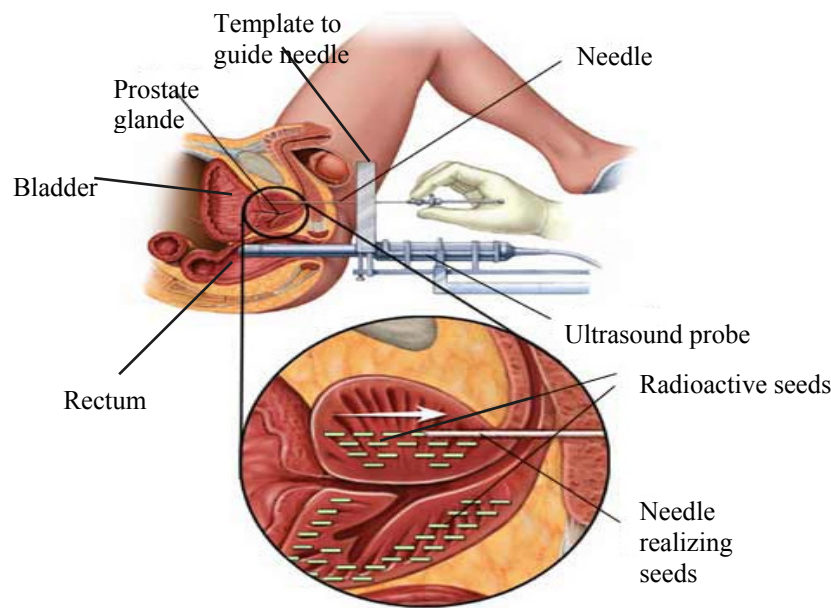


Figure 1. Schematic of Prostate Seed Implant Procedure

The volume study is the pre-planning stage, in which the size of the prostate is identified at least one week, but no more than four weeks, prior to the planned implant. The volume study is the first steps in prostate implants acquired through a series of transverse ultrasound images. If the gland is too large (over 50 cc) and/or the pubic arch is too narrow, then hormonal therapy may have to be done before prostate seed implantation in order to decrease the prostate size. The target volume definitions are, for the most part, based upon the *ICRU Report 58, Dose and Volume Specification for Reporting Interstitial Therapy* (Table 2).

The seeds have to be calibrated before implantation. A random sampling of at least 10% of the seeds shall be calibrated in such a manner such that there is direct traceability to either the NIST or an AAPM ADCL (Accredited Dosimetry Calibration Laboratory) as described by AAPM Report TG-43U1 (Rivard 2004). The measured activity will be compared against the vendor's statement of activity. If seeds in sterile absorbable material are used, then one seed from every 5 packets will be removed and calibrated.

At the time of the implant, a transrectal ultrasound probe is used to acquire transverse images of the prostate gland at intervals of about 1 mm (Figure 2). A grid is placed on these images, which represents the perineal template coordinates. The template is the physical grid that is placed on the patient to guide needles to the proper position (Figures 3).

The prostate is visualized and drawn on each image (Figure 2). To measure the length of the prostate a sagittal image is taken. Target outlines from the volume study are digitized into a computer using treatment-planning software. The planning software is used to place seeds in the template grid throughout the ultrasound images (Figure 2). In the software, seeds can be added or deleted as necessary to obtain an optimal dose to cover the target volume. Also, the source strength can be modified, but an homogeneous source strength is used in a single implant. When the plan is completed, a worksheet is printed that provides the number of needles, seeds in the needles, and the coordinates of the needles. The prostate implant procedure is a nonsurgical procedure performed on an outpatient basis. It is done in an operating room with the patient under general anesthesia.

Table 2. Target volume definitions based upon the ICRU Report 58 for reporting interstitial therapy

CTV (Clinical Target Volume)

Pre-implant TRUS definition of the prostate

PTV (Planning Target Volume) :

An enlargement of the CTV as follows:

1. Expand the TRUS definition of the prostate by 2 to 3 mm in the lateral dimension for each TRUS axial image. Thus, the lateral dimension of the prostate will increase by approximately 5 mm
2. Expand the TRUS definition of the prostate by 2 to 3 mm in the anterior dimension for each TRUS axial image.
3. Maintain the same posterior border of the prostate as defined by TRUS.
4. Project the expanded most cephalad axial definition to a plane 5 mm cephalad to the cephalad most TRUS plane.
5. Project the expanded most caudad axial definition to a plane 5 mm caudad to the caudad most TRUS plane.

The PTV is approximately 10 mm longer in the caudad-cephalad dimension than the CTV.

ETV (Evaluation Target Volume)

The ETV is defined as the post-implant CT definition of the prostate (*the ETV concept is not found in the ICRU report*).

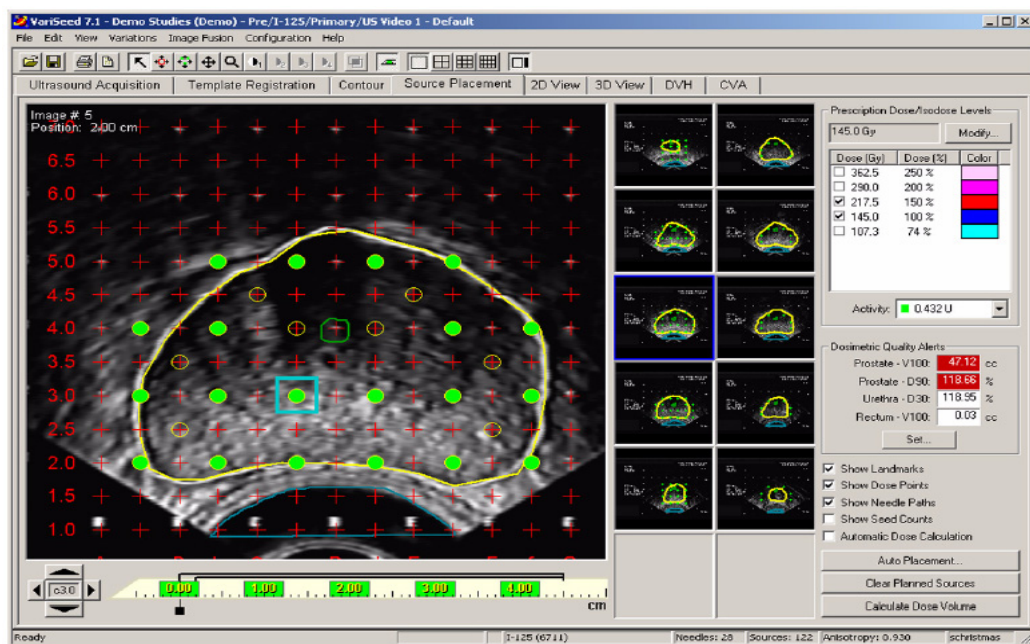


Figure 2. Ultrasound transverse images of the prostate gland at intervals of about 5mm with drawn contours of prostate and organs at risk showing seed positions.

A transrectal ultrasound and a transperineal template are used to guide seed containing needles into position, as shown in Figure 4. The needles are preloaded with the planned number of seeds and spacers and the tip is sealed with sterile wax. By using the ultrasound

images and distance measurements from the hub of the needle to the template the needle tip is positioned to the correct plane and depth. Afterwards, the needle is withdrawn while the plunger is held stationary. Thus the seeds and spacers are injected into the tissue along the track of the withdrawing needle. The implant is verified using anterior-posterior fluoroscopy. If any cold spots are identified extra seeds can be added.



Figure 3. Front View of Template.

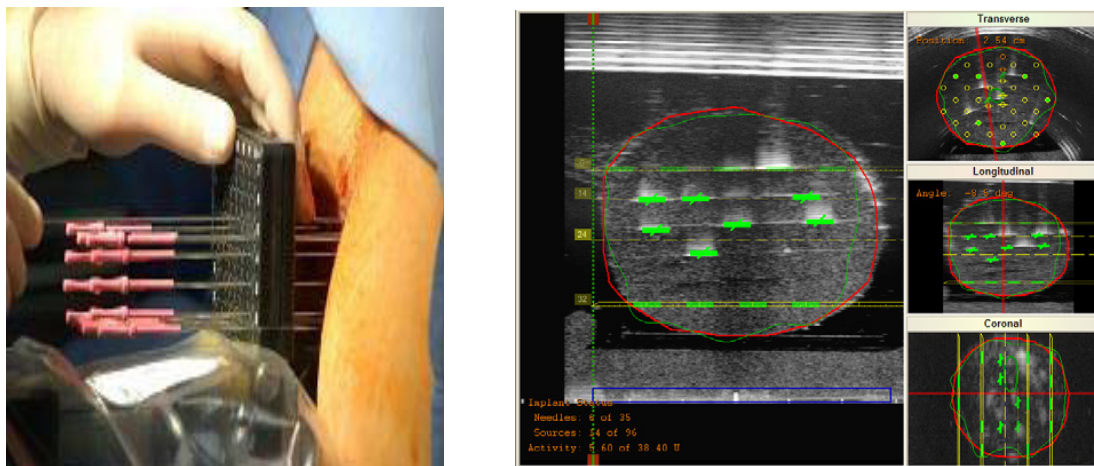


Figure 4. Transrectal ultrasound and a transperineal template used to guide seed containing needles into position.

A post-implant CT shall be taken between 3 to 5 weeks after the implant. This time period represents approximately two half-lives of swelling reduction, i.e. the swelling caused by the procedure will be significantly reduced. The patient shall be positioned in a supine position. Contrast will not be used. Axial 5 mm thick slices or less shall be acquired from at least 20 mm cephalad to the base of the prostate to at least 20 mm caudal to the apex of the prostate.

1.3 Guidelines on primary treatment of prostate cancer

In table 3 we present a summary of guidelines on primary treatment of prostate cancer.

Table 3. Summary of guidelines on primary treatment of prostate cancer

Stage	Treatment	Comment
T1a	Watchful waiting	Standard treatment for well-, and moderately, differentiated tumors and < 10-year life expectancy. In patients with > 10-year life expectancy, re-staging with TRUS and biopsy is advised (grade B recommendation).
	Radical prostatectomy	Optional in young patients with a long life expectancy, especially for poorly differentiated tumors (grade B recommendation).
	Radiotherapy	Optional in younger patients with a long life expectancy, especially for poorly differentiated tumors. Higher complication risks after TURP, especially with interstitial radiation (grade B recommendation).
	Hormonal	Not an option (grade A recommendation)
	Combination	Not an option (grade C recommendation)
T1b-T2b	Watchful waiting	Asymptomatic patients with well-, and moderately, differentiated tumors and a life expectancy < 10 years. Patients who do not accept treatment-related complications (grade B recommendation).
	Radical prostatectomy	Standard treatment for patients with life expectancy > 10 years who accept treatment-related complications (grade A recommendation).
	Radiotherapy	Patients with a life expectancy > 10 years who accept treatment-related complications. Patients with contraindications for surgery. Unfit patients with 5-10 years of life expectancy and poorly differentiated tumors (combination therapy is recommended; see below) (grade B recommendation).
	Hormonal	Symptomatic patients who need palliation of symptoms unfit for curative treatment (grade C recommendation). Antiandrogens are associated with poorer outcome in comparison with watchful waiting and are not recommended (grade A recommendation).
	Combination	Neoadjuvant hormonal therapy (NHT) + radical prostatectomy: no proven benefit (grade A recommendation) NHT + radiotherapy: better local control. No proven survival benefit (grade B recommendation). Hormonal (3 years) + radiotherapy: better than radiotherapy in poorly differentiated tumors (grade A recommendation).
T3-T4	Watchful waiting	Option in asymptomatic patients with T3, well-differentiated and moderately differentiated tumors, and a life expectancy < 10 years (grade C recommendation).
	Radical prostatectomy	Optional for selected patients with T3a and a life expectancy > 10 years (grade C recommendation).
	Radiotherapy	T3 with > 5-10 years of life expectancy. Dose escalation > 70 Gy seems to be of benefit. If this is not available, a combination with hormonal therapy could be recommended (see below) (grade A recommendation).

Stage	Treatment	Comment
T3-T4	Hormonal	Symptomatic patients, extensive T3-T4, high PSA level (> 25 ng/mL), unfit patients. Better than watchful waiting (grade A recommendation).
	Combination	Radiotherapy + hormonal seems better than radiotherapy alone (grade A recommendation). NHT + radical prostatectomy: no proven benefit (grade B recommendation).
N+, M0	Watchful waiting	Asymptomatic patients. Patient driven. May have worse survival (grade C recommendation).
	Radical prostatectomy	No standard option (grade C recommendation).
	Radiotherapy	No standard option (grade C recommendation).
	Hormonal	Standard therapy (grade A recommendation).
	Combination	No standard option. Patient driven (grade B recommendation).
M+	Watchful waiting	No standard option. May have worse survival/more complications than with immediate hormonal therapy (grade B recommendation).
	Radical prostatectomy	Not an option (grade C recommendation).
	Radiotherapy	Not an option (given for cure) (grade C recommendation).
	Hormonal	Standard therapy. Symptomatic patients should not be denied treatment (grade B recommendation).
	Combination	Not an option (grade C recommendation).

2. Radiation dosimetry

Radiation therapy involves the use of a certain type of energy to kill cancer cells and shrink tumors. Radiation therapy injures or destroys cells in the area being treated by damaging their genetic material, making it impossible for these cells to continue to grow and divide. Although radiation damages both cancer cells and normal cells, most normal cells can recover from the effects of radiation and function properly. The goal of radiation therapy is to damage as many cancer cells as possible, while limiting harm to nearby healthy tissue.

Different tissues can tolerate various amounts of radiation. Dose limits are, therefore, empirically determined according to tissue tolerance in order to help doctors to optimize treatment and limit adverse effects as much as possible.

In general, radiation dosimetry is the calculation of the amount of radiation energy absorbed in matter (absorbed dose) as a result of exposure to indirect and direct ionizing radiation. In applications of ionizing radiation for medical conditions, it is important to measure this delivered amount. For example, in diagnostic procedures, such as X-ray examinations, nuclear medicine, CT scans, PET etc, this measurement is important both for optimizing image quality and for radiation protection purposes. However, the need for accurate dosimetry is greatest in radiotherapy in which high doses are delivered intermittently to a tumor to kill it but also to give normal cells the time necessary for repair. The total dose delivered to tumors is typically 10 times the dose that would kill a person receiving this dose to the entire body. From the above, we can see how important dosimetry, the accurate estimation of the dose delivered to tissues, is in radiation therapy.

Radiation dosimetry is performed using a device, instrument or system called a dosimeter. The dosimeter measures or evaluates, either directly or indirectly, the exposure quantities, kerma, absorbed dose or equivalent dose, or their time derivatives (rates), or related quantities of ionizing radiation (Reniers 2005).

To function as a radiation dosimeter, the dosimeter must possess at least one physical property that is a function of the measured dosimetric quantity and that can be used for radiation dosimetry with proper calibration. Moreover, radiation dosimeters must exhibit several desirable characteristics. For example, in radiotherapy exact knowledge of the absorbed dose in water at a specified point and its spatial distribution are both of importance, as is the possibility of determining the dose in an organ of interest in the patient. In our work, we were interested in permanent brachytherapy dosimetry for prostate treatment using iodine-125 and palladium-103 seeds.

Several recent studies have demonstrated that clinical outcomes in permanent prostate brachytherapy correlate closely with the dose delivered and the prostate volume coverage {Zelefsky and Whitmore (1997), Nath et al. (1998), Stock et al. (1998), Potters et al. (2001) and (Rivard 2004)}. The quality of the implant depends on the dosimetric evaluation consisting of the dose delivered to the prostate compared to the dose delivered to the normal tissue (Roberson 1997).

In permanent brachytherapy, because radiation is continuously delivered over a period of time, repair of sub-lethal and potentially lethal damage, proliferation and other cell kinetic effects modify the radiation response of tumor and normal tissues, resulting in complex dose rate effects that also influence the therapeutic ratio for brachytherapy. Accurate determinations of the dosimetric characteristics of permanent brachytherapy sources are, therefore, very important.

2.1 Source dosimetry used for permanent prostate brachytherapy

Iodine-125 and palladium-103, in the form of seeds, are the most common radioactive sources used for permanent interstitial prostate implants. The dosimetry of these seeds is based on new dosimetric information that is contained in the AAPM report, TG-43, and its first update (see chapter 2, II.A. and chapter 6, section 2.1). Because we work in a low energy region in which the photoelectric effect dominates, a small variation in the internal composition of the source could considerably affect the dosimetric data around the source. Therefore, the AAPM recommends that a dosimetric characterization of each new brachytherapy source marketed for medical applications should be carefully determined by one or two independent sets of measurements and one Monte Carlo calculation (Rivard 2004).

2.1.1 Update of AAPM Task Group No. 43 Report

TG43U1 (Rivard *et al.* 2004) published by AAPM (American Association of Physicists in Medicine) is generally used for Brachytherapy treatment dose calculations. Dose rate distribution around radioactive seed in water is calculated using an analytical approximation of dosimetric quantities, e.g. air kerma strength, dose rate constant, geometry factor, radial dose function and anisotropy function. TG43U1 equations are used in all Brachytherapy TPS for prostate permanent implant however; they do not take into account the interseed effect. In this protocol two dose rate equations are given: cylindrically symmetric line source (2D) and point source (1D) formalisms.

2.1.1.1 General two dimension formalism

The general, two-dimensional (2D), dose-rate equation is expressed as:

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

This formalism applies to sources with cylindrically symmetric dose distributions with respect to the source longitudinal axis. The subscript ‘‘L’’ has been added to denote the line source approximation used for the geometry function, S_K is the air-kerma strength of the source (U), Λ is the dose rate constant ($\text{cGy h}^{-1} \text{U}^{-1}$), $G(r, \theta)$ is the geometry factor, $g(r)$ is the radial dose function and $F(r, \theta)$ is the two-dimensional (2D) anisotropy function. The reference point (r_0, θ_0) is chosen to be along the transverse plane ($\theta_0=90^\circ$) at a distance of 1 cm from the source center.

2.1.1.2 General one dimension formalism

This formalism is used to eliminate the need to determine the orientation of the source longitudinal axis from imaging studies by approximating the true complex 2D dose distribution with 1D isotropic point-source approximation.

$$\dot{D}(r, \theta) = S_k \times \Lambda \times \frac{G_X(r, \theta)}{G_X(r_0, \theta_0)} \times g_X(r) \times \phi_{an}(r)$$

The subscript ‘‘X’’ is used to the radial dose function and geometry function to indicate whether a point-source. ‘‘P.’’ or line-source ‘‘L.’’ geometry function was used in transforming the data. We should thus adopt one of the following implementations of last equation:

$$\dot{D}(r, \theta) = S_k \times \Lambda \times \left(\frac{r_0}{r} \right)^2 \times g_P(r) \times \phi_{an}(r) \quad (\text{Point source})$$

This equation is used in most treatment planning systems. However, we recommend using the following equation due to improved accuracy at small distances, e.g., <1 cm.

$$\dot{D}(r, \theta) = S_k \times \Lambda \times \frac{G_L(r, \theta)}{G_L(r_0, \theta_0)} \times g_L(r) \times \phi_{an}(r) \quad (\text{Line source})$$

where $\phi_{an}(r)$, the one-dimensional (1D) anisotropy function, is given by the following equation:

$$\phi_{an}(r) = \frac{\int_0^\pi \dot{D}(r, \theta) \sin(\theta) d\theta}{2\dot{D}(r, \theta_0)}$$

2.1.2 Measurements

The AAPM recommends that the dosimetric characteristics of the seed are specified in a liquid water phantom. However, the high dose gradients around the seeds make it very difficult to measure absorbed doses directly in water. Therefore, a solid medium phantom was used to enable TLDs to be precisely positioned in a fixed geometry relative to a centrally located source. Solid water was used as a measurement medium in our work because Monte Carlo results {(Meigooni 1988),(Williamson 1991)} confirm that the radiological properties of this material approximate those of liquid water better than other commercial plastics.

The choice of a radiation dosimeter and its reader must also be made judiciously, taking into account the purpose of the measurements. For example, use of low energy photons induces some dosimetric complications. At these energies, photon attenuation is very high, which makes measurement quite difficult because of the high gradients. For measuring brachytherapy dosimetry parameters, detectors should have, first of all, a relatively small active volume such that effects of averaging of high-gradient dose fields over this volume are negligible or are accurately accounted for by correction coefficients; secondly, detectors should have a well-characterized energy-response function, such that differences between the calibration energy and experimentally measured energy are either negligible or may be quantitatively accounted for; and finally, they should have sufficient precision and reproducibility to permit dose rate estimation with 1σ statistical uncertainty $\leq 5\%$, and 1σ systematic uncertainty $< 7\%$.

A variety of dosimeters, including LiF TLD (Das 1996), diodes (Ahmad 1992), diamond detectors (Rustgi 1998), miniature ionization chambers (Mishra 1997), plastic scintillators (Williamson 1999), liquid ionization chambers (Johansson 1995), polymer gels (Maryanski 1996), radiographic (Chiu-Tsao 1994) and radiochromic film (Bohm 2001), and chemical dosimeters (Hasson 1998), have been used for brachytherapy dosimetry.

LiF TLD (thermoluminescent detectors) remains the most extensively (but not only) validated methodology for relative dose measurement of low-energy photon-emitting brachytherapy sources (Patel 2001 & Das 1996), and is currently the method of choice for experimental determination of the dose-rate constant (Rivard 2004). Therefore, $1 \times 1 \times 1 \text{ mm}^3$ LiF TLD-100 chips were considered in our work.

LiF TLD-100 chips were calibrated using a 6 MV linear accelerator photon beam with dosimetry performed following the NCS (Nederlandse Commissie voor Stralingsdosimetrie) protocol (Mijnheer 1986) (dose to water) and applying the same procedure as that described by Reniers *et al.* (Reniers 2002). A Harshaw model 3500 TLD reader was used. The calibration procedure was repeated several times before and after the seed dosimetry to assess

possible variations in the calibration factor and/or instability of the reader, and TLD detectors were then selected to obtain a standard deviation of less than 3.5% (see chapter 2, II.C. and chapter 3, II.C.).

For experimental measurement of absolute dose rates in water, at least one source should have direct traceability to a primary standard. Other sources used in the experiment should be precisely transferred using high-precision transfer devices such as well-characterized well-ionization chambers and secondary standards maintained by the investigator as well as the manufacturer's laboratories.

The first primary standard for ^{125}I sources was developed by Loftus in 1985 based on the Ritz parallel-plate free-air chamber (FAC), the national primary X-ray standard for superficial therapy beams {(Loftus 1984),(Ritz 1960)}. This chamber was used to measure the exposure rate in free-space on the transverse plane of model 6711 and 6702 sources. Because the Ritz FAC background current was high relative to the signal strength expected from a single source, this device was limited to a calibration arrangement of a combination of 4 to 6 sources.

Moreover, most seeds are made of titanium, which generates fluorescent photons (Ti K-shell characteristic X-rays) of 4.5 and 4.9 keV because of the interaction of the photons emitted by iodine-125 or palladium-103 with it. Kubo drew attention to the influence of these Ti K-shell characteristic X-rays on exposure measurements made in air (Kubo 1985). These low-energy X-rays will not contribute significantly to tissue/water dose because they are largely absorbed by tissue or water within 1 mm of the source; however, they can affect air-kerma strength measurements. Monte Carlo calculations done by Williamson showed that the air-kerma rate was overestimated because of the contributions of X-rays in the measurements (Williamson 1988).

The development of the wide-angle free-air chamber (WAFAC) by Loevinger (Loevinger 1993) helped NIST to develop a new standard for brachytherapy sources in 1999, in which air-kerma rate can be measured directly from individual sources and Ti K-shell characteristic X-rays are eliminated using an aluminum filter. The new standard reduced the air-kerma strength by 11% and all measured dose-rate constant data given by the TG-43U1 protocol have been normalized to this new 1999 standard.

2.1.3 Monte Carlo simulation

Historically, Monte Carlo methods have played an important role in computational dosimetry. Monte Carlo simulation is a method for iteratively evaluating a deterministic model using sets of random numbers as inputs. This method is often used when the model is complex, nonlinear, or involves more than just a couple of uncertain parameters. Monte Carlo simulation was first used successfully to solve particle transport problems and this is still one of the areas of most extensive use (Carter 1975).

Stanislaw Ulam is a Polish mathematician who participated in the Manhattan Project and proposed the Teller–Ulam design of thermonuclear weapons. While in Los Alamos, he suggested the Monte Carlo method for evaluating complicated mathematical integrals that arise in the theory of nuclear chain reactions (not knowing that Enrico Fermi and others had used a similar method earlier). This suggestion led to the more systematic development of Monte Carlo by Von Neumann, Metropolis, and others.

Von Neumann was taken by the idea of doing statistical sampling using newly developed electronic computing techniques. The approach seemed to him to be especially suitable for exploring behavior of neutron chain reactions in fission devices. In particular, neutron multiplication rates could be estimated and used to predict the explosive behavior of the various fission weapons then being developed.

A team headed by Metropolis carried out the first actual Monte Carlo calculations on the ENIAC computer (the world's first electronic digital computer, built at the University of Pennsylvania) in 1948.

In the first half of the 20th century up until the early years of the AAPM in the 1960s, clinical brachytherapy dose distributions were generally determined using lookup tables (i.e., along-away tables) based on ionization measurements and Sievert integrals (Sievert 1921);(Shalek et al. 1968). Based on modeling, dose distributions in solid-state media around brachytherapy source was performed using radiation transport. One of the earliest publications about using Monte Carlo methods to simulate a geometrically realistic cylindrically symmetric brachytherapy source was by Krishnaswamy in 1971. Over a decade passed before, another investigators had simulated brachytherapy sources to the same level of detail as Krishnaswamy. For example, isotropic point-source build-up factor-based approaches to brachytherapy dose distribution derivation were performed by Berger in 1968, Webb and Fox in 1979, and in the paper by Meisberger et al in 1968. More sophisticated approaches using 3D modeling were pursued later, and were largely spearheaded by Williamson in 1983 and 1988.

Various Monte Carlo codes for radiation (i.e., 0.03 to ~1 MeV photon) transport had been used since the 1950s, but medical physicists transcended the gap between basic physics and the needs of the clinic, often by developing homemade radiation transport codes (Williamson in 1983);(Williamson *et al.* 1993). Once brachytherapy source dose distributions were calculated, these results were readily integrated into approaches for treatment planning (Shalek *et al.* 1968);(Batten 1968).

With increases in processor speed, accessibility of operating systems, and more widespread use across medical research, Monte Carlo methods for simulating brachytherapy dose distributions reached a critical threshold in the 1990s. A key event was the publication of the 1995 AAPM TG-43 report (Nath *et al.* 1995). This report significantly advanced the standard brachytherapy dosimetry formalism, required separate brachytherapy dosimetry parameters for different source models of the same radionuclide, promoted consistent use of brachytherapy dosimetry parameters at separate institutions, and through its popularity, informed medical physicists far and wide of the possibilities of Monte Carlo methods for simulating brachytherapy source dose distributions. Monte Carlo methods for brachytherapy dosimetry were further popularized by Williamson using his PTRAN code, where different source types and aspects of brachytherapy were examined (Williamson 1987).

The AAPM methodologically examined the role of Monte Carlo codes for simulating brachytherapy source dose distributions (Rivard et al. 2004). Specifically, Monte Carlo radiation transport codes were identified that have been well benchmarked for brachytherapy dosimetry. Only EGS (Kawrakow 2001), MCNP (Briesmeister 2000), and Williamson's PTRAN code (Williamson 1987) were mentioned in the TG-43U1 report as examples of well-benchmarked codes.

The field of Monte Carlo simulation of brachytherapy source dose distributions is mature; however, there is room for improvement towards better simulating the clinical environment. Since Krishnaswamy, it has been shown that improved dose simulation accuracy, determined through comparisons with measurements, are obtained through accurate modeling of the brachytherapy source and capsule. This approach has been extended to investigation of interseed interactions (Meigooni *et al.* 1992);(Rivard 2001) and motion of internal components (Rivard 2001). In fact, the principal equipment used to produce calibration results, i.e., the wide-angle free-air chamber at the National Institute of Standards and Technology (Seltzer *et al.* 2003), has been simulated for direct comparison with experimental measurements (Williamson 2002). Further advances include simulations of material heterogeneities (Lymperopoulou *et al.* 2006);(Low et al. 2002), scatter conditions

(Perez-Calatayud *et al.* 2004);(Melhus *et al.* 2006), and localization in the patient through image-guidance (Low *et al.* 2002).

In addition, Monte Carlo results, unlike experimental measurements, cannot account for modeling errors, e.g., contamination of radionuclide spectrum, errors in implementing calibration standards, etc. Comparison of Monte Carlo and experimental results is needed to detect unanticipated discrepancies between the assumed and actual properties of the system under investigation.

Efforts are underway to incorporate Monte Carlo methods into clinical brachytherapy treatment planning systems due to their proven utility to simulate radiation scatter conditions and account for material heterogeneities (Chibani *et al.* 2005);(Yegin *et al.* 2004). Other approaches not using Monte Carlo methods, such as the collapsed cone employing superposition of primary and scatter dose, may also account for dosimetric effects not modeled by the AAPM TG-43 dosimetry formalism (Carlsson *et al.* 2000);(Russell *et al.* 2005). Thus, it remains to be seen whether or not Monte Carlo methods for brachytherapy dosimetry will transition from a research tool to the backbone of the treatment planning algorithm. Investigation of a similar shift occurred for external beam treatment planning (Boudreau *et al.* 2005). However, the competing standard treatment planning algorithms for external beam radiotherapy provide much better agreement with measurements than the TG-43 dosimetry formalism for measurements of brachytherapy dose under challenging scatter and material heterogeneity conditions.

Monte Carlo N particle (MCNP) code versions 4C and 5 were used in our work. This code is a generalized, continuous energy, 3D coupled neutron/photon/electron Monte Carlo transport code, which takes into account the transport of photons and electrons over an energy range of 1 keV–1 GeV. The detailed photon physics option of MCNP was used and includes Compton scattering with bounding effect, Rayleigh scattering, and the photoelectric effect with emission of fluorescence photons. Because of the short range of the secondary electrons produced by interactions from photons emitted by the iodine-125 and palladium d-103, electron transport is not required and it is assumed that they deposit their energy locally (Rivard 2004). The Monte Carlo seed model was approved in solid water by comparing it with measurements, and dosimetric data recommended by the TG-43U1 protocol were then obtained in liquid water (see chapter 2, II.D. and chapter 3, II.D.).

2.2 Permanent prostate brachytherapy dosimetry

After dosimetric data of the source had been calculated in liquid water as the average of measured and Monte Carlo data, the 3D dose rate distribution around the source was calculated based upon two analytical approximations recommended by the TG-43U1 protocol (two dimension (2D) and one dimension (1D) dose calculation formalisms, see chapter 6, section 2.1) (Rivard 2004). 2D formalism is a function of distance (r) and angle (θ) taking into account the dose variation around the source (with angle), while 1D formalism is a function of distance and independent of angle (Rivard 2004).

As mentioned before, many seeds are implanted during permanent prostate brachytherapy. The dose delivered to the prostate is calculated by a simple addition of dose rate distribution in water for each implanted source. Several dosimetric parameters used for prostate brachytherapy optimization are presented below:

a. Prescribed Dose

The prescribed dose is the dose that the oncologist intends to deliver to the whole treated volume and is the dose entered into the treatment record. For the purposes of

this protocol, the prescribed doses to the PTV were 145 Gy and 125 Gy for I-125 and Pd-103, respectively (TG-43U1 dosimetry).

b. Low Dose Volume

ICRU 58 defines the low dose volume as the volume within the clinical target volume, encompassed by an isodose corresponding to 90% of the prescribed dose. For the purposes of this protocol, the low dose volume was defined in terms of the evaluation target volume, the ETV. The maximum dimensions of the low dose volume in any plane that contains the ETV were reported on the appropriate form.

c. High Dose Volume

For the purposes of this protocol, the high dose volume was defined as the volume enclosed by 200% of the prescribed dose. The maximum dimensions of the high dose volume in all axial planes were reported on the appropriate data form.

d. Minimum Target Dose

ICRU 58 defines the minimum target dose as the minimum dose at the periphery of the CTV. For the purposes of this protocol, the minimum target dose was defined as the minimum dose to the ETV. This can be determined by an evaluation of the dose distribution in each CT image containing the prostate.

e. Dose Volume Histograms

e.1. A DVH for the ETV was calculated in 10 Gy increments and presented in tabular form.

e.2. A DVH for the rectum, as defined in the region of the prostate such that the high dose volume of the implant was included, was calculated in 10 Gy increments and presented in tabular form.

e.3. A DVH for the bladder, as defined in the region of the prostate such that the high dose volume of the implant was included, was calculated in 10 Gy increments and presented in tabular form.

The size of the grid and the voxels used in these calculations were noted.

Post-implant dosimetric analysis is standard practice following temporary brachytherapy procedures. It relies on knowledge of seed location, knowledge of seed orientation, and the resolution of the imaging device. The seed locations and orientations are extracted from the post-implant imaging study, and the dose distribution in the prostate is then computed and compared to the treatment plan.

The evaluation criteria of treatment in post-implant analysis are as follows:

1. *Per Protocol*: at least 80% of the ETV receives at least 90% of the prescription dose.
2. *Variation, Acceptable*: at least 50% of the ETV receives at least 90% of the prescription dose.
3. *Deviation, Unacceptable*: at least 50% of the ETV receives less than 90% of the prescription dose.

The dosimetric related data to be submitted for each patient included:

- Copies of pre-implant TRUS images
- Drawing of the PTV which also displays the CTV (the TRUS images), and includes the projection of the PTV 5 mm in the cephalad and caudad directions.

- A pre-implant form that describes the actual prostate seed loading pattern. The pre-implant form was attached to the above material.
- Film copies of the post-implant CT in a format that displays four images on a 14 x 17 inch film. Films were provided of the entire prostate and any other axial level which contained seeds. Two separate sets of films were provided. The first set contained no annotations. The second set was annotated to display the definition of the prostate, rectum, and bladder.
- A post-implant form that describes the volumes, the dose description, and the dose volume histograms as defined above. The post-implant form was attached to the above material.

2.3 Sources of errors in permanent prostate brachytherapy dosimetry

Since low energy photon emitters, such as Pd-103 and I-125, are used in prostate seeds, uncertainty in the estimated dose because of localization errors of only a few millimeters can be significant due to the sharp dose rate fall-off.

Despite increasingly sophisticated mathematical methods, the accuracy of the dose reconstruction algorithms is still hindered by undesirable uncertainties. For example, in phantom studies, orthogonal film reconstruction techniques can locate only 66% of the seeds to within 5 mm of their actual location {(Bice 1999);(Tubic 2001)}.

Recent efforts using CT-based localization have shown improved accuracy in determining the positions of seeds, but detection of the orientations of overlapping seeds is still only a rough estimate. Moreover, although seed orientation can be input into the post-plan software, only one seed orientation will be used for all seeds throughout the computations. Additional problems include artifacts in the images because of the titanium shell and difficulties with localizing seeds across multiple CT images.

Most dose computation methods in use do not take into account seed shadowing effects and the fact that the tissue composition of the prostate is not water equivalent. Recent studies indicate that the seed shadowing effect (called the interseed effect, which is the attenuation effect of one seed on the dose distribution of all other implanted seeds), when correctly computed, can amount to a 3% to 5% discrepancy from the dose calculated when individually computed doses are superimposed {(Yegin and Rogers 2004),(Carrier, 2006)}. This effect is due to seed marker and the metallic shell. When prostate tissue composition is also taken into account, the total discrepancy from water-based dose computations using the superposition technique is up to about 13% (Carrier, 2006).

Some brachytherapy companies tried to solve some of the above- mentioned problems by producing a new generation of seeds with a biocompatible polymer shell. Two palladium-103 and iodine-125 seeds made in polymer were produced for clinical applications by the IBt Bebig group. The dosimetric study of these seeds was the first subject of this work.

Full Monte Carlo Simulation (FMCS) directly calculates the total dose of a given seed distribution, taking into account the interseed and tissue heterogeneity effects but is too slow to be used in real-time dosimetry. An accelerated Monte Carlo code, named MCPI (Chibani 2005), has been developed for dose calculation in prostate brachytherapy. MCPI takes into account the interseed and tissue heterogeneity effects and is faster than FMCS. However, the calculation time is about one minute for 83 ¹⁰³Pd-based seeds if using a single Pentium 4 PC, 2.4 GHz, so is not fast enough for real-time implant dosimetry.

Since, in real-time dosimetry we have no information about tissue heterogeneity from the ultrasound image we focused our study on how we could correct the interseed effect online? Therefore, a new Monte Carlo dose calculation engine, which takes into account the

interseed effects for real time dosimetry, was developed and was the second topic of this work.

3. Objectives of the thesis

To clarify the goals of this thesis, I will summarize our objectives:

A. Dosimetric study for new sources made in polymer produced by the IBt Bebig group for use in clinical applications.

Since low energy photon emitters, such as Pd-103 and I-125, are used, the dosimetric characteristics around the seed are very dependent on the internal design of the source. Therefore, in the TG-43U1 protocol, the AAPM recommends a new dosimetric study for each new source.

A.1 Palladium-103 source (OptiSeed^{exp}):

The first paper (chapter 2) describes the dosimetric study of an experimental palladium-103 seed (OptiSeed^{exp}) in a biocompatible polymer without marker. The interseed effect of the gold marker was investigated in this study.

A.2 Iodine-125 source (SmartSeed):

The second paper (chapter 3) describes the dosimetric study of the first polymer-encapsulated iodine seed (SmartSeed). The dosimetric impact of the fluorescence X-rays with energies of 3 keV, 5 keV and 12 keV, produced by the plumbed glass marker was investigated in this study. This opened the door to a new investigation to improve the primary NIST 1999 standard, which eliminates X-rays with energies up to 5 keV

B. New Monte Carlo dose calculation engine which takes into account the interseed effects for real time dosimetry.

The interseed effect is the attenuation effect of one seed on the dose distribution of all other implanted seed. Since the interseed effect is a function of several variables, e.g., seed composition, density of implanted seeds in the treated volume, type of radioactive source and the distance between implanted seeds, it is complicated to consider it in analytical methods, such as the TG-43 protocol. For this purpose, the Monte Carlo simulation is considered the best way to investigate this effect; however, this method requires a long calculation time and it is, therefore, impossible to include the interseed effect in real-time dosimetry. The goal of this section was to quantify the interseed effect and correct it in real-time dosimetry.

B.1 The output of this work is a new Monte Carlo-based dose calculation engine, which takes into account the interseed effects for real-time dosimetry. A patent, number EP10177977.5, has been submitted to the European patent office (chapter 4).

4. Additional studies

A collaboration with the RIMA Laboratory was made to investigate dosimetry around low energy sources, such as iodine-125 and iridium-192, at short distances. This dosimetry was performed at the RIMA laboratory using electron paramagnetic resonance imaging (EPRI) by Vanea and Kolbun and was compared by us, using 3D Monte Carlo simulation. The output of this collaboration is two published articles:

1. Evaluation of the dose distribution gradient in the close vicinity of Amersham iodine-125 seed using EPR imaging (chapter 8), published in *Magnetic Resonance in Medicine* in 2009.
2. Experimental determination of the radial dose distribution in high gradient regions from a low dose rate iridium-192 wire sources using EPR imaging (chapter 10), published in *Medical Physics* in 2010.

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Chapter 2

Publication 1

An experimental palladium-103 seed (OptiSeed^{exp}) in a biocompatible polymer without a gold marker: Characterization of dosimetric parameters including the interseed effect

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Permanent implantation of ¹²⁵I (iodine) or ¹⁰³Pd (palladium) sources is a popular treatment option in the management of early stage prostate cancer. New sources are being developed, some of which are being marketed for different clinical applications. A new technique of adjuvant stereotactic permanent seed breast implant, similar to that used in the treatment of prostate cancer, has been proposed by [N. Jansen *et al.*, *Int. J. Radiat. Oncol. Biol. Phys.* **67**, 1052–1058 (2007)] with encouraging results. The presence of artifacts from the metallic seeds, however, can disturb follow-up imaging. The development of plastic seeds has reduced these artifacts. This paper presents a feasibility study of the advantages of palladium-103 seeds, encapsulated with a biocompatible polymer, for future clinical applications, and on the effect of the gold marker on the dosimetric characteristics of such seeds. Experimental palladium seeds, OptiSeed^{exp}, were manufactured by International Brachytherapy (IBt), Seneffe, Belgium, from a biocompatible polymer, including the marker. Apart from the absence of a gold marker, the studied seed has an identical design to the OptiSeed¹⁰³ [*Phys. Med. Biol.* **50**, 1493–1504 (2005)]; [*Appl. Radiat. Isot.* **63**, 311–321 (2005)]. Polymer encapsulation was preferred by IBt in order to reduce the quantity of radioactive material needed for a given dose rate and to reduce the anisotropy of the radiation field around the seed. In addition, this design is intended to decrease the interseed effects that can occur as a result of the marker and the encapsulation. Dosimetric measurements were performed using LiF thermoluminescent dosimeters (1 mm³) in solid water phantoms (WT1). Measured data were compared to Monte Carlo simulated data in solid water using the MCNP code, version 4C. Updated cross sections [*Med. Phys.* **30**, 701–711 (2003)] were used. As the measured and calculated data were in agreement, Monte Carlo calculations were then performed in liquid water to obtain relevant dosimetric data as required by TG-43U1 recommendations. Comparison of the results with previous studies of OptiSeed¹⁰³ [*Phys. Med. Biol.* **50**, 1493–1504 (2005)]; [*Appl. Radiat. Isot.* **63**, 311–321 (2005)], and of InterSource¹⁰³ [*Appl. Radiat. Isot.* **57**, 805–811 (2002)] showed very good agreement for the dose rate constant and for the radial dose function. With respect to the anisotropy function, the relative dose (anisotropy value relative to 90°) from the polymer seed at a distance of 3 cm was close to unity (105%) at 0°, whereas the relative values for the OptiSeed¹⁰³ with a gold marker and the titanium-encapsulated InterSource¹⁰³ seed decreased to 70% and 40%, respectively. The interseed effect from one seed was negligible and in the order of calculation uncertainty, making calculation of the dose rate distribution of the studied seeds, according to TG43U1 recommendations, more accurate and closer to reality. This feasibility study shows that due to the low energy of palladium-103, the negligible interseed effect and the reduced artifacts in postimplant medical imaging, this experimental plastic seed would be a good source for breast brachytherapy. This feasibility study was carried out in collaboration with IBt and will be continued with a study of its visibility in different tissues. © 2008 American Association of Physicists in Medicine.
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Key words: brachytherapy, experimental Palladium source, dosimetry, calculation Monte Carlo

I. INTRODUCTION

Permanent brachytherapy implants have come into widespread use for the treatment of early stage carcinoma of the prostate gland.⁴ Historically, interstitial brachytherapy implants in various anatomical sites, especially the prostate gland, have used ¹²⁵I or ¹⁰³Pd isotopes contained in small encapsulated metallic “seeds” of various designs. The low-

energy photon emissions of these isotopes, combined with the small size of the seeds, enable to localize the required irradiation and minimize the dose to the surrounding normal tissue. In addition, the protracted, continuous, low dose-rate irradiation used in permanent seed implants has also been considered to have a radiobiological advantage.⁵

Recent increased demand for such implantable sources has led to the introduction of new source designs by various

manufacturers. In this work, a feasibility study was conducted on the dosimetric parameters of an experimental OptiSeed^{exp} (palladium-103 source) model from IBt—made with a biocompatible polymeric shell, the internal gold marker being replaced by a biocompatible polymer—based on the AAPM Task Group No. 43 Updated (TG43U1) recommendations.¹ The used polymer is known as PEEK (polyetheretherketon) and has a density of 1300 kg/m³. Its Hounsfield number (HU) lies around 200 HU, depending on the CT scan used. This makes it comparable to spongy bone structures. The goal of our study was to illustrate the impact and the advantages of using such polymer seeds in future clinical applications, such as for permanent breast brachytherapy. For these applications, the polymer seeds will produce much fewer artifacts on the classical imaging techniques used for postimplant patient follow up. The original OptiSeed¹⁰³ with gold marker was designed for prostate applications. Our findings on the dosimetric characteristics of the experimental OptiSeed^{exp} are also valid for prostate applications; however, our initial goal was to study the impact on breast applications.

Accurate measurement of the dose distribution around a ¹⁰³Pd source in a phantom is complicated by strict requirements for precise and small dosimeters and for measuring geometry, as significant dose gradients exist around the source. Previous investigators have used thermoluminescent dosimeters^{2,3} (TLDs) or semiconductor diode detectors⁶ in ¹⁰³Pd dosimetry, with corrections applied for energy dependent dosimeter responses. In the present study, TLD-100 LiF thermoluminescent dosimeters of 1 mm³ (Harshaw/Bicron 6801 Cochran Rd. Solon, OH 44139) were used in a solid water phantom (WT1, model 457, Radiation Measurement Inc., RMI, Middletown, WI) to measure the dose distribution of the OptiSeed^{exp} source.

The AAPM recommends that the dosimetric characteristics of the seed are specified in a liquid water phantom. However, the high dose gradients around the seeds make it very difficult to measure absorbed doses directly in water. Therefore, a solid water phantom was used to enable TLDs to be precisely positioned in a fixed geometry relative to a centrally located source.

The dosimetric parameters in liquid water were then calculated using the Monte Carlo code, MCNP version 4C, after validating the model in the solid water phantom by comparing Monte Carlo calculated results in solid water with the experimental measurements under the same conditions. As the gold marker is replaced by a polymer one in the OptiSeed^{exp}, special attention was paid to the variation in anisotropy.

This study also considered the interseed shadow effect. The importance of this effect had been demonstrated in the literature; for example, a shadow effect decreased the dose by 10% for a ¹²⁵I seed,⁷ by 13% for the titanium-encapsulated InterSource¹⁰³² and by 7% for the polymer-encapsulated OptiSeed¹⁰³ with a gold marker.³ The effect of the marker on the dosimetric parameters of the seed was studied by comparing two seeds, the present one

(OptiSeed^{exp}) and the OptiSeed¹⁰³ studied by Bernard and Vynckier.³

Final commercialization of the seed is, however, up to the companies' policy. It is presently not planned due to the fusion of the companies IBt and Bebig for seed commercialization. Their interest is presently more focused on the development of a polymer ¹²⁵I seed, for which the dosimetric characterization is in progress.

II. MATERIALS AND METHODS

II.A. Dose calculations using the TG-43U1 protocol

This protocol contains methodological guidelines to obtain dosimetry parameters for brachytherapy sources using calculative methods and experimental techniques. The dose formalisms recommended by the AAPM in the TG-43U1 report¹ are described in terms of a polar coordinate system, and the reference point (r_0, θ_0) is chosen on the transverse bisector of the source ($\theta=90^\circ$) at 1 cm from its center. The general, two-dimensional (2D), dose-rate equation is expressed as

$$\dot{D}(r, \theta) = S_k \times \Lambda \times \frac{G(r, \theta)}{G(r_0, \theta_0)} \times g(r) \times F(r, \theta), \quad (1)$$

where S_k is the air-kerma strength of the source (U), Λ is the dose rate constant (cGy h⁻¹ U⁻¹), $G(r, \theta)$ is the geometry factor, which takes into account the physical shape of the radioactive material inside the source (an effective active length of 3.7 mm was used for the sources in this study^{1,3}), $g(r)$ is the radial dose function and $F(r, \theta)$ is the anisotropy function.

For an implant containing a large number n of sources randomly oriented, the dose rate to tissue can be approximated using a point source formalism. In this approximation, the dose rate at any point can be expressed using Eq. (2),

$$\dot{D}(r, \theta) = S_k \times \Lambda \times \frac{G_X(r, \theta)}{G_X(r_0, \theta_0)} \times g_X(r) \times \phi_{an}(r), \quad (2)$$

where the subscript X indicates whether a point source “P” or line source “L” is used.

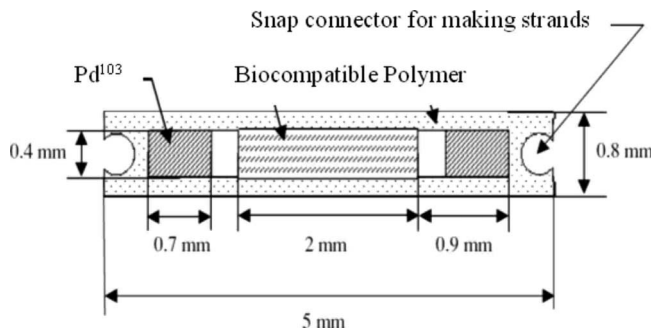
ϕ_{an} , the anisotropy factor, is given by Eq. (3),

$$\phi_{an}(r) = \frac{\int_0^\pi \dot{D}(r, \theta) \sin(\theta) d\theta}{2\dot{D}(r, \theta_0)}. \quad (3)$$

This is recommended when using 1D approximation.

II.B. Source of Pd¹⁰³ (OptiSeed^{exp})

Figure 1 shows a schematic diagram of the design of this experimental, polymer-encapsulated OptiSeed^{exp}. The OptiSeed^{exp} has an identical design to the OptiSeed¹⁰³^{3,23} but the central gold marker is replaced with biocompatible polymer material. According to IBt, during seed production, pressure is applied to join the two parts of the seed together, modifying slightly the theoretical effective active length from 3.8 to 3.7 mm.³

FIG. 1. Schematic of the new polymer OptiSeed^{exp}.

II.C. Measurements in solid water phantom

Thermoluminescent dosimetry (TLD LiF) of 1 mm³ (Harshaw/Bicron 6801 Cochran Rd., Solon, OH 44139) was performed in a phantom consisting of solid water (WT1, model 457, Radiation Measurement Inc., RMI, Middletown, WI). Solid water was used as a measurement medium since Monte Carlo results^{8,9} confirm that this solid water approximates to the radiological properties of liquid water better than other commercial plastics. Two phantoms with different geometries were employed, one for the measurements of radial dose function at distances of 1, 1.5, 2, 3, 4, and 5 cm from the center of the source; an angle of 7.5° was left between the source direction and the adjacent TLDs to avoid them being in each other's shadow.² The other phantom was used for the measurements of anisotropy function where the TLDs were placed each 10° at radii of 2, 3, 5, and 7 cm from the center of the source. At least 5 cm of solid water was placed around the source to ensure full scattering conditions. The measurements were repeated three times to minimize measurement uncertainties as much as possible.

The TLDs were calibrated according to a protocol described by Reniers *et al.*² Each TLD was calibrated individually, seven times before and after the seed dosimetry to correct for possible variation in the TLD calibration factor and for possible instability of the reader. The TLDs were selected to obtain a standard deviation of the measurements of less than 3.5%. The dose rate in solid water at the point (r , θ) was calculated from the TLD reading after application of different correction factors.^{2,10} All the given doses were in the linear response region of the TLDs, i.e., from 0.25 Gy up to 1.5 Gy,¹⁰ so no correction was applied for supralinearity.¹⁰

II.D. Monte Carlo calculations

The AAPM (Ref. 11) recommends that the dosimetric characteristics for a new seed be obtained in liquid water. However, the high dose gradients in the vicinity of the seed require precise TLD positioning and make it very difficult to measure doses directly in liquid water. A solid water phantom enables precise positioning of the detectors used for the measurements, on the other hand, Monte Carlo calculations are necessary to convert the results from solid water to liquid water. Code MCNP version 4C was used to calculate the dose distribution around the source. This code is a generalized,

continuous energy, three dimensional coupled neutron/photon/electron Monte Carlo transport code, which takes into account the transport of photons and electrons over an energy range of 1 keV–1 GeV. The detailed photon physics option of MCNP was used in this work and includes the Compton scattering with bounding effect, Rayleigh scattering, and the photoelectric effect with emission of fluorescence photons. The cross-section data and the form factors for coherent and incoherent photon scattering, used in this work, are taken from Storm and Israel¹² (for $Z=84, 85, 87, 88, 89, 91$, and for energy from 1 keV to 15 MeV) and from ENDF (Ref. 13) (for all other elements from $Z=1$ through $Z=94$ and for energy from 1 keV to 100 MeV); the fluorescence data are taken from Everett and Cashwell.¹⁴ A new, updated library of photoelectric cross sections by Bohm *et al.*¹⁵ was used because the difference due to photoelectric effect data can be up to 10% less when comparing the MCNP default database with the NIST database.¹⁶ DeMarco *et al.*¹⁷ showed that MCNP cross-section data underpredict the value of the total cross section for low Z materials and low energies by as much as 7% at 20 keV. This difference is caused by discrepancies as high in the photoelectric data as 10% for 20 and 30 keV photons. Spheres with a diameter of 1 mm defined the acquisition cells (to simulate the TLDs). The F6 tally was used to calculate the average energy deposition in these cells. Due to the short range of the secondary electrons produced by interactions from photons emitted by the ¹⁰³Pd, electron transport is not required and it is assumed that they deposit their energy locally,¹⁸ so only the photons were transported with a low-energy cutoff of 1 keV.

The source was modeled using data provided by IBt (see Fig. 1). The solid water phantom, made of WT1 using the composition given in ICRU44,¹⁹ was also modeled. After validating the model by comparing the calculations with the measurements performed in solid water, the dosimetric data of our source were calculated in liquid water.

To obtain the dose rate constant, the kerma per particle was first calculated at 5 cm in air.²⁰ The inverse square law was used to calculate the kerma rate in air at 1 m from the center of the source; this result being equivalent to the source strength. For this calculation, the cutoff for the photons was set at $\delta=4.6$ keV to suppress the low-energy or contaminant photons. The dose at 1 cm from the center of the source on the transverse axis was then calculated, following which the dose rate constant for each medium could be obtained. 1×10^9 histories were chosen in this simulation to reduce the maximum statistical uncertainty for the Monte Carlo calculations for a cell acquisition situated at 7 cm from the source to about 8%.

II.E. Interseed effects

To calculate the interseed effects, two methods were modeled by Monte Carlo simulation in order to calculate the attenuation of one seed by another.

For the first method, three Monte Carlo simulation files were programmed as shown in Figs. 2(a)–2(c).

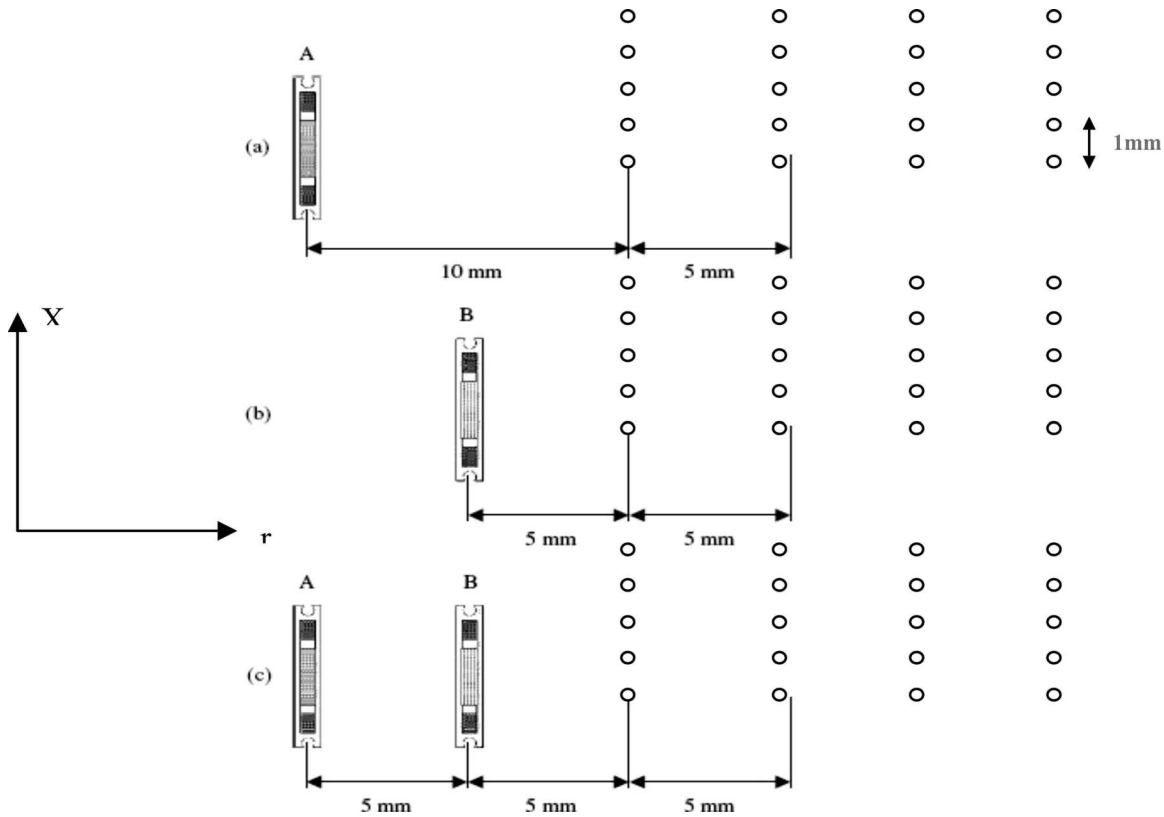


FIG. 2. Different modeling situations for seed combinations in order to calculate the attenuation of one seed to another.

- (a) One active seed, A, is placed at 10 mm from a series of calculation points, separated by a distance of 5 mm.
- (b) One active seed, B, is placed, this time at 5 mm from the series of calculation points.
- (c) The two active seeds, A and B, are modeled and placed at the same distances as the sources in (a) and (b).

The sum of the calculations at the corresponding points of cases (a) and (b) yields the dose from seeds A and B together ($D_{A\text{-active}} + D_{B\text{-active}}$), whereas in case (c), the calculation gives the corresponding doses including the attenuation effect of seed B on the dose contribution from seed A ($D_{A\text{-active, B-active}}$). The difference between the two is the interseed effect, which we call in this study the interseed effect on the total measured dose rate (ISE_{TDR}), and which is formulated by Eq. (4).

For the second method, two Monte Carlo simulation files were programmed as shown in Figs. 2(a) and 2(c) but the seed B, in case c, was inactive. The difference between cases (a) and (c) we call the interseed effect on the measured dose rate of the first seed, seed A, (ISE_{DRFS}) [Eq. (6)]. We can also calculate this interseed effect from the first method using Eq. (5).

The ISE_{DRFS} factor varies with the distance between the two seeds and the measurement point position (r, θ) and it can be calculated for one seed in the same way as, for example, the anisotropy function. These data can be useful for correcting the dose rate around one seed for the interseed

effect, as the TG43U1 does not foresee this effect. More detailed calculations will be done in the future to investigate this parameter.

The interseed effect calculations were also performed for the experimental Optiseed and for the OptiSeed¹⁰³ with the gold marker^{3,23} using the new photoelectric cross-section library. The interseed effect factors, ISE_{TDR} (Table VI) and ISE_{DRFS} (Fig. 6 and Table V), were calculated for two seeds separated by 5 and 10 mm at all measurement points shown in Fig. 2, using Eqs. (4)–(6),

$$ISE_{TDR}(\%) = \frac{D_{A\text{-active, B-active}} - (D_{A\text{-active}} + D_{B\text{-active}})}{D_{A\text{-active, B-active}}} \times 100, \quad (4)$$

$$ISE_{DRFS}(\%) = \frac{(D_{A\text{-active, B-active}} - D_{B\text{-active}}) - D_{A\text{-active}}}{D_{A\text{-active, B-active}} - D_{B\text{-active}}} \times 100, \quad (5)$$

and for the second method,

$$ISE_{DRFS}(\%) = \frac{D_{A\text{-active, B-nonactive}} - D_{A\text{-active}}}{D_{A\text{-active, B-nonactive}}} \times 100. \quad (6)$$

Equations (5) and (6) yield the same ISE_{DRFS} results, however, the second method is an easier and faster Monte Carlo method than the first.

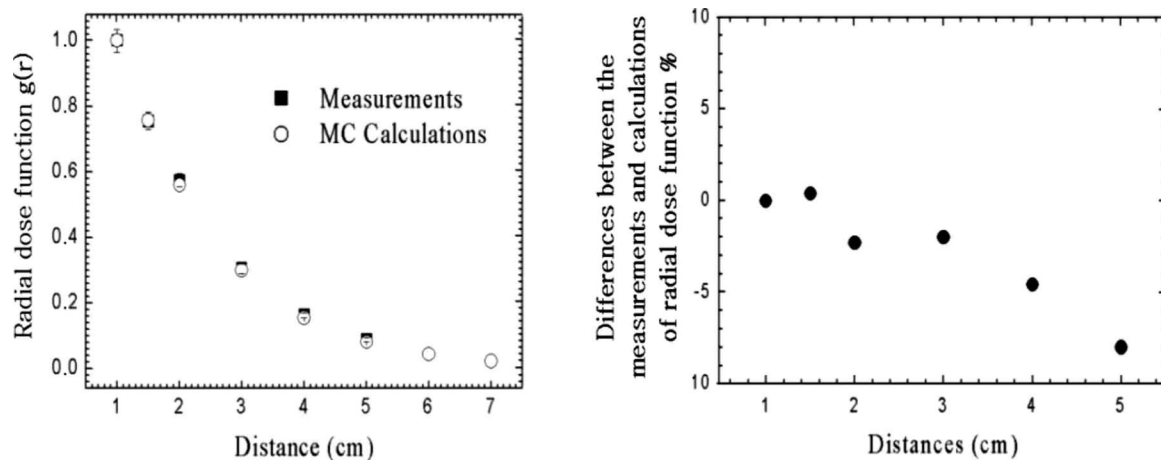


FIG. 3. Comparison between the measured and Monte Carlo calculated radial dose function performed in WT1.

III. RESULTS

The same methodology used for a commercialized seed was followed for this experimental seed. The dosimetric parameters recommended in TG43U1 were recalculated in liquid water for the OptiSeed^{exp} source using the MCNP code version 4C. At first, the experiment was modeled in the solid water phantom and validated by comparing the results with experimental measurements, then the dosimetric parameters in liquid water were calculated.

III.A. Radial dose function

Figure 3 shows the differences between the measurements and the Monte Carlo calculations of the radial dose function performed in WT1. The differences were about 1% at 1.5 cm

and increased to 8% at 5 cm due to the loss of photons at longer distances. These differences are small and within the order of measurement uncertainty (i.e., 3.5% up to 9% at long distances). Therefore, MCNP-4C was used to calculate the radial dose function in water. Table I shows this result and compares it with other results for OptiSeed¹⁰³ (Bernard and Vynckier³ and Wang and Hertel²³) and InterSource¹⁰³ (Meigooni *et al.*²⁰ and Reniers *et al.* 2002²) also calculated in water. All these studies, except that by Wang and Hertel,²³ used the old library of photoelectric cross sections (Hubbell and Seltzer 1995),²¹ explaining why our results are similar to those of Wang and Hertel²³ while different to the results of Bernard and Vynckier.³ The difference between the old²¹ and updated¹⁵ photoelectric cross-section libraries was also stud-

TABLE I. Radial dose function $g(r)$ calculated in water.

r (cm)	This work	OptiSeed ¹⁰³ ^a	OptiSeed TM ^b	InterSource ¹⁰³ ^c	InterSource ¹⁰³ ^d
0.1	0.710	0.671	0.649		
0.15	0.942	0.961	0.949		
0.2	1.081	1.117	1.180		
0.3	1.215	1.204	1.190	1.247	1.216
0.4	1.242	1.246	1.232	1.241	1.236
0.5	1.235	1.239	1.219	1.214	1.212
0.6	1.204	1.194	1.186	1.195	1.179
0.7	1.161	1.153	1.144	1.160	1.136
0.8	1.114	1.117	1.097	1.104	1.089
0.9	1.062	1.055	1.049	1.051	1.044
1.0	1.000	1.000	1.000	1.000	1.000
1.5	0.768	0.795	0.769	0.777	0.787
2.0	0.579	0.637	0.579	0.589	0.610
3.0	0.318	0.360	0.319	0.327	0.352
4.0	0.172	0.193	0.172	0.180	0.202
5.0	0.092	0.120	0.092	0.098	0.113
6.0	0.049		0.049		
7.0	0.026		0.027		

^aReference 3.

^bReference 23.

^cReference 20.

^dReference 2.

TABLE II. Double and triple exponential fit for radial dose function $g(r)$ calculated in water.

Double exponential fit		
$g(r)=y_0+A_1 \cdot \exp(r/t_1)+A_2 \cdot \exp(r/t_2)$		
$R^2=0.999\ 62$		
Parameter	Value	Error
y_0	-0.025 08	0.009 81
A_1	1.748 77	0.015 84
t_1	1.873 84	0.048 12
A_2	-1.744 01	0.036 99
t_2	0.154 17	0.005 72

Triple exponential fit		
$g(r)=y_0+A_1 \cdot \exp(r/t_1)+A_2 \cdot \exp(r/t_2)+A_3 \cdot \exp(r/t_3)$		
$R^2=0.999\ 96$		
Parameter	Value	Error
y_0	-0.008 25	0.004 38
A_1	-0.786 81	0.133 57
t_1	0.296 03	0.046 59
A_2	1.866 4	0.034 5
t_2	1.720 94	0.034 36
A_3	-1.353 36	0.121 96
t_3	0.096 73	0.010 29

ied: A difference of 20% was noted in the radial dose function calculated at 5 cm, which is comparable to the difference reported in Table I.

The difference between the Intersource¹⁰³ and the OptiSeed^{exp} results is due to the differences in the seeds themselves (their construction) and the different measurement methods applied, for example, using larger TLDs at the extreme distances in the phantom.²⁰ A double and triple exponential fits give very good fits to the radial dose function data with regression coefficients (0.999) very close to 1 and yield an acceptable approximation for distances of 1 cm up to 5 cm from the source (Table II).

III.B. Anisotropy function

The anisotropy variation in this experimental seed is different from the variation usually observed. There is no more anisotropy, the anisotropy function of the experimental seed is slightly larger than unity since the seed was nearly totally made of polymer. The results of the anisotropy function measured in the solid water phantom were in agreement with the Monte Carlo calculations, with a mean difference of less than 3% (see the Fig. 4). Table III and Fig. 5 illustrate that the new polymer-encapsulated seed without a marker has the advantage of greater symmetry in its radiation field; for example, at 0° it has a value of about unity, whereas for the titanium-encapsulated InterSource¹⁰³ (Ref. 2) and OptiSeed¹⁰³ (Ref. 3), these values are in the orders of 40% and 70%, respectively. The value (105%) is attributed to the nonabsorption of the very low-energy palladium-103 x-radiation by either the marker, such as the gold marker contained in OptiSeed¹⁰³,³ or by the polymer encapsulation which absorbs the low-energy photons much less than the titanium encapsulation in InterSource¹⁰³.² The same seed geometry was used to calculate the anisotropy function in liquid water. These results are presented in Table IV. The effect on anisotropy function of replacing the old photoelectric cross-section library²¹ with the updated¹⁵ one was also studied, and had minimal effect.

III.C. Dose rate constant Λ

The dose rate constant was measured and calculated in solid and liquid water. In solid water, the dose rate was measured at eight points, situated 1 cm from the source in the perpendicular plane of the seed center. The source air-kerma strength was provided by the company IBt using a Capintec CRC-15-R well chamber, used for the OptiSeed¹⁰³ calibration and traceable to NIST. This seed was, however, not directly calibrated at NIST according to NIST 1999 standards. A supplementary uncertainty of 1%–2% in dose rate constant determination was estimated from the chamber accuracy. If the seed is to be used for clinical applications, an additional

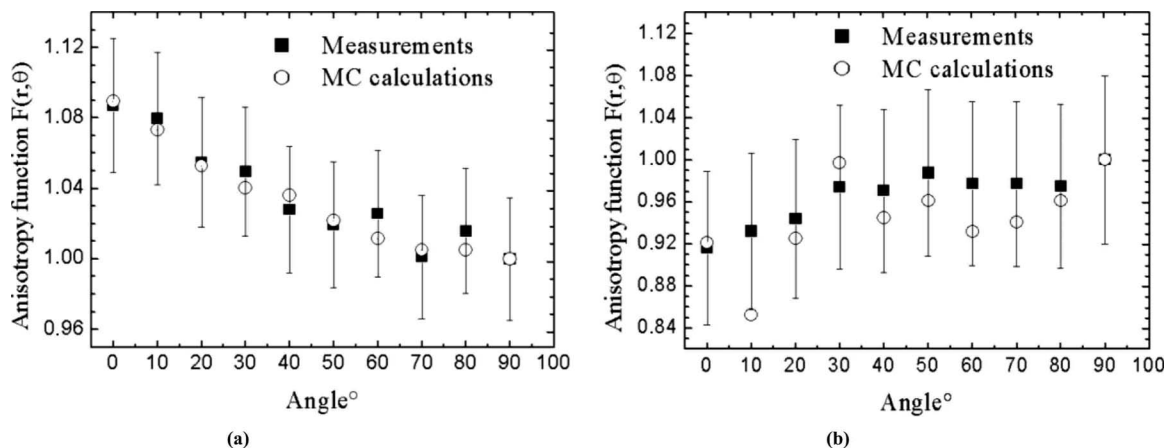


FIG. 4. Comparison of the measured and calculated anisotropy functions of the OptiSeed^{exp} source as function of the angle θ for the distances of (a) 2 cm and (b) 7 cm with showing the errors of measurements.

TABLE III. Comparison of anisotropy function measured in solid water phantom for different sources with our source.

$\theta^\circ r$	This work				OptiSeed ¹⁰³ ^a				InterSource ¹⁰³ ^b		
	2 cm	3 cm	5 cm	7 cm	2 cm	3 cm	5 cm	7 cm	2 cm	3 cm	5 cm
0	1.087	0.978	0.949	0.916	0.820	0.750	0.760	0.770	0.456	0.498	0.514
10	1.080	0.988	0.963	0.932	0.870	0.840	0.810	0.860	0.464	0.494	0.551
20	1.055	0.975	0.964	0.944	0.910	0.870	0.860	0.950	0.641	0.651	0.671
30	1.050	0.974	0.977	0.974	0.990	0.960	0.920	0.970	0.737	0.741	0.757
40	1.028	0.971	0.982	0.971	1.020	0.980	1.000	0.950	0.810	0.833	0.829
50	1.019	0.969	0.994	0.988	1.030	1.000	0.980	1.010	0.879	0.909	0.885
60	1.026	0.983	0.992	0.977	1.030	1.010	0.970	1.010	0.932	0.947	0.923
70	1.001	0.981	0.988	0.977	0.990	0.980	1.000	1.010	0.964	0.997	0.949
80	1.016	0.990	1.003	0.975	1.010	1.020	1.020	0.980	1.004	0.993	0.985
90	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000

^aIt was studied by Bernard and Vynckier, Ref. 3.^bIt was studied by Reniers *et al.*, Ref. 2.

calibration at NIST will be mandatory as per TG43U1 recommendations. The value obtained for the dose rate constant measured in solid water was $0.710 \pm 7\%$ cGy h⁻¹ U⁻¹, which is comparable with previous studies which gave results of $0.720 \pm 6\%$ cGy h⁻¹ U⁻¹ (Bernard and Vynckier)³ and $0.727 \pm 6.9\%$ (Wang and Hertel)²³ for the OptiSeed¹⁰³ and $0.657 \pm 6\%$ cGy h⁻¹ U⁻¹ for the InterSource¹⁰³ seed (Reniers *et al.*).² Comparison of the measured and Monte Carlo calculated dose rates in solid water was within the experimental uncertainty, yielding a calculated dose rate of $0.721 \pm 1\%$ cGy h⁻¹ U⁻¹. Therefore, a calculated value for the dose rate in liquid water of $0.672 \pm 1\%$ cGy h⁻¹ U⁻¹ was obtained. This result is comparable with previous studies which gave results of $0.712 \pm 6\%$ cGy h⁻¹ U⁻¹ (Bernard and Vynckier)³ and $0.665 \pm 2.1\%$ (Wang and Hertel)²³ for the OptiSeed¹⁰³ and $0.692 \pm 1\%$ cGy h⁻¹ U⁻¹ for the InterSource¹⁰³ seed (Reniers *et al.*).²

III.D. Seed shadowing (Interseed attenuation)

Early studies of interseed attenuation effects were conducted by Chibani and Williamson.²² For I¹²⁵ (Symmetra) and Pd¹⁰³ (Theragenics model 200) seeds, these investigators

showed that dose errors due to the absence of interseed attenuation ranged between 2% and 10% with an average value of 4%. This effect was also reported by Mobit and Badragan.⁷ These authors showed that a reduction in dose rate of 10% for titanium clad iodine seeds could be attributed to seed shadowing. For palladium seeds this effect is expected to be larger than 10% because of the higher attenuation of the low-energy palladium-103 photons by titanium. This effect can reach a significant level when reporting correlations between a clinical effect and the deposited dose. Hence, for the OptiSeed^{exp} used in this work it was important to calculate this effect.

We noticed, in general, that the ISE_{DRFS} (interseed effect on the dose rate of the first seed) and ISE_{TDR} (interseed effect on the total dose rate) were negligible for the studied seed (Fig. 6, Tables V and VI) because of the polymer encapsulation and the polymer marker. This advantage will make this seed useful for current treatment planning systems (TPSs) which do not account for the interseed effects. The ISE_{DRFS} and ISE_{TDR} for the OptiSeed¹⁰³ are larger (Tables V and VI) including a comparison with Bernard and Vynckier³. This difference can be attributed to the presence of the central gold marker which attenuates more photons than the biocompatible polymer marker. We can also see that the two factors (ISE_{DRFS} and ISE_{TDR}) vary over the calculation grid: along the *x*-axis as the seed B composition varies along this axis and along the *r*-axis, since close to the seed the primary photons are attenuated rapidly by the gold marker while at greater distances more scattered dose remains.

Overall, the new factor, ISE_{DRFS}, seems to be easier to insert in the current TPS calculations than the ISE_{TDR} because it can be calculated for a single seed as is the case for radial dose and anisotropy functions. It will, therefore, be possible to estimate the interseed effect in live time implantation and avoid the systematic inaccuracies associated with this effect. In this paper we made a schematic representation of the interseed effect; more detailed calculations and realistic investigation will be part of a study currently in progress.

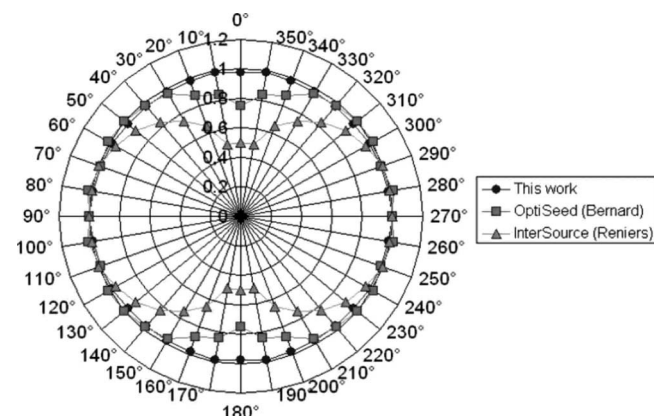


FIG. 5. Comparison of anisotropy function measured at 3 cm in solid water phantom for different sources.

TABLE IV. Anisotropy function for the OptiSeed^{exp} source calculated in water. The 1D anisotropy function $\phi_{an}(r)$ is tabulated as the last line.

	$\frac{F(r, \theta)}{r(\text{cm})}$													
θ°	0.5	1	1.5	2	2.5	3	3.5	4	4.5	5	5.5	6	6.5	7.0
0	1.368	1.135	1.088	1.072	1.064	1.059	1.045	1.049	1.075	1.061	1.088	1.023	1.029	0.950
5	1.368	1.137	1.088	1.070	1.061	1.054	1.045	1.039	1.044	1.082	1.079	0.990	1.006	0.978
10	1.356	1.119	1.078	1.060	1.047	1.043	1.036	1.018	1.041	1.035	1.088	1.052	1.056	1.045
15	1.328	1.113	1.073	1.049	1.039	1.027	1.026	0.999	1.022	1.035	1.034	0.992	1.006	0.992
20	1.303	1.100	1.069	1.047	1.037	1.027	1.036	1.018	1.038	1.040	1.052	1.021	1.054	1.024
25	1.273	1.098	1.059	1.043	1.040	1.044	1.026	1.027	1.020	1.045	1.061	1.025	1.047	0.968
30	1.238	1.077	1.056	1.035	1.035	1.028	1.007	0.998	1.026	1.025	1.061	1.002	0.992	1.017
35	1.209	1.061	1.046	1.034	1.033	1.023	1.007	1.015	1.026	1.014	1.052	1.033	1.072	1.105
40	1.175	1.060	1.037	1.029	1.029	1.018	1.008	1.000	1.020	1.025	1.044	1.001	1.052	1.024
45	1.151	1.044	1.034	1.023	1.015	1.024	1.008	0.986	1.039	1.030	1.044	0.983	0.977	1.024
50	1.117	1.037	1.025	1.019	1.019	1.014	1.008	1.015	1.005	1.015	1.053	0.976	1.045	1.021
55	1.093	1.036	1.021	1.013	1.017	1.025	1.018	1.003	1.036	1.010	1.044	0.979	1.048	0.996
60	1.069	1.019	1.017	1.010	1.009	1.009	1.009	0.997	1.024	1.036	1.080	1.042	1.007	1.067
65	1.042	1.015	1.013	1.003	1.007	1.010	0.999	0.991	1.015	1.010	1.026	0.981	1.034	1.021
70	1.025	1.002	1.009	1.004	1.005	1.005	1.000	0.987	1.015	1.026	1.036	0.989	1.034	0.958
75	1.014	0.997	1.004	1.003	1.011	1.000	0.990	0.989	1.012	1.026	1.018	0.942	1.007	0.993
80	1.007	1.008	1.005	1.001	1.003	0.994	0.989	0.988	0.988	0.995	1.045	1.003	1.027	0.975
85	0.999	0.996	1.000	0.999	0.994	0.995	0.990	0.991	1.012	1.016	1.027	1.000	0.995	0.993
90	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
ϕ_{an}	1.178	1.049	1.030	1.019	1.017	1.014	1.006	0.999	1.018	1.020	1.042	0.996	1.024	1.009

IV. DISCUSSION AND CONCLUSION

This paper presents a dosimetric characterization of an experimental, biocompatible ^{103}Pd seed; the final goal of this study was to determine the dosimetric parameters, using

Monte Carlo calculations and LiF TLD detectors, in order to quantify the influence of the gold/biocompatible marker on these dosimetric parameters. The recommendations of TG43U1 were followed.

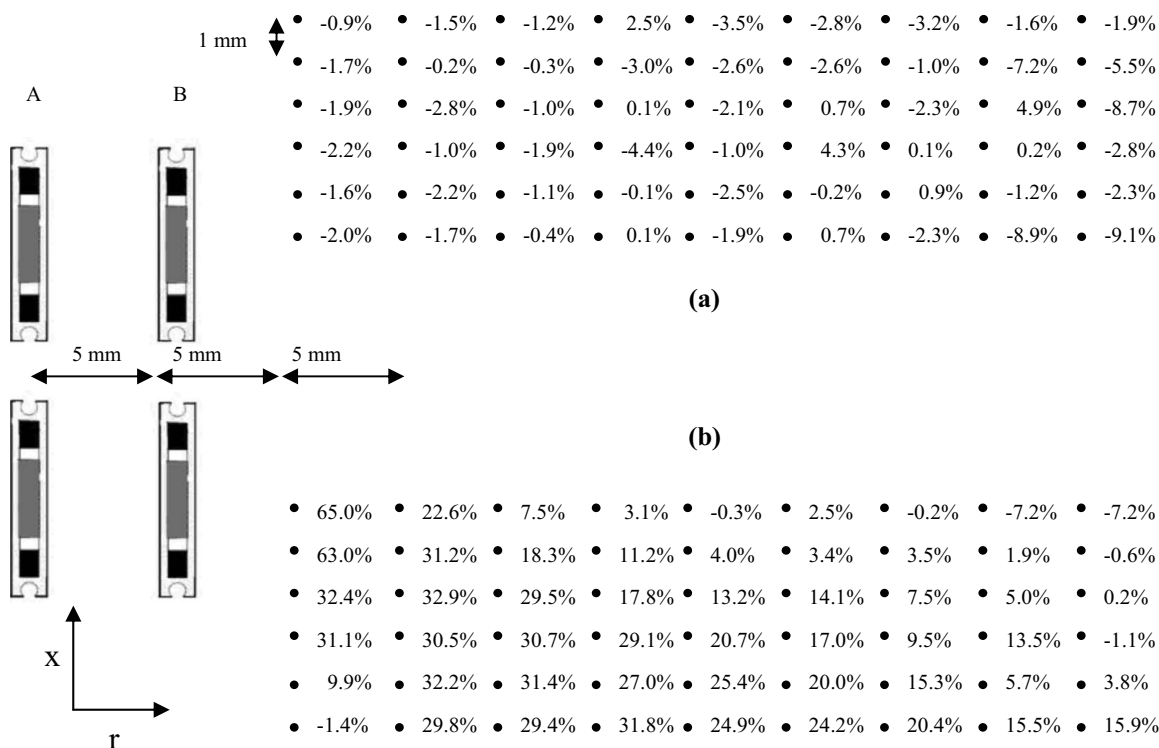


FIG. 6. Effect of the interseed attenuation (seed shadowing) on the dose rate of the first seed A, ISE_{DRFS} , for two seeds separated by 5 mm. (a) OptiSeed^{exp} without marker; (b) OptiSeed¹⁰³ with gold marker (this work).

TABLE V. Effect of the interseed attenuation (seed shadowing) on the dose rate of the first seed A, ISE_{DRFS} , for two seeds separated by 10 mm.

OptiSeed ^{exp} without marker (this work)								
The distance between the first seed (A) and the measured point $-r$								
X (mm)	1.5 (%)	2 (%)	2.5 (%)	3 (%)	3.5 (%)	4 (%)	4.5 (%)	5 (%)
0	-2.3	0.5	-0.4	-0.8	-1.2	0.3	-11.3	-12.6
1	-1.9	-2.2	-0.6	0.4	-1.8	0.0	5.5	-3.1
2	-3.5	-1.7	-0.8	-5.5	-2.7	4.7	2.2	6.9
3	-4.3	-2.0	-0.8	1.0	-1.1	5.1	-4.4	3.7
4	-2.3	1.1	2.2	-4.0	-3.5	2.0	-4.4	-1.4
5	-0.7	-0.7	-3.7	4.1	-1.2	-6.8	3.1	-7.1

OptiSeed ¹⁰³ with gold marker (this work)								
0	59.4	54.2	32.5	17.6	8.6	6.5	-8.0	-10.8
1	34.5	29.3	29.0	26.9	17.5	13.3	15.6	5.4
2	24.6	29.1	27.9	22.3	24.0	29.5	22.1	21.6
3	-2.4	27.7	27.4	27.4	25.0	30.0	19.5	26.5
4	-2.4	9.0	30.3	22.6	22.0	25.8	18.5	19.4
5	-3.2	0.0	13.5	30.5	23.7	19.1	24.3	17.5

The radial dose function $g(r)$ was measured and calculated at 1, 1.5, 2, 3, 4, and 5 cm in solid water. The anisotropy function $F(r, \theta)$ was measured and calculated every 10° at 2, 3, 5, and 7 cm. The new library of photoelectric cross sections¹⁵ was used for the Monte Carlo calculations. The agreement between the calculations and the measurements was acceptable (within the order of measurement and calculation errors). The same calculations were then performed for liquid water. The radial dose function was calculated between 0.1 and 7 cm (Table I) and the anisotropy

function was calculated every 5° between 0.5 and 7 cm (Table IV). The global error (1σ) for the relative TLD measurements was 3.5%. The variation in the anisotropy function was less than 8% compared to about 30% and 60% for the OptiSeed¹⁰³ and titanium-encapsulated InterSource¹⁰³, respectively.

The dose rate constant in water for the OptiSeed^{exp} was calculated using the MCNP-4C Monte Carlo code and was found to be $0.672 \pm 1\%$ cGy h⁻¹ U⁻¹. This is comparable with previous studies which report $0.712 \pm 6\%$ cGy h⁻¹ U⁻¹

TABLE VI. Effect of the interseed attenuation (seed shadowing) on the total dose rate, ISE_{TDR} , for two seeds separated by 10 mm.

OptiSeed ^{exp} without marker (this work)								
The distance between the first seed (A) and the measured point $-r$								
X (mm)	1.5 (%)	2 (%)	2.5 (%)	3 (%)	3.5 (%)	4 (%)	4.5 (%)	5 (%)
0	-0.2	0.1	-0.1	-0.1	-0.3	0.1	-2.6	-3.0
1	-0.1	-0.3	-0.1	0.1	-0.4	-0.0	1.4	-0.8
2	-0.3	-0.2	-0.1	-1.1	-0.6	1.1	0.6	1.8
3	-0.3	-0.3	-0.1	0.2	-0.2	1.2	-1.1	0.9
4	-0.2	0.2	0.4	-0.8	-0.8	0.5	-1.1	-0.4
5	-0.1	-0.1	-0.7	0.8	-0.3	-1.5	0.8	-1.8

OptiSeed ¹⁰³ with gold marker (this work)									OptiSeed ¹⁰³ Bernard
X (mm)	1.5 (%)	2 (%)	2.5 (%)	3 (%)	3.5 (%)	4 (%)	4.5 (%)	5 (%)	1.5 (%)
0	4.2	7.5	5.8	3.6	1.9	1.5	-1.9%	-2.6	7
1	2.4	3.9	5.1	5.6	4.0	3.2	4.0	1.4	...
2	1.8	3.9	4.9	4.7	5.5	7.4	5.8	5.8	...
3	-0.2	3.9	5.0	5.7	5.8	7.6	5.1	7.3	...
4	-0.2	1.3	5.6	4.7	5.1	6.5	4.7	5.3	...
5	-0.3%	0.0	2.5	6.5	5.5	4.7	6.5	4.6	...

(Bernard and Vynckier),³ $0.665 \pm 2.1\%$ (Wang and Hertel)²³ for the OptiSeed¹⁰³, and $0.692 \pm 1\%$ cGy h⁻¹ U⁻¹ for the InterSource¹⁰³ seed (Reniers *et al.*).²

The interseed effect was studied by Monte Carlo calculations for both seeds. There was a negligible ISE_{TDR} (interseed effect on the total dose rate) distribution for the studied seed, OptiSeed^{exp} without marker, but an effect of about 4.2% for the OptiSeed¹⁰³ with gold marker. This effect has also been calculated by Bernard and Vynckier³ using the old cross-section library and reported to be on average of 7% (confirmed by our calculations when using these libraries). The ISE_{TDR} was compared with those of other types of seeds, for example, 14% for a titanium-encapsulated ¹⁰³Pd seed and about 30% for a titanium-encapsulated ¹²⁵I seed.⁷

A new factor, ISE_{DRFS} (interseed effect on the dose rate of the first seed), was used. This factor reflects the shadowing effect of the seed on the dose rate distribution of one seed only and varies with the position of the obstacle seed, its composition, and with the measured point positions. This factor is easier to insert in the current TPS calculations than the ISE_{TDR} because it can be calculated for a single seed as can the radial and anisotropy functions. In this paper we made a schematic representation of this effect; more detailed calculations and investigation in clinical situations will be part of a study currently in progress. The disadvantage of using this seed is the visibility. The polymer of the seed is PEEK (polyetheretherketon) and has a density of 1300 kg/m³ and is not easily detectable in tissue using a CT scan (Hounsfield number around 200 HU). This should, however, be quantified using different imaging modalities (CT, MRI, ultrasound, and mammography) and is the subject of a next paper.

Our feasibility study with the experimental palladium seeds has shown that, in addition to the known advantage of the low energy of palladium for radiation protection issues, the negligible shadowing effect of this seed makes the dose rate calculations with actual TPS systems more accurate and closer to reality. In addition, since this seed has no marker, it will eliminate the artifacts that can occur in traditional medical imaging because of the metallic shell and marker of conventional seeds. Finally, this seed does not have a large anisotropy effect. These effects, when taken together, make these seeds potentially useful sources for permanent breast brachytherapy.

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Comment on “An experimental palladium-103 seed (OptiSeed^{exp} in a biocompatible polymer without a gold marker: Characterization of dosimetric parameters including the interseed effect” [Med. Phys. 35, 5841–5850 (2008)]

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We read with great interest the article from Abboud *et al.* on a novel experimental palladium-103 seed (OptiSeed^{exp}) in a biocompatible polymer without a gold marker.¹ Yet, we would like to comment about incorrect statements in the Abstract and in the Introduction. Abboud *et al.* stated that a justification for the OptiSeed^{exp} development was permanent breast seed implants (PBSIs), a technique “proposed” by Jansen *et al.* in 2007,² because “the polymer seeds will produce much fewer artifacts on the classical imaging techniques used for postimplant patient follow up.”

We believe that these statements and the reference to Jansen *et al.* are misleading. First, the PBSI technique was pioneered in Canada, and this has been emphasized by a press release from ASTRO after the publication of the first patients treated.^{3,4} Second, while palladium-103 was indeed used in Canada for PBSI (which is the isotope used by Abboud *et al.* for the OptiSeed^{exp}), Jansen *et al.* used iodine-125 seeds as a boost technique after whole breast radiotherapy. It might be misleading not accurately reporting the two isotopes. The issue is that for exclusive PBSI, Keller *et al.* published two papers showing that palladium-103 would be safe for PBSI, while the exposure to partners and to the public would be unacceptable using iodine-125.^{5,6} References to the Canadian experience could have avoided a potentially dangerous confusion. Finally, it is the Canadian experience that shows that the technique is safe, well tolerated, and efficient.^{7,8} Also, contrary to what was suggested by Abboud *et al.*, there was no issue on reading follow-up mammograms. There may be some imaging advantages using the new Optiseed^{exp} in prostate or breast implants, but it is speculative to assume that

follow-up mammograms would be easier to read using the Optiseed^{exp}.

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¹F. Abboud, P. Scalliet, and S. Vynckier, “An experimental palladium-103 seed (OptiSeed^{exp}) in a biocompatible polymer without a gold marker: Characterization of dosimetric parameters including the interseed effect,” *Med. Phys.* **35**, 5841–5850 (2008).

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Response to “Comment on ‘An experimental palladium-103 seed (OptiSeed^{exp}) in a biocompatible polymer without a gold marker: Characterization of dosimetric parameters including the interseed effect’ ” [Med. Phys. 36, 2343 (2009)]

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Although we agree completely that we have to set the publications stated by Pignol and Keller¹ as references in our article, we do not think that referring to the article of Jansen *et al.*² might be misleading because of the following:

- (1) We did not make a clinical study of breast brachytherapy in order to compare with their work; simply we have studied the dosimetric characteristics around an experimental polymer source to show the interest of such sources during treatment planning due to the low interseed effect.
- (2) We have mentioned some advantages of using palladium. However, we did not make a comparison between palladium and iodine. It is right, however, that the experimental seed studied in our article is a palladium seed; therefore we agree that it would have been opportune to make a reference to their article.³ Mentioning the article of Jansen *et al.* will, however, not confuse the reader.
- (3) Finally, the article of Jansen *et al.* gives supplementary information; however, the first Canadian experience in breast brachytherapy which is, unfortunately, missing in our work would give more information to the reader. For

this reason we agree completely that a reference to the article of Keller *et al.*³ would be an added value to our publication.

As they stated, until now, there is no issue on reading follow-up mammograms, so indeed we are not sure that the follow-up mammogram is easier to read when the OptiSeed^{exp} is applied; however, as the seed is made in plastic and has no marker, it has been assumed so.

¹J.-P. Pignola and B. M. Keller, “Comment on ‘An experimental palladium-103 seed (OptiSeed^{exp}) in a biocompatible polymer without a gold marker: Characterization of dosimetric parameters including the interseed effect’ [Med. Phys. 35, 5841–5850 (2008)],” Med. Phys. 36, 2343 (2009).

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Chapter 3

Publication 2

Experimental and theoretical dosimetry of a new polymer encapsulated iodine-125 source—SmartSeed: Dosimetric impact of fluorescence x rays

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Purpose: The detailed study of a new permanent iodine-125 brachytherapy source, SmartSeed, is presented in this article. It is the first iodine seed made with biocompatible polymer and is manufactured by the IBt-Bebig group.

Methods: Three dosimetric studies have been performed: The first one used thermoluminescent detectors in a solid water phantom with NIST (National Institute of Standards and Technology, USA) calibrated seeds, and two separate studies were of Monte Carlo photon transport calculations (MCNP5 code). The TG-43U1 protocol was applied to derive dosimetric parameters for clinical applications.

Results: The radial dose function $g(r)$ was determined at different distances ranging from 0.5 to 10 cm; and the anisotropy function $F(r, \theta)$ at angles ranging from 0° to 350° in 10° increments. Monte Carlo calculations were performed in liquid water to obtain values for Λ , $g(r)$, $F(r, \theta)$, and $\phi_{an}(r)$ as recommended by the TG-43U1 protocol for use in treatment planning system software. SmartSeed's biocompatible polymer capsule permits fluorescence x rays (3, 5, and 12 keV), generated by lead glass marker, to be present in the emission spectrum, influencing the dose rate constant. The impact on near field dosimetry in water from these x rays was also investigated and reported. The capsule also attenuates iodine-125 energies much less than typical titanium encased sources, resulting in a highly isotropic source.

Conclusions: SmartSeed has a dose rate constant of $0.895 \pm 7.3\%$ cGy h⁻¹ U⁻¹, a radial dose function nearly identical to the IBt-Bebig model I25.S06 seed, and a highly isotropic dose distribution. Fluorescence x rays account for the relatively low value of Λ , yet their variable contribution to dosimetry arising from seed dimensional uncertainties is estimated to be $<0.2\%$.

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Key words: brachytherapy, seed, SmartSeed, biocompatible polymer, MCNP5, iodine-125, fluorescence x rays

I. INTRODUCTION

This work introduces the new IBt-Bebig iodine-125 interstitial seed (SmartSeed) intended for use in permanent brachytherapy implants. As the mean photon energy of iodine-125 is about 28 keV, the dose distribution around the seed is very sensitive to design specifications and manufacturing differences. The American Association of Physicists in Medicine (AAPM) therefore recommends that a dosimetric characterization of each new brachytherapy source marketed for medical applications should be carefully determined by one or two independent sets of measurements and one Monte Carlo calculation.¹ In this study, TLD-100 LiF thermoluminescent dosimeters with a volume of 1 mm³ (Harshaw/Bicron 6801 Cochran Rd, Solon, OH 44139) were used in a solid water

phantom to measure the dose distribution of the SmartSeed source, with corrections applied for energy dependent dosimeter responses. Monte Carlo calculations performed with MCNP5 verified the dose distributions in WT1 and due to the difficulties of measuring in liquid water, the same Monte Carlo seed model validated in WT1 was used to calculate the dosimetric quantities in liquid water, as recommended by the TG-43U1 report.¹ A second MCNP5 study was separately performed by the second author to verify calculated TG-43U1 clinical parameters. MCNP calculations were also performed with energy bins 1 keV wide to evaluate how the fluorescence x rays affect the dosimetric parameters. Specifically, the impact on air-kerma was evaluated by cutting the spectrum at 1, 5, and 14 keV and the dose to water was calculated (see Sec. III C) along the transverse plane in the near field from 0.1 to 2 cm in 0.1 cm increments.

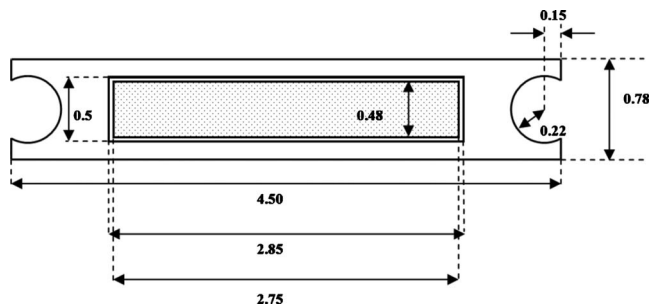


FIG. 1. Schematic of the new polymer SmartSeed (all dimensions are in mm).

II. MATERIALS AND METHODS

II.A. Radioactive seed (SmartSeed)

The internal construction and dimensions of the source are shown in Fig. 1 and the individual component details are listed in Table I. Externally, the source is a right cylinder with a physical length of 4.5 and 0.78 mm diameter. The encapsulation is made of a biocompatible polymer molded into the shape of two cups; right circular cylinders are open on one end and closed on the other, designed to accept the central core. The core is a cylindrical radiopaque leaded glass marker 2.75 mm in length and 0.48 mm in diameter, with a 0.023 mm thick layer of SiO_2 on its outer surface. This layer contains ion-implanted xenon-124 atoms, distributed uniformly throughout, which is transmuted to iodine-125 by neutron irradiation. All are coated with 0.002 mm layer of SiO_2 . The active core incorporates the radionuclides within the glass, a technique used to safely store long-lived waste because of its chemical stability. The open ends of the partially filled polymer cups are slid over the core and bonded together to form a hermetically sealed source. The ends of the seed capsules each contain a spherical socket that can accept a “snap-in” ball of a connector, easily producing a custom strand of seeds with specific seed-spacer combinations. Five seeds were calibrated on 4 July 2008, in accordance with the current NIST 1999 WAFAC standard² which is optimized for removing the contribution of ~ 5 keV Ti x rays to air-kerma strength determination. This calibration is mandatory as per TG-43U1 recommendations before the seed can be used in clinical applications.

TABLE I. SmartSeed component details.^a

Component	Material	Density (g/cm ³)
Capsule	Polyacryletheretherketone (PEEK)	1.32
Core base	Leaded glass	4.88
Active layer	Quartz with ion-implanted Xenon-124	2.54
Capping layer	Quartz	2.21

^aFor further information please contact IBT-BEBIG group.

II.B. TLD dosimetric measurements

The TLD dosimetric measurements were performed in a solid water phantom (WT1) (model 457, Radiation Measurement Inc. RMI, Middleton, WI) using two seeds, provided by IBt-Bebig, calibrated by Capintec CRC-15-R well chamber, traceable to the NIST 1999 revised standard. TLD-100 (LiF: Mg, Cu, P) are the detectors that have been used in our measurements. They were calibrated using a 6 MV linear accelerator photon beam whose dosimetry was performed following the protocol NCS (Ref. 3) (dose to water) and applying the same procedure described by Reniers *et al.*⁴ The TLDs were annealed by heating them at 400 °C for 1 h followed by a 100 °C anneal of 2 h. A delay of 24 h was kept between irradiation and reading. TLDs were read with a Harshaw model 3500 TLD reader. Each TLD was recalibrated five times before and after the seed dosimetry to assess possible variations in the calibration factor and/or instability of the reader and then selected to obtain a standard deviation of less than 3.5%.

The dose rate $\dot{D}$ was calculated as described in Eq. (1) (Ref. 4)

$$\frac{\dot{D}}{S_K} = \frac{R}{CF \times EF \times S_K \times T}, \quad (1)$$

where R is the reading of the TLDs; CF is the calibration factor for the TLD response measured in the 6 MV beam; EF is the energy correction factor assumed from the literature to be $1.40 \pm 5\%$ (Refs. 4 and 5) which was treated as distance independent constant; S_K is the air-kerma strength; and T is the irradiation time corrected for the decay of the source.

All doses delivered were in the linear response region of the TLDs, [from 0.25 up to 1.5 Gy (Ref. 6)] so no correction for supralinearity was applied.⁶

II.C. Solid water phantoms (WT1)

Solid water was used as a measurement medium since Monte Carlo results^{5,7} confirm that the radiological properties of this material approximate those of liquid water better than other commercial plastics. The composition of the WT1 solid water phantom is given in ICRU44 as⁸ H: 8.1%; C: 67.2%; N: 2.4%; O: 19.9%; Cl: 0.1%; and Ca: 2.3%. Two phantoms ($20 \times 20 \times 10$ cm³) with different geometry were employed:⁹ One for the measurements of the radial dose function and another for the measurements of anisotropy function. The radial dose function was measured at distances of 1, 1.5, 2, 3, 4, 5, 6, and 7 cm from the center of the source. An angle of 7.5° was left between the line from one TLD to the source and the adjacent TLDs to avoid shadowing effects.⁴ For the anisotropy function measurement, the TLDs were placed every 10° at radii of 2, 3, 5, and 7 cm from the center of the source. All measurements were repeated at least three times to minimize measurement uncertainties. The dose rate at the reference point was measured 27 times for each seed in order to calculate dose rate constant precisely.

II.D. Monte Carlo simulation (MCNP5)

The MCNP5 (Monte Carlo N Particle version 5) code was used to model the source and calculate the dose rate distributions around it in the solid water phantom. Agreement between measurements and calculations validated the two methodologies and so, the source model. Clinical parameters are, therefore, calculated in liquid water as recommended by TG-43U1 protocol. A separate MC study had been performed in liquid water before our study, using also MCNP5, by the second author without validating the seed model by measurements in solid water (differences between the two MC methods will be detailed below). Agreement between the two MC studies was obtained. Both studies used a detailed photon physics treatment that accounts for coherent (Thomson) scattering and also includes fluorescent photons after photoelectric absorption. Form factors are used with coherent and incoherent (Compton) scattering to account for electron binding effects. MCPLIB04,¹⁰ the nonstandard photoatomic data library for MCNP5 code was used in place of the default MCPLIB01. The core of MCPLIB04,¹⁰ derived from EPDL97,¹¹ is a completely new set of data taken from ENDF/B-VI Release 8,¹² including cross-sections, form factors, scattering functions, and fluorescence data. This library does not significantly differ from the NIST XCOM photon interaction library¹³ although it is a significant improvement over the previously released library, primarily for low-energy photoelectric interactions in low Z materials.¹⁴ Energy deposits averaged over volume tallies (*F4, *F8, and F6) were used to calculate dose rate distributions and air-kerma strengths for SmartSeed. The number of histories chosen was 1×10^9 to minimize statistical uncertainty while keeping computation times reasonable.

II.D.1. Monte Carlo simulation (MCNP5)—Air-kerma strength S_K

The emission spectrum of SmartSeed reveals that fluorescence x rays from 3 to 12 keV are generated by the lead glass marker. These low-energy x rays will contribute to air-kerma strength but not significantly to tissue/water dose (see Sec. III C). It was therefore important to evaluate their effects by using different cutoff energies when calculating air-kerma strength. Our situation can be compared to the situation mentioned by Kubo.¹⁵ Consequently, the NIST 1999 WAFAC standard included an aluminum filter to eliminate Ti K -shell x rays of 5 keV and lower. In the case of SmartSeed, the x rays from the Pb L -shell have energies ~ 12 keV which are included in the current $S_{K,N99}$, where “N99” refers to NIST 1999. Both of the following calculation methods were performed with cutoff energies of 1, 5, and 14 keV to illustrate the influence of low-energy x rays on air-kerma strength.

The first method involved the calculation of kerma rate with the F6 tally at 5 cm in air¹⁶ from the center of the source in the transverse plane, then applying the inverse square law to calculate the kerma strength S_K . Here, the kerma rate is approximated by absorbed dose because secondary charged particle equilibrium for low-energy photon emitters can be

assumed.¹⁷ Unexpected deviations of WAFAC air-kerma strength from the inverse square law may be a general feature of all encapsulated sources containing radioactivity distributed on or near the surfaces of a radiopaque structure with sharp corners,¹⁸ but SmartSeed has an isotropic photon fluence distribution near the transverse axis that validates using the inverse square law.¹⁸ Moreover, the same MC calculation for air-kerma strength was repeated in vacuum following TG-43U1 recommendations in order to confirm our first methods. Difference was within calculation accuracy (i.e., less than 1%). However, result in vacuum is presented in this work according to TG-43U1 recommendations.

The second method for calculation of air-kerma strength in free space S_K was modeled by creating a ring tally of air 2 m in diameter centered in the transverse plane of the source. The air tally ring consisted of a volume defined as the space inside a 2 cm thick spherical shell with inside radius of 99 cm and outside of 101 cm. The space was further restricted to $\pm 2^\circ$ from the transverse plane. Medich *et al.*¹⁹ have shown volume averaging errors from this angle to be on the order of 0.2%. This geometry was chosen to maximize the tally volume without compromising its representation of a point detector in an effort to gain statistical significance with a reasonable number of histories. The *F4 tally was used, yet modified such that photons depositing energy in this volume were put into 1 keV energy bins to help assess contributions from the entire seed spectrum, including characteristic x rays from xenon and lead at 3, 5, and 12 keV. Each bin was multiplied by its respective mass-energy absorption coefficient μ_{en}/ρ to obtain air-kerma per source photon ($\text{MeV g}^{-1} \text{ photon}^{-1}$). Data were then normalized to percentage of total kerma vs energy and presented in the results section. This data spectrum was then cut at the three key energies to generate suitable S_K results. All modeled space other than the source and the air was chosen as a void to satisfy TG-43U1 free space (*in vacuo*) conditions, which eliminates the need for corrections of photon attenuation and scattering for both the surrounding air and nearby objects. In both methods, all secondary electrons were forced to deposit their energy locally. This forces charged particle equilibrium, a necessary condition for a good representation of kerma and especially important considering there is a void surrounding the tally cell (second method). The simulations required 1×10^9 histories to achieve less than 1% uncertainty.

II.D.2. Monte Carlo simulation (MCNP5)—Solid water

For comparison with the measurements, the Monte Carlo simulations were performed with the SmartSeed source in solid water phantoms. The TLDs, their positions, size, and materials were modeled as precisely as possible with respect to the experimental setups to take into account the attenuation of signal by the TLDs (see Sec. II C). F6 and *F8 tallies were used in this simulation by the first and second methods, respectively.

II.D.3. Monte Carlo simulation (MCNP5)—Dose distribution in water

The first method used to calculate dosimetric quantities in liquid water as recommended by TG-43U1 (Ref. 1) was applied as previously described in Abboud *et al.*⁶

The second method modeled the SmartSeed centered within a 2 m diameter sphere of water. Dose tally points were recorded from 0.5 to 10 cm along the radius and from 0° to 180° using the *F8 tally. Differences from the first method were that of technique and consisted of cell construction and tally modes. The first method utilized small spherical tallies of 1 mm³ volume, while the second used cells comprised of spherical shells and cones ($\pm 2^\circ$) construction, which allows tally cells to grow in volume as they increase in distance while maintaining less than 0.2% error from volume averaging. This method statistically compensates for flux loss due to geometry ($1/r^2$) and attenuation of photons. Both methods ran in photon-only mode to reduce computation time. Photon-only mode deposits the electron energy locally, which is a reasonable assumption considering the range of the maximum energy electron (35 keV) in water is only 0.04 mm.^{20,21} Fundamental variables such as the iodine-125 spectrum, cutoff energies, and source design were otherwise identical. Outputs of both methods are compared in Sec. III. Since dose rate constant in liquid water recommended by TG-43U1 protocol is the average of the measured and calculated one, measured dose rate in solid water at the reference point was corrected based on Williamson's Monte Carlo calculations⁷ for differences between solid water and liquid water.

II.E. Dosimetry formalism of brachytherapy sources: TG-43U1 protocol

As in the original TG-43 protocol,²² the dose formalisms recommended by the AAPM are described in terms of a polar coordinate system, in which r is the distance to the point of interest and θ is the angle from the longitudinal axis of the source. In this work, one-dimensional (1D) and two-dimensional (2D) formalisms, as proposed in Rivard *et al.*,¹ were used to determine dose rate equations for a cylindrically symmetrical line source of 2.75 mm active length.

III. RESULTS

III.A. TLD vs MCNP-dose distribution in solid water

Seeds that were cross calibrated by Capintec CRC-15-R well chamber traceable to NIST (Ref. 23) in accordance with the current WAFAC standard yielded a measured dose rate at the reference point ($r=1$ cm, $\theta=90^\circ$) in solid water of 0.0085 Gy h⁻¹ for the decay-corrected reported seed strength of 0.707 U. The dose rate constant Λ was then calculated in solid water by dividing the measured reference dose rate by the measured air-kerma strength and was found to be $\Lambda_{TLD,09D,N99S}=0.858 \pm 5.9\%$ cGy h⁻¹ U⁻¹, where $\Lambda_{TLD,09D,N99S}$ follows the notation recommended in Rivard *et al.*¹

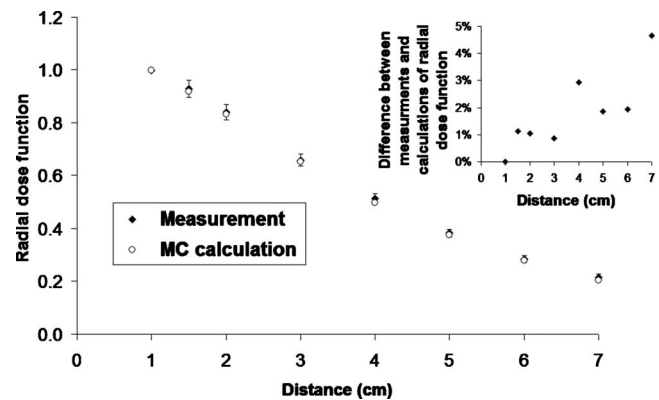


FIG. 2. Comparison between the measured and Monte Carlo calculated radial dose function $g(r)$ in WT1.

The result of the calculated dose rate constant in solid water, $\Lambda_{MC(WT1)}$, is $0.879 \pm 2.7\%$ cGy h⁻¹ U⁻¹. This is 2.4% above the measured value, well within the measurement uncertainty.

Figure 2 shows the comparison between measurements and the MC calculations of the radial dose function in WT1. Differences range from 1% at 1.5 cm up to 5% at 7 cm due to the loss of the photons at long distances that decrease the signal to noise ratio. These differences remain acceptable compared to measurement uncertainties (Table II).

TABLE II. Generic uncertainty assessment for experimental measurements using TLDs and Monte Carlo methods for radiation transport calculations. Type A and B uncertainties correspond to statistical and systematic uncertainties, respectively. All values provided are for $k=1$.

TLD uncertainties		
Component	Type A (%)	Type B (%)
Repetitive measurements	1.5	
TLD dose calibration (including linac calibration and TLD reader)	1.8	1.7
LiF energy correction ^a		5
Measurement medium correction factor ^a		3
Seed/TLD positioning		1
Quadrature sum	2.3	6.2
Total uncertainty		6.6
S_K uncertainty (including NIST and Capintec CRC-15-R well chamber)		1.7
Total combined uncertainty in Λ		6.8
Monte Carlo uncertainties		
Component	$r=1$ cm (%)	$r=5$ cm (%)
Statistics	0.2	1.3
Ionization cross-sections ^a	1.5	4.5
Seed geometry (provided by IBT-Bebig company)	1	1
Source energy spectrum	0.1	0.3
Total uncertainty (quadrature sum)	1.8	4.8
S_K uncertainty	2	
Total combined uncertainty in Λ	2.7	

^aAs suggested in the TG-43U1 report (Ref. 1).

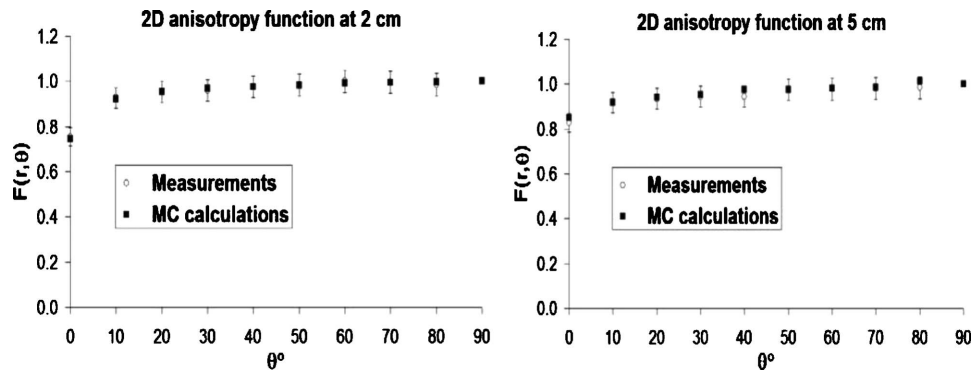


FIG. 3. Comparison between the measured and Monte Carlo calculated 2D anisotropy function performed in WT1.

The measured anisotropy function was also in agreement with the one calculated by MCNP5 in solid water with a mean difference of less than 2% (Fig. 3). Measured and calculated 2D anisotropy functions in solid water are presented in Table III.

We therefore conclude that the primary MC model is well validated and can be used for calculations of TG-43U1 parameters in liquid water.

III.B. MCNP5 TG-43U1 parameters (in liquid water)

Results are presented for dose rate constant, radial dose function, and the one-dimensional and two-dimensional anisotropy functions. The anisotropy and radial dose function results listed are an average of both MC methods. These results were compared with other iodine-125 seed models.

III.B.1. MCNP5 dose rate constant in water Λ

The dose rate constant in liquid water $_{MC}\Lambda_{(Water)}$ was calculated with the air-kerma results cut at 5 keV and yielded results of $0.895 \pm 2.7\%$ cGy h⁻¹ U⁻¹ for the first method and $0.905 \pm 2.7\%$ cGy h⁻¹ U⁻¹ for the second, a difference of 1.7%. Corrections were applied to $_{TLD}\Lambda_{09D,N99S}$ based on Williamson's Monte Carlo calculations⁷ for differences between Solid Water and liquid water to obtain $0.885 \pm 6.8\%$ cGy h⁻¹ U⁻¹. Therefore, $_{CON}\Lambda$, the average of

the experimental and Monte Carlo Λ values of $0.895 \pm 7.3\%$ cGy h⁻¹ U⁻¹, is recommended for clinical applications.¹

These results are much lower than other iodine-125 seeds on the market because of the influence of the 12 keV photons to NIST measured air-kerma (see Sec. III C). When the dose rate constant was calculated with the air-kerma results cut at 14 keV the results became $1.024 \pm 2.7\%$ cGy h⁻¹ U⁻¹ for the first method and $1.023 \pm 2.7\%$ cGy h⁻¹ U⁻¹ for the second. Previous studies in water gave results of $1.02 \pm 6\%$ cGy h⁻¹ U⁻¹ for InterSource-125 (Ref. 24) and $1.002 \pm 1\%$ for the I25.S06 seed.²⁵

III.B.2. MCNP5 radial dose function $g(r)$

Calculation results performed in liquid water are presented in Table IV and compared to published data for InterSource-125 (Ref. 24) and Symmetra model I25.S06.²⁴ The $g(r)$ values from both methods were averaged and a fifth order polynomial fit was generated for the data range of 0.5–10 cm. Figure 4 shows the fit results along with the data points. A statistically equivalent result between the two methods was seen at all points. The radial dose function was also calculated in the near field from both MC models with good agreement (<1%) except at 0.1 cm where there was a 2.4% difference due to the difference in voxel volume of

TABLE III. 2D anisotropy functions measured and calculated in solid water phantom (WT1).

θ° / r (cm)	TLD measurements			Monte Carlo calculations				
	2.0	3.0	5.0	7.0	2.0	3.0	5.0	7.0
0	0.755	0.808	0.828	0.852	0.747	0.820	0.848	0.867
10	0.928	0.940	0.919	0.928	0.923	0.948	0.920	0.915
20	0.953	0.945	0.935	0.943	0.954	0.965	0.941	0.940
30	0.960	0.960	0.945	0.954	0.969	0.983	0.954	0.954
40	0.975	0.972	0.943	0.951	0.976	0.991	0.975	0.947
50	0.984	0.970	0.976	0.970	0.983	1.002	0.976	0.949
60	1.000	0.988	0.977	0.979	0.990	1.003	0.983	0.977
70	0.998	0.995	0.981	0.985	0.994	1.011	0.985	0.950
80	0.985	1.000	0.984	0.991	0.999	1.005	1.014	0.975
90	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000

TABLE IV. Radial dose function $g(r)$ calculated and measured in solid water (WT1) and calculated in liquid water for 1D and 2D approximations. Fifth order polynomial fit for radial dose function $g_L(r)$ calculated in water is presented below.

r (cm)	Measurements		Monte Carlo calculations			
	WT1 SmartSeed $g_L(r)$	WT1 SmartSeed $g_L(r)$	SmartSeed $g_L(r)$	SmartSeed $g_P(r)$	Liquid water I25.S06 ^a $g_L(r)$	InterSource-125 ^b $g_L(r)$
0.1			1.169	0.845	1.01	
0.2			1.135	1.011	1.03	
0.3			1.107	1.047	1.03	0.938
0.4			1.085	1.051		0.980
0.5			1.070	1.047	1.03	1.000
0.6			1.056	1.041		1.006
0.7			1.040	1.033		1.010
0.8			1.027	1.023		1.009
0.9			1.017	1.011		1.004
1.0	1.000	1.000	1.000	1.000	1.000	1.000
1.5	0.928	0.918	0.932	0.933	0.937	0.953
2.0	0.840	0.831	0.855	0.857	0.857	0.891
2.5			0.768	0.772	0.774	0.813
3.0	0.658	0.653	0.689	0.692	0.689	0.738
3.5			0.617	0.620	0.609	0.662
4.0	0.512	0.497	0.538	0.538	0.538	0.591
4.5			0.483	0.487	0.470	0.525
5.0	0.383	0.376	0.420	0.425	0.409	0.469
6.0	0.285	0.279	0.315	0.316	0.313	0.362
7.0	0.215	0.205	0.235	0.234	0.232	0.273
8.0			0.172	0.173	0.176	
9.0			0.125	0.125	0.134	
10			0.099	0.103	0.0957	

$$Y = a + b^*X + c^*X^2 + d^*X^3 + e^*X^4 + f^*X^5$$

$$a = 1.196\ 82$$

$$b = -2.4313 \times 10^{-1}$$

$$c = 5.0270 \times 10^{-2}$$

$$d = -1.2160 \times 10^{-2}$$

$$e = 1.4100 \times 10^{-3}$$

$$f = -5.620\ 87 \times 10^{-5}$$

$$r^2 = 0.999\ 92$$

^aSymmetra (Ref. 25).

^bInterSeed-125 (Ref. 24).

tally cells used by the two methods.²⁶ Both data sets were averaged and a fifth order polynomial fit was generated for the data range of 0.1–2 cm. Results of these data are plotted in Fig. 5. These data will help the user to recalculate near field doses with high precision.

III.B.3. MCNP5 1D and 2D anisotropy functions

The 1D anisotropy function $\phi_{an}(r)$ and 2D anisotropy function $F(r, \theta)$ were calculated in water as recommended by TG-43U1 protocol (Table V). Both methods yielded results very close to unity suggesting this source closely approximates a point. Figure 6 shows a comparison of the 2D anisotropy function for SmartSeed with previous studies from the literature and indicates a clear improvement in isotropy especially near the seed axis ($-40^\circ < \theta < 40^\circ$). The dose rate at $\theta = 5^\circ$ and $r = 3$ cm, for example, has a value of about 92%

of the reference value, whereas the titanium encapsulated InterSource-125,²⁴ Symmetra model I25.S06,²⁵ and Amersham model 6702 (Ref. 1) have dose rates on the order of 71%, 61%, and 59%, respectively. Treatment planning systems should therefore use the mean values of $\phi_{an}(r)$ and $F(r, \theta)$ from Table V.

III.C. Impact of fluorescence x rays on air-kerma strength S_K (MCNP5)

As previously mentioned, air-kerma strength evaluation is strongly dependent on the cutoff energy selected. Results of this study are displayed in Table VI for cutoff energies at 1, 5, and 14 keV from both calculations. The full energy-fluence spectrum was then expressed as a percentage of the total kerma vs photon energy bin and is plotted in Fig. 7. Manufacturing differences have the greatest influence over

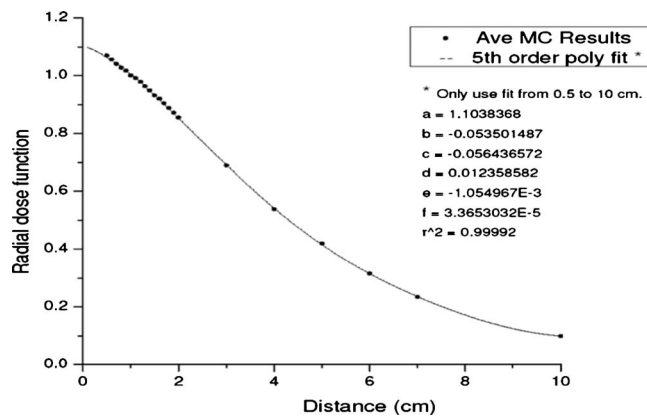


FIG. 4. Averaged results from both MC calculations of the radial dose function performed in water fitted by a fifth order polynomial.

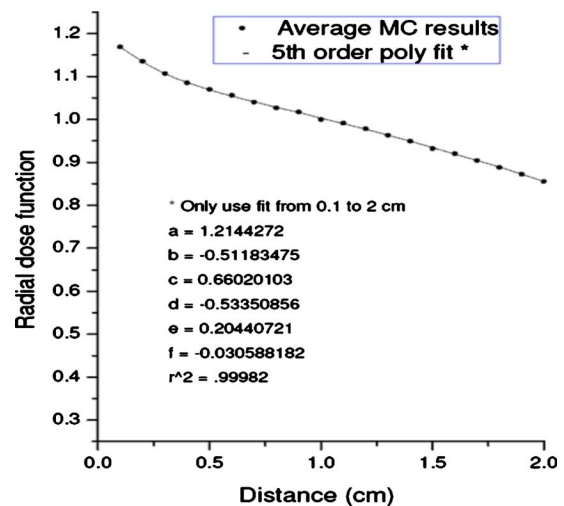


FIG. 5. Radial dose function in the near field of SmartSeed.

low-energy photons which we show in Fig. 7 to contribute 2% and 10.5% to air-kerma for 5 and 12 keV photons, respectively. We therefore performed simple attenuation calculations for both energies through the 0.14 mm thick plastic wall of the source and assumed a dimensional variation in wall thickness of 10%. The polymer shell is a molded product so this assumed variation is a conservative estimate. Attenuation calculations resulted in a 10% and 0.24% change in emissions for 5 and 12 keV photons, respectively. The shell attenuation effect on air-kerma is a second order effect, resulting only in a 0.2% (10% of 2%) change in air-kerma from 5 keV and 0.025% (0.24% of 10.5%) from 12 keV. The 5 keV however, is removed from air-kerma measurements made by NIST with an aluminum filter so errors due to shell wall variations were calculated to be only 0.025% from the 12 keV contributions.

The same analysis was then performed for the active coating on the core. This layer is very thin (0.023 mm) but has a higher density (2.54 g cm^{-3}) than the shell, so a 10% variation in thickness was again assumed and the attenuation of the 12 keV photons through this layer resulted in only a 0.1% difference in emissions. NIST, however, will check if the 12 keV emissions are proportional to the 35 keV emissions from iodine-125 both within and between batches of seeds sent for

calibrations. Soares *et al.*²⁷ have shown that manufacturing tolerances can have a measurable effect on various sources. However, we feel that the unique construction of SmartSeed will minimize errors of this type and we therefore omitted them from further reporting.

To evaluate the contribution to dose in water from these x rays, SmartSeed was modeled via MCNP in water and energy binning was performed on tally points from 0.1 up to 2 cm at 0.1 cm increments along the transverse plane. Each tally point spectrum was normalized to the percent of total dose at that point, which removes geometrical effects and plotted as function of energy and distance in Fig. 8.

Dose from the 5 keV xenon x rays cannot be seen in the plot as their contribution at 0.1 cm is only 0.01%. The lead x rays at 12 keV, however, contribute 8.7% of the dose at 0.1 cm and rapidly fall to 2.7% at 0.5 cm and become negligible at 1 cm. Percent of dose deposited in the 25 keV regions actually increases with distance and is due to the build-up of scattered photons.

The cutoff energy chosen for the clinical application was 5 keV because the current NIST WAFAC standard also cuts at this energy with the use of an aluminum filter.

TABLE V. 1D and 2D anisotropy functions calculated in liquid water (average of the two methods).

$\theta^\circ / r \text{ (cm)}$	0.5	1.0	2.0	3.0	4.0	5.0	6.0	7.0	10.0
0	0.432	0.630	0.761	0.816	0.852	0.869	0.857	0.878	0.869
10	0.800	0.867	0.910	0.927	0.941	0.944	0.922	0.923	0.924
20	0.888	0.933	0.945	0.952	0.966	0.975	0.956	0.949	0.956
30	0.930	0.956	0.960	0.967	0.983	0.969	0.969	0.965	0.966
40	0.956	0.970	0.970	0.977	0.993	0.979	0.979	0.971	0.979
50	0.973	0.985	0.983	0.996	0.991	0.979	0.988	0.989	0.989
60	0.977	0.992	0.986	1.000	1.000	1.002	0.996	0.992	0.994
70	0.993	0.997	0.997	1.002	1.015	0.990	1.002	0.996	0.997
80	0.993	1.006	0.997	1.003	1.006	1.012	1.002	0.999	1.003
90	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
$\phi_{an}(r)$	1.017	1.009	1.003	1.011	1.018	1.009	0.986	0.982	0.985

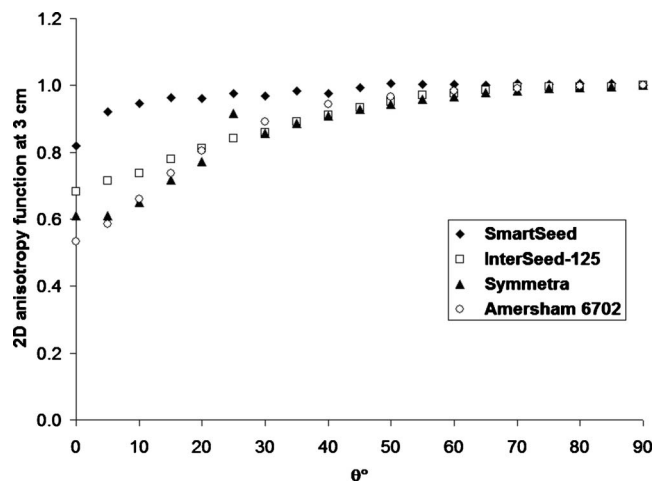


FIG. 6. Comparison between the 2D anisotropy function calculated in water at 3 cm for several seed models: The SmartSeed, InterSeed-125 (Ref. 24), Symmetra (Ref. 25), and Amersham 6702 (Ref. 1).

III.D. Uncertainty analysis

The measured and calculated uncertainties are presented in Table II. The uncertainties estimated here are standard uncertainties, $k=1$, approximating a 68% level of confidence. The combined standard uncertainty ($k=1$) on the absorbed dose obtained by TLD measurement was 6.6%.

IV. DISCUSSION AND CONCLUSION

A dosimetric characterization of a new biocompatible iodine-125 seed was presented using Monte Carlo calculations (MCNP5 code) and LiF TLD detectors.

The consensus value of dose rate constant recommended in TG-43U1 was calculated to be $_{CON}\Lambda = 0.895 \pm 7.3\%$ cGy h⁻¹ U⁻¹. The radial dose function $g(r)$ was measured and calculated at 1, 1.5, 2, 3, 4, 5, 6, and 7 cm in solid water. The small differences of radial dose function between

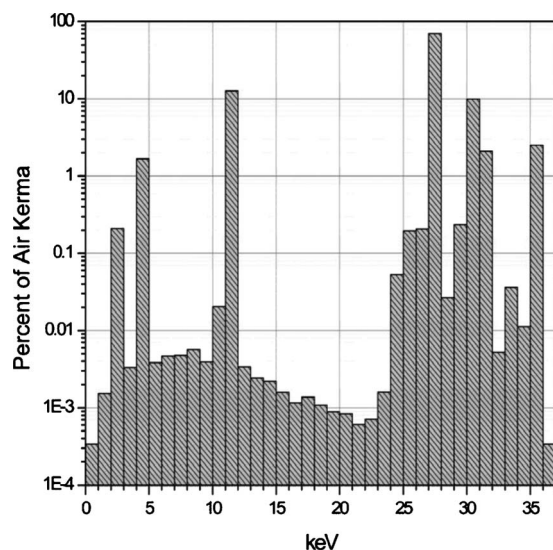


FIG. 7. The full energy-fluence spectrum expressed as percent of total air-kerma vs photon energy bin.

Percent Dose in water vs. Energy at Radii of 0.1 to 2.0 cm along the transverse plane of new SmartSeed

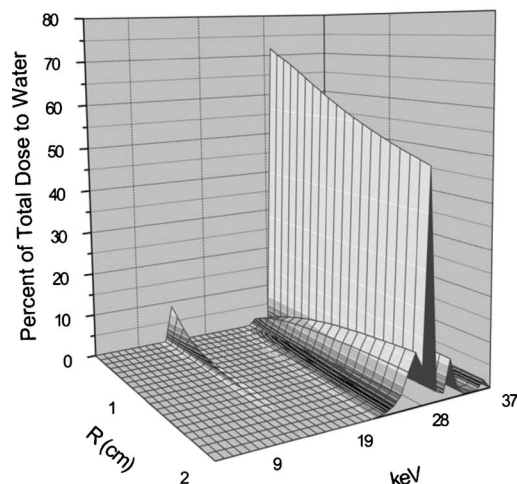


FIG. 8. Percent dose in water vs energy along the transverse plane of new SmartSeed.

the Intersource-125, Symmetra seed, and the SmartSeed results are due to the differences in the seeds themselves (their construction and replacement of the titanium shell with a biocompatible polymer). The anisotropy function $F(r, \theta)$ was measured and calculated every 10° at 2, 3, 5, and 7 cm. The agreement between the calculations and the measurements was acceptable (within the order of measurement and calculation uncertainties). Calculations were then performed for liquid water. The radial dose function was calculated between 0.1 and 10 cm (Table IV) and the 2D anisotropy function was calculated every 10° between 0.5 and 10 cm (Table V). The variation in the anisotropy function was less than 18% compared to about 32%, 39%, and 47% for the InterSource-125,²⁴ Symmetra I25.S06,²⁵ and Amersham model 6702,¹ respectively. The high value for the SmartSeed anisotropy function at small angles is attributed to the polymer encapsulation, which absorbs the low-energy photons much less than the titanium encapsulation in the other sources. The magnitude of this effect is also realized when one considers that the path length through the shell increases significantly when scoring dose near the axis and attenuation of photons follows exponential behavior.

TG-43U1 suggests cutting low-energy photons from air-kerma calculations provided they do not significantly contribute dose to tissue at distances greater than 0.1 cm. This cutoff is typically 5 keV due to the titanium x rays present in most brachytherapy sources of this type. The SmartSeed is polymer encapsulated and thus contains no titanium. The major x rays (~12 keV at 12.3%, ~5 keV at 1.5%, and ~3 keV at 0.2%) are due to the lead glass and xenon components in the seed. The polymer capsule is less attenuating than typical titanium so the low-energy x rays are visible in the emission spectrum as can be seen in the air-kerma vs energy plotted in Fig. 7. The lead x rays at 12 keV, therefore, affect the air-kerma strength value while not contributing to

TABLE VI. Air-kerma strength S_K per unit activity dependent on the cutoff energy.

MCNP- S_K	Method 1 (cGy hr ⁻¹ cm ²)	Method 2 (cGy hr ⁻¹ cm ²)
cutoff=1 keV	0.932	0.935
cutoff=5 keV (TG-43U1)	0.920	0.918
cutoff=14 keV	0.810	0.798

the dose rate at the reference point, thus decreasing the dose rate constant value by about 15%. As mentioned, when Kubo¹⁵ called attention to contaminant photons from Ti x rays, NIST adopted a new measurement standard and the updated TG-43 guidelines implemented a cutoff energy parameter to aid in the MC calculations of air-kerma. NIST, however, cannot be expected to change their measurement methods for each new product; therefore, this paper presents both values for S_K (Table VI) and Λ of $0.895 \pm 7.3\%$ cGy h⁻¹ U⁻¹ at cutoff 5 keV (as recommended by TG-43U1 for clinical applications) and $1.024 \pm 2.7\%$ cGy h⁻¹ U⁻¹ at cutoff 14 keV. Finally, this seed has only a very small anisotropy effect and because of its unique design allows for greater flexibility of seed-spacer combinations during treatment. Furthermore, using a polymer shell may substantially reduce the artifacts that can occur with metallic shells in traditional medical imaging techniques. This should, however, be quantified using different imaging modalities (CT, MRI, ultrasound, and mammography) and is the subject of future papers.

ACKNOWLEDGMENTS

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Chapter 4

Submitted patent

SYSTEM AND METHOD FOR DETERMINING RADIATION DOSE DISTRIBUTION



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Reference	Application No./Patent No. 10177977.5 - 2305
Applicant/Propriétaire Université Catholique De Louvain, et al	

Designation as inventor - communication under Rule 19(3) EPC

You have been designated as inventor in the above-mentioned European patent application. Below you will find the data contained in the designation of inventor and further data mentioned in Rule 143(1) EPC:

DATE OF FILING : 21.09.10
PRIORITY : //
TITLE : System and method for determining radiation dose distribution
DESIGNATED STATES : AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HR HU IE IS IT LI LT LU LV MC MK MT NL NO PL PT RO SE SI SK SM TR

INVENTOR (PUBLISHED = 1, NOT PUBLISHED = 0):

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DECLARATION UNDER ARTICLE 81 EPC:

The applicant(s) has (have) acquired the right to the European patent as employer(s).

Receiving Section



1. Introduction

A critical part of treatment planning system (TPS) for brachytherapy is an accurate determination of dose distribution in the patient. Most treatment planning systems for permanent prostate brachytherapy generally use the TG-43 algorithm and its update, TG-43U1 for dose calculations (Nath *et al.* 1995), (Rivard *et al.* 2004). TG-43 protocol assumes a line or point source approximation (see chapter 2 section 2.1.1), homogeneous medium dosimetry and no interseed effect (attenuation effect performed by one seed on the irradiation fields of the other implemented seeds). TPS considers that the total dose distribution for a multi-seed implant is merely the superposition of the dose distributions due to each seed independently. These assumptions however, do not accurately represent the dose distribution for brachytherapy using low-energy photon emitters. The clinical influence of cold spots on the treatment quality is unknown; they may lead to prostate cancer recurrence, while hot spots may lead to damage of the rectum or bladder.

The efficacy of the Monte Carlo (MC) simulation technique in radiation dosimetry has been demonstrated over the past several years (Sempau *et al.*). Moreover the use of MC techniques for brachytherapy had gained more interest the last years (Ye *et al.*). MC calculations have extensively been used for dosimetry purposes around single seeds but are also capable to calculate for benchmarking goals and dose distributions in a patient for a given seed distribution. MC based treatment planning system would correct all TG-43U1 inaccuracies for a given implant. The major problem, however with general-purpose Monte Carlo codes is the prohibitive computing time. It takes about 16h per calculation for one patient using a processor such as Intel Core Duo 2.83 GHz so it can't be used for real-time dosimetry.

An accelerated Monte Carlo code, named MCPI, has been developed for dose calculation in prostate brachytherapy (Chibani *et al.* 2005) and takes into account the interseed effect. However, the calculation time is about one minute for 83^{103}Pd -based seeds if one uses a single Pentium 4 PC, 2.4 GHz that is considered too long comparing to one performed with the actual treatment planning system based on TG-43 algorithms (less than a second). Moreover, the MCPI technique requires a deep modification of the used Monte Carlo algorithms inducing new complex computational steps

The object of the present invention is to determine the radiation dose distribution created by a set of radioactive seeds placed in prostate and to correct the interseed effect rapidly, for the purpose of use for real-time dosimetry. A fast Monte Carlo dose calculation engine, taking into account the interseed effect, has been developed for this goal, using the MCNP5 code and MATLAB program.

Contrary to a full Monte-Carlo calculation method and MCPI technique, the method of the invention is fast (it requires less than 2 sec using a processor Intel Core Duo 2.83 GHz to perform one calculation). Due to this fast response, it is possible, using the method and apparatus of the invention to perform a verification of the dose distribution for real-time permanent prostate brachytherapy. The method of the invention is also simple: it does not require new complex mathematical steps as it is the case in the MCPI technique.

2. Materials and Methods

MCNP V5 code (Monte Carlo N Particle) and MATLAB program were used in this invention. The method of the present invention includes different steps (see index):

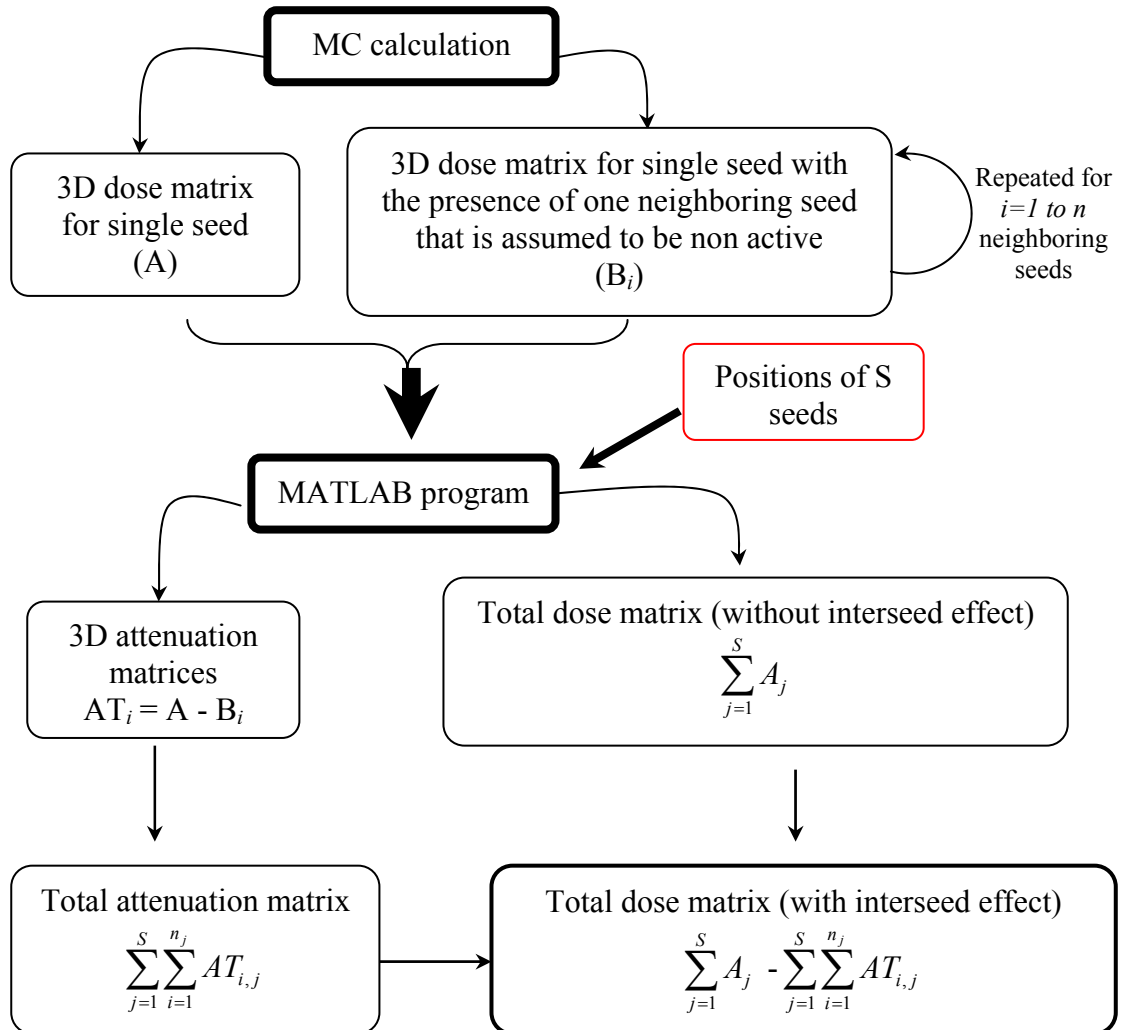
A. Using MCNP V5 code:

1. A 3D voxel matrix was chosen to calculate the 3D dose distribution around single seed where its centre is positioned at the center of matrix. Result was benchmarked with one published in literature.
2. A 3D dose distribution matrix was calculated for a single seed with the presence of one neighboring seed that is assumed to be non active. This was performed for all neighboring seeds of the studied one in the first step.

B. Using MATLAB program:

3. Attenuation matrix for every neighboring seed was calculated by subtracting the two matrices calculated in the first and second steps.
4. Determining the total dose distribution matrix without the interseed effect by adding all dose distribution matrices created by each implemented seed (calculated in the first step).
5. Determining for each implemented seed the attenuation matrix that represents the total attenuation created by the neighboring seeds (simple addition of attenuation matrices calculated by step 3).
6. Determining the total attenuation matrix by adding attenuation matrices calculated in step 5.
7. Determining the total dose distribution matrix with the interseed effect by adding the two matrices calculated in step 5 and 6.

All these steps could be concluded in the following flowchart:



3. Results and discussion

The I25S06 source (Symmetra) commercialized by IBt-Bebig group used for prostate Brachytherapy in St-Luc hospital was modeled using the drawings and data published by Hedtjärn *et al.* Benchmarking of seed model was obtained by comparing MC dosimetric parameters with one in literature (Hedtjärn *et al.*).

The importance of the attenuation carried out by a neighboring seed on the radiation dose distribution created by another one decreases as the distance between such two seeds increases. For I25.S06 seeds, we have quantified the distance above which the attenuation due to a seed can be neglected in the calculation of the interseed effect. For neighboring seeds that do not lie along the same $\bar{z}$ axis of a seed (the $\bar{z}$ axis being parallel to the direction of insertion of seeds and to seed axes), we have found that the interseed effect mainly results from those whose centers are strictly closer than 10 mm from the center of this seed (see figure 5 and 6 in Index). For neighboring seeds that lie along the same $\bar{z}$ axis of a seed, the interseed effect mainly results from seeds whose centers are strictly closer than 20 mm from the center of this seed (see figure 7 in Index).

The performance of the method of present invention was clearly showed in figure 1 and figure 2. Figure 1(a) shows in a plane iso-value curves for the absolute value of the difference in percent between the dose distributions calculated without taking into account the interseed effect and by a full Monte Carlo technique. Figure 1(b) shows in a plane iso-value curves for the absolute value of the difference in percent between the dose distribution calculated by the method of the invention and by a full Monte Carlo technique. Both figures 1(a) and 1(b) correspond to the insertion of forty-five I25.S06 seeds. The black dots of figures 1(a) and 1(b) represent the seeds that are positioned in the planes of these figures (the scales presents the number of used voxel). By comparing figures 1(a) and 1(b), we clearly observe that the method of the invention corresponds to an increase of precision with respect to a simple superposition technique: for the latter, the difference with respect to the dose distribution calculated by the full Monte-Carlo technique reaches around 12%. With the method of the invention, the maximum difference is around 5% in figure 1(b).

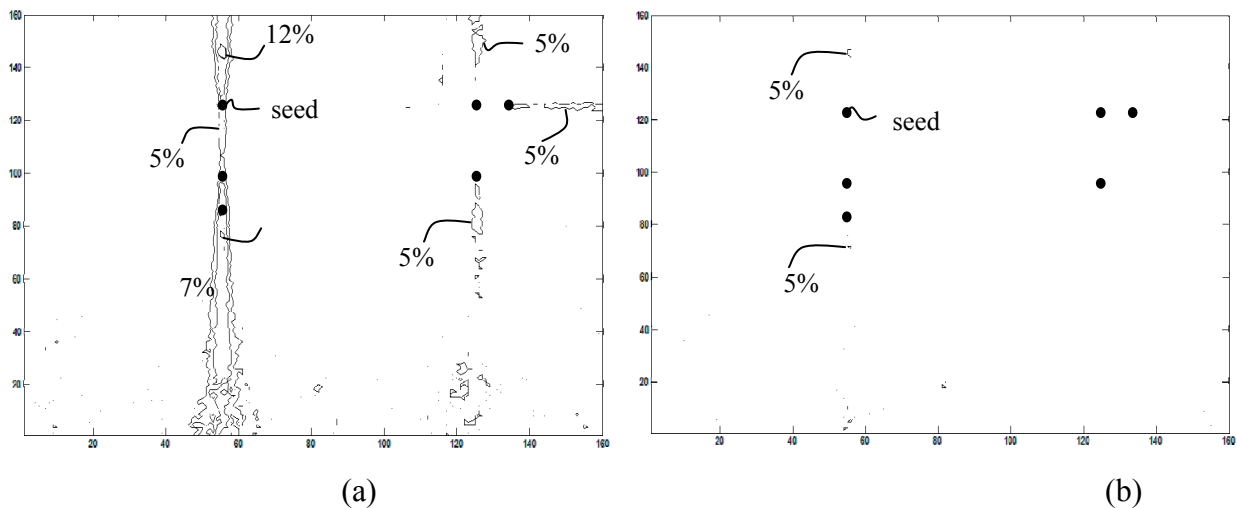


Figure. 1. Iso-value curves in a plane for the absolute value of the difference in percent between (a) the dose distribution calculated by a method that does not take into account the interseed effect (superposition of unit radiation dose distributions) and by the full Monte Carlo technique, (b) between the dose distribution calculated by the method of the invention and by the full Monte Carlo technique.

The iso-dose curves of 116 Gy, 145 Gy and 230 Gy calculated by the three above mentioned methods (figure 2). A clear difference is observed at the level of the 116 Gy iso-dose curve that is more curved inside the prostate when the interseed effect is taken into account by the full Monte Carlo (see figure 2(a)). As a consequence, the dose distributions calculated without taking into account the interseed effect are overestimated in the prostate, while the iso-dose curves calculated by the method of the invention are close to one calculated by the full Monte Carlo method (figure 2(b)). This indicates the efficiency of the method of the invention to take into account the interseed effect. Actually, a complete comparison between the full Monte Carlo method and the method of the invention for this seeds distribution leads to differences that are at most equal to 3 %, whereas differences up to 12 % are observed between results obtained with the full Monte Carlo technique and the method that does not take into account the interseed effect for the seeds distribution corresponding to figures 2(a) and 2(b).

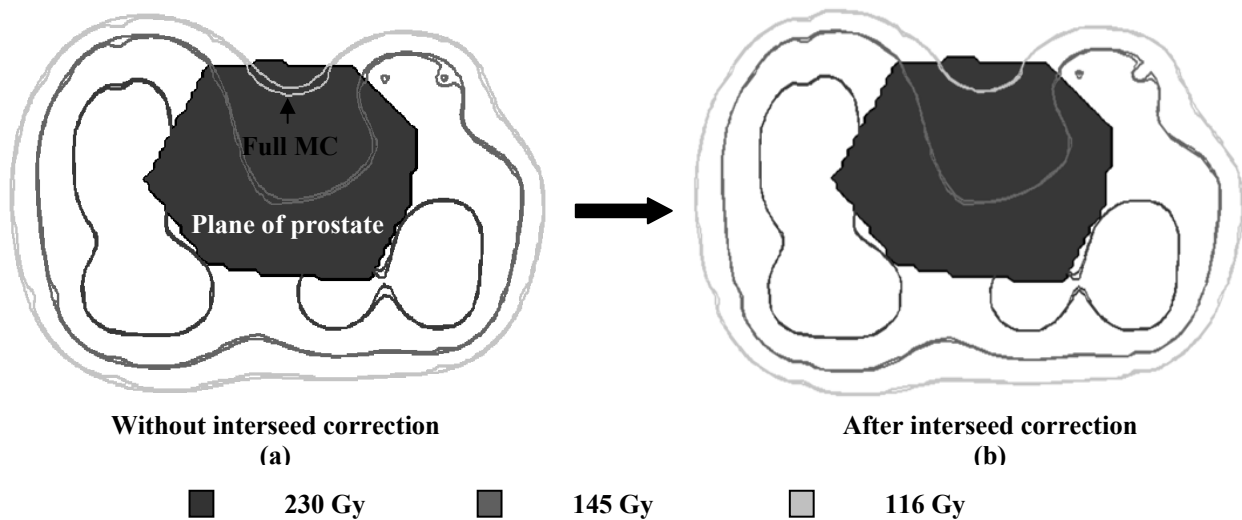


Figure. 2. A cross-section of a prostate with iso-dose curves calculated by the Full Monte Carlo method and by a method that does not take into account the interseed effect (a) and by the Full Monte Carlo method and by the method of the invention (b).

Published data by Chibani O. and Williamson J. F. explained that dose errors due to the absence of interseed attenuation effect for Symmetra seed vary between 2% and 10% with an average value of 4%. This is comparable with our results. Moreover, we have investigated the interseed effect on DVHs that was performed at the level of the D_{90} , D_{98} , D_{min} and D_{mean} values. These values are overestimated with an average of 2% (~ 5 Gy comparing to prescribed dose of 145 Gy). Published data show that D_{90} , D_{80} and D_{100} vary from 3% up to 5% depending on density of seeds per unity of volume (seed/cm³) (Chibani O. and Williamson J. F, 2005).

Stock et al. at Mount Sinai Hospital published, in 1998, the first report that quantitatively linked treatment outcome to implant quality. The key factor that correlated with probability of biochemical control was the D_{90} . It was shown that where the D_{90} exceeded 140 Gy, biochemical control rates of 80% to 90% were achieved, whereas those patients with a D_{90} of less than 140 Gy had a 40% to 50% biochemical relapse rate by 5 years.

Overall, cold spots may lead to prostate cancer recurrence while hot spots may lead to damage of the rectum or bladder. If a “cold spot” were judged (which is not precisely known using TG-43 clinical application) to be occurring in a clinically significant location and did

not resolve after repeat CT dosimetry analysis, additional radiation treatment might be contemplated to correct this, particularly if the patient had an intermediate or unfavorable cancer characteristic. Therefore, the main reason for developing a fast Monte Carlo technique such as the present invention is to account in a rigorous way, on line, for the effects of interseed attenuation and the influence of the different approximations of TG-43U1 protocol on the planned and delivered dose to the prostate and organs at risk.

Conclusion

The accuracy of calculated and delivered doses to tumor was being the major concern in radiation therapy, especially in brachytherapy. Actual treatment planning systems based on TG-43 algorithms do not accurately represent the dose distribution for brachytherapy because of several approximations. Many attempts to increase this accuracy and correct all TG-43U1 inaccuracies had been performed using MC calculations. However, the problem with general-purpose Monte Carlo codes is the prohibitive computing time so, it can not used for real-time dosimetry. Therefore, this invention presents a fast dose calculation engine based on a Monte Carlo method that has been developed for real-time dosimetry, taking into account the interseed effect.

Note: More detailed description is given in the index

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Chapter 5

Publication 3

Second European Workshop on Monte Carlo Treatment Planning, October 2009

Fast Monte Carlo treatment planning for prostate brachytherapy: a comparison with VariSeed.

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1. Introduction

Treatment planning systems for prostate Brachytherapy with seeds uses mainly the TG43U1⁽³⁾ algorithm for dose calculations. This algorithm does not take into account the interseed attenuations (known as the interseed effect) due to its complexity. In order to evaluate the magnitude of this effect for real clinical cases, VariSeed-calculated dose distributions were compared to full Monte Carlo (MC) calculations in 8 patients treated in our hospital. Because full Monte Carlo calculations can take as long as 48 hours, they cannot be used as “online”. A fast Monte Carlo dose calculation engine, taking into account the interseed effect, using the MCNP5 code has been developed and will be presented.

2. Material and methods

2.1 VariSeed program (VARIAN)

VariSeed, a largely employed treatment planning program (TPS) for real-time prostate brachytherapy dosimetry is commercialized by VARIAN Company (Varian Medical Systems, Inc. 3100 Hansen Way, Palo Alto, CA 94304-1038). The calculations in this TPS are derived from the TG43U1 protocol ⁽³⁾ (2D anisotropy approximation was used for our comparison). It uses a simple mathematical addition of the dose distribution around seeds to calculate the total dose given to prostate. However; it does not take into account the attenuation effect done by each implanted seed on the irradiation fields of the other seeds that we call the interseed effect. We investigated this effect using Monte Carlo simulation.

2.2 Monte Carlo (MC) simulation (MCNP5)

Three MC techniques were used to calculate the dose distributions of the prostate implants using MCNP code version 5: MC “One-Seed-Superposition” Technique (MCOSST), a Full MC Technique (FMCT) and a MC “One-Seed-Superposition Interseed” Technique (MCOSSIT). MCOSST uses a simple mathematical addition as like as VariSeed however; the dose distribution around single seed is directly derived from MCNP5 calculations. MCOSSIT does the same as MCOSST but corrects supplementary for interseed effect by a mathematical correction matrix. The interseed effect was also taken into account by complete simulation of all implemented seeds using FMCT. A 3D voxel matrix of 0.5×0.5×5 mm was chosen to calculate the 3D dose distribution; this is a matrix, identical to the one used in the VariSeed software.

3. Results and discussion

First, the Monte Carlo model for a single “IsoSeed” was previously carefully validated by comparing the radial dose, anisotropy functions and dose rate constant with the one published by Hakan *et al.* ⁽²⁾. A 3D comparison has then been performed to validate the new MC techniques for 8 patients implanted with “IsoSeed” (IBt-Bebig group; “IBt s.a. Rue J. Bordet Zone Industrielle C 7180 Seneffe, Belgium”, “Eckert & Ziegler BEBIG GmbH. Robert-Rössle-Str. 10, 13125 Berlin, Germany”) seeds at our hospital. Dose distributions are compared on each ultrasound imaging slice. Moreover, a DVH comparison is also performed for some organs.

The clinical technique, based on TG43U1 ⁽³⁾ for prostate brachytherapy systematically overestimates the dose deposited in the prostate and in the organs at risk close to the seeds ⁽¹⁾. This overestimation should be attributed to the combination of two effects: the interseed attenuation and the TG43U1 approximation close to the seeds. Comparing both methods of calculation (TG43U1 “2D anisotropy function” and MC), differences range from -2% up to 2% except at distances from 5 mm down to 1 mm from the seed centre, differences ranging from 2% up to 20% are observed (see figure 1). This is due to the fact that TG43U1 protocol is an approximation and not accurate for regions close to the seed. Clinical impact is however limited regarding the high deposited dose in this region.

The interseed effect was investigated by comparing MCOSST with FMCT. It leads to the appearance of cold spots in the planar dose distribution. In the literature, interseed effect ranges between 7% up to 20% depending on number, position and type of seeds ⁽¹⁾. For IsoSeed, it varies from 5% to 10% for planar dose distribution (see figure 2). Moreover, the interseed effect becomes more important as the density of implanted seeds increases: this can especially be noticed behind a set of coplanar/aligned seeds implanted each 5 mm. Therefore, when using VariSeed (TG43U1), we could recommend to avoid as much as possible coplanar-aligned seeds separated by less than 10 mm.

Different contours (prostate, rectum and urethra) were modelled to compare the DVH calculated by VariSeed for the 8 patients with the one calculated by MC techniques. Generally, for the prostate, the difference is negligible with respect to the D90, D80 and V145. However TG43U1 overestimates the average dose deposited in the prostate by more than 5% using 2D anisotropy function for all 8 patients studied.

Although the long calculation time spent by FMCT (48 h), it will be a good application for the post implant calculations, especially when our model includes the tissue heterogeneities. On the other hand, the MCOSST calculation speed (< 1 sec) is fast. Therefore it can be considered being a more accurate calculation method compared to TG43U1 for implant dosimetry in a near future as it can also be applied on line. Moreover, we have included the interseed effect in the MCOSST model to get MCOSST applying a mathematical correction matrix. This model calculates the dose distribution for a patient within 2-3 sec, taking into account the interseed effect.

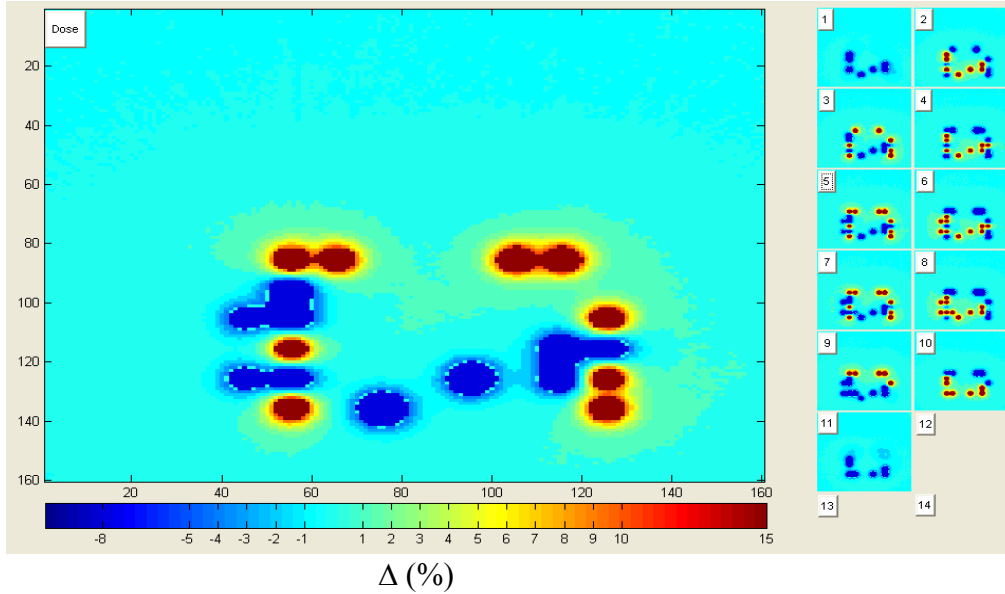


Figure. 1. Dose difference in % between VariSeed “F(r,θ)” & MCOSST in real patient implanted with 72 seeds.

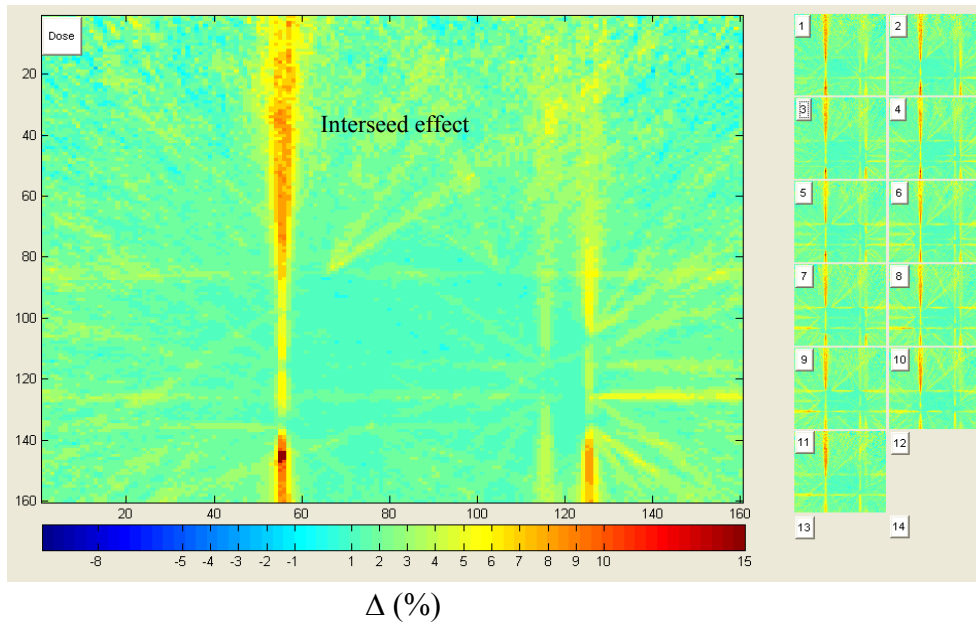


Figure. 2. Dose difference in % between MCOSST & FMCT in real patient implanted with 72 seeds shows the interseed effect.

4. Conclusion

Monte Carlo method is efficient for Brachytherapy dosimetry in real clinical cases; it can be used for all types of seeds and all brachytherapy dosimetry in water. MCOSST is fast enough to be used for real-time dosimetry as VariSeed. FMCT will be a good candidate for post dosimetry especially when heterogeneity could be taken into account. Finally, MCOSST is a new accurate and fast technique for prostate brachytherapy dosimetry that can take into account, online, the interseed effect. All these advantages make it the preferable dosimetric planning system for real-time permanent prostate brachytherapy.

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Chapter 6

*Article prepared for
submission*

FAST MONTE CARLO TREATMENT PLANNING SYSTEM FOR PROSTATE BRACHYTHERAPY: A COMPARISON WITH VARISEED™

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Abstract

Purpose

Treatment planning system (TPS) for prostate Brachytherapy with seeds uses mainly the TG-43 algorithm for dose calculations. It does not take into account the interseed attenuations (known as the interseed effect) due to its complexity, neither is it very accurate in the proximity of the seeds. In order to evaluate the magnitude of this effect for real clinical cases, VariSeed™-calculated dose distributions were compared to full Monte Carlo (MC) calculations for 8 patients treated in our hospital. Because of full Monte Carlo calculations take a long time (e.g. +/- 48 hours), they cannot be used “online”. A fast Monte Carlo dose calculation engine, taking into account the interseed effect, has been developed for real-time dosimetry, using the MCNP5 code. This paper compares the MC calculated dose distributions with the VariSeed™-calculated ones. Moreover the effect of using the 1D and 2D anisotropy approximations within the TG-43U1 algorithm will be discussed.

Methods and Materials

Three MC techniques were used to calculate and to compare the dose distributions of the prostate implants:

- MCOSST: a single superposition of the MC calculated seed kernels;
- FMCT: a full MC calculated dose distributions. The MC calculation engine MCNP_v5 (X-5 MC team);
- MCOSST: a single superposition of the MC calculated seed kernels, taking into account the interseed effect using a mathematical correction matrix.

A 3D voxel matrix of 0.5×0.5×5 mm was chosen to calculate the 3D dose distribution; this is identical to the one used for the VariSeed™ technique (clinical cases). First, the Monte Carlo model for a single “IsoSeed, I25S06” was carefully validated by comparing the radial dose, anisotropy functions and dose rate constant with those published by Hakan *et al* (2000). A 3D comparison has then been performed to validate the new MC techniques for 8 patients treated with “IsoSeed” (Bebig) seeds at our hospital. As it consists of real clinical cases, patients were carefully selected among those previously treated with seed distributions optimized by the VariSeed™ treatment planning program. Dose distributions are compared for each ultrasound imaging slide. Moreover, a DVH comparison is also performed for the prostate.

Results

VariSeed™ overestimates the dose deposited at distances from 5 mm down to 1 mm from the seed centre by 2% up to 20% respectively. This is due to the fact that TG-43

protocol is an approximation for regions close to the seed (Nath *et al* 1995). Clinical impact is however limited regarding the high deposited dose in this region.

The interseed effect was investigated by comparing MCOSST with FMCT. It leads to the appearance of cold spots in the planar dose distributions. In the literature, interseed effect ranges between 7% up to 11% depending on number, position and type of seeds (Carrier *et al.* 2007). For IsoSeed, I25S06, it varies from 4% to 10%. Moreover, the interseed effect becomes more important as the density of implanted seeds by volume unity increases. This can especially be noticed behind set of seeds implanted each 5 mm in the same and next plane. Prostate contour is modeled to compare the DVH calculated by VariSeedTM with the one calculated by MC techniques. Average dose deposited in the prostate is always overestimated by TG-43U1 models with more than 3% and 5% using 1D and 2D anisotropy functions respectively. As DVH gives only an idea about the dose-volume relationship, the effect of the interseed attenuation will be pronounced in the planar dose distributions.

We have included the interseed effect in the MCOSST model to get MCOSSTIT. The calculation speed of this engine (2-3 sec) is fast. Therefore it can be used “on line” and be considered as being a more accurate calculation method compared to TG-43.

Conclusions

MCOSSTIT is a new technique for the calculation of the dose distribution for prostate Brachytherapy based on a MC model of the single seed distribution. It is very accurate and fast system for real-time permanent brachytherapy of the prostate, taking into account the interseed effect. On the other hand, when using VariSeedTM (TG-43), we recommend avoiding as much as possible coplanar-aligned seeds separated by less than 10 mm and using 2D anisotropy function in preference to the others.

Key words: Brachytherapy, treatment planning system, Fast Monte Carlo, Interseed effect

1. Introduction

The efficacy of the Monte Carlo (MC) simulation technique in radiation dosimetry has been demonstrated over the past several years (Sempau *et al.*). Moreover the use of MC techniques for brachytherapy had gained more interest the last years (Ye *et al.*). One of the major concerns in radiation treatment is the accuracy of calculated and delivered doses and their distributions relative to the prescribed dose. Currently, the dose calculations for patient treatment in brachytherapy are based on TG-43 protocol (Nath *et al.*), which assumes a line or point source approximation, homogeneous medium dosimetry and no interseed effect. These assumptions however, do not accurately represent the dose distribution for brachytherapy using low-energy photon emitters. Studies show up to 50% perturbation in the dose distribution of ¹²⁵I coplanar aligned seeds when the interseed attenuation effect is ignored (Burns *et al.*). The difference between dose distributions based on 1D (point source model) and 2D approximations exceeds, for instance, for the ¹⁰³Pd Theragenics model 200, can amount up to 10% for 20%–40% of the target volume because of the anisotropy effect (Lindsay *et al.*). MC calculations have extensively been used for dosimetry purposes around single seeds but are also capable to calculate for benchmarking goals, dose distributions in a patient for a given seed distribution. MC based treatment planning system would correct all TG-43U1 inaccuracies for a given implant. The major problem, however with general-purpose Monte Carlo codes is the prohibitive computing time. It takes about 48h per calculation for one patient so it can't be used for real-time dosimetry. A fast Monte Carlo

dose calculation engine, taking into account the interseed effect, has been developed for this goal, using the MCNP5 code.

2. Materials and Methods

2.1 TG-43U1 Protocol

TG-43U1 (Rivard *et al.* 2004) published by AAPM (American Association of Physicists in Medicine) is generally used for Brachytherapy treatment dose calculations. Dose rate distribution around radioactive seed in water is calculated using an analytical approximation of dosimetric quantities, e.g. air kerma strength, dose rate constant, geometry factor, radial dose function and anisotropy function. TG-43U1 equations are used in all Brachytherapy TPS for prostate permanent implant however; they do not take into account the interseed effect. In this protocol two dose rate equations are given: cylindrically symmetric line source (2D) and point source (1D) formalisms.

2.1.1 General two-dimension formalism

The general, two-dimensional (2D), dose-rate equation is expressed as:

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

This formalism applies to sources with cylindrically symmetric dose distributions with respect to the source longitudinal axis. The subscript ‘‘L’’ has been added to denote the line source approximation used for the geometry function, S_k is the air-kerma strength of the source (U), Λ is the dose rate constant ($\text{cGy h}^{-1} \text{U}^{-1}$), $G(r, \theta)$ is the geometry factor, $g(r)$ is the radial dose function and $F(r, \theta)$ is the two-dimensional (2D) anisotropy function. The reference point (r_0, θ_0) is chosen to be along the transverse plane ($\theta_0=90^\circ$) at a distance of 1 cm from the source center.

2.1.2 General one dimension formalism

This formalism is used to eliminate the need to determine the orientation of the source longitudinal axis from imaging studies by approximating the true complex 2D dose distribution with 1D isotropic point-source approximation.

$$\dot{D}(r, \theta) = S_k \times \Lambda \times \frac{G_X(r, \theta)}{G_X(r_0, \theta_0)} \times g_X(r) \times \phi_{an}(r) \quad (2)$$

The subscript ‘‘X’’ is used to the radial dose function and geometry function to indicate whether a point-source. ‘‘P.’’ or line-source ‘‘L.’’ geometry function was used in transforming the data. We should thus adopt one of the following implementations of last equation:

$$\dot{D}(r, \theta) = S_k \times \Lambda \times \left(\frac{r_0}{r} \right)^2 \times g_P(r) \times \phi_{an}(r) \quad (\text{Point source}) \quad (3)$$

This equation is used in most treatment planning systems. However, we recommend using the following equation due to improved accuracy at small distances, e.g., <1 cm.

$$\dot{D}(r, \theta) = S_k \times \Lambda \times \frac{G_L(r, \theta)}{G_L(r_0, \theta_0)} \times g_L(r) \times \phi_{an}(r) \quad (\text{Line source}) \quad (4)$$

where $\phi_{an}(r)$, the one-dimensional (1D) anisotropy function, is given by the equation 5 :

$$\phi_{an}(r) = \frac{\int_0^\pi \dot{D}(r, \theta) \sin(\theta) d\theta}{2\dot{D}(r, \theta_0)} \quad (5)$$

2.2 VariSeed™ program

The VariSeed™ application is a brachytherapy treatment-planning package for transperineal ultrasound-guided implants commercialized by VARIAN Company (Varian Medical Systems, Inc. 3100 Hansen Way Palo Alto, CA 94304-1038, USA). The software package allows you to carry out pre-operative planning, intra-operative planning, and post-operative evaluation of prostate cancer treatment courses. The VariSeed™ dose calculations are derived from the TG-43 method. It utilizes a choice of two source geometry approximations and three types of anisotropy corrections. VariSeed™ calculates the dose as follows:

$$D(r) = \dot{D}(r, \theta) \times AL \quad (6)$$

$D(r)$: the dose (cGy).

AL (Average Life) = $1.44 \times 24 \times HL$ (Half Life in days).

$\dot{D}(r, \theta)$ = dose rate (cGy/hr) at point r, θ .

VariSeed™ proposes several models to calculate the dose rate basing on TG-43U1 equations, for example: Point factor (Eq. 3), Line factor (Eq. 4) and Line function (Eq. 1). The dose calculation algorithm linearly interpolates radial dose function, anisotropy factor, and anisotropy function values and calculates the dose around one seed, then it adds the dose distribution of another implemented seeds to get the dose distribution in patient without taking into account the interseed effect (attenuation done by seed on the irradiation field of the other seeds).

2.3 Monte Carlo simulation (MCNP5)

All Monte Carlo simulations of this work are based on the general-purpose Monte Carlo code MCNP5 (Monte Carlo N-Particles version 5). The detailed photon physics treatment was used. It accounts for coherent (Thomson) scattering and also includes fluorescent photons after photoelectric absorption. Form factors are used with coherent and incoherent (Compton) scattering to account for electron binding effects. Mcplib04 (White 2002), the non-standard photoatomic data library for MCNP5 code was used in place of the default MCPLIB01. The core of mcplib04, derived from EPDL97 (Cullen 1997), is a completely new set of data taken from ENDF/B-VI Release 8 (Report BNL-NCS-17541) including cross sections, form factors, scattering functions and fluorescence data. This library does not significantly differ from the NIST XCOM photon interaction library (Hubbell *et al.*) although it is a significant improvement over the previously released library, primarily for low-energy photoelectric interactions in low Z materials (DeMarco *et al.*). The superimposed mesh tally (FMESH4) was used; it uses only track-length (type 4). Other track-length quantity such as energy deposition was calculated with the use of a tally multiplier (FM) card to determine dose rate distributions. Numbers of histories of 1×10^9 were chosen to minimize statistical uncertainty up to 7 % at 8 cm far from one source and up to 1.5% at 5 cm far from the center of a real implant.

A set of radioactive seeds (IsoSeed) were simulated with arbitrary positions and orientations, merged in a three-dimensional (3D) homogeneous water phantom representing the prostate and surrounding tissue (as recommended by TG-43U1). A matrix of voxels ($8\text{ cm} \times 8\text{ cm} \times [\text{number of slides} \times 0.5\text{ cm}]$) was used to calculate the dose rate distribution in each voxel of $0.05 \times 0.05 \times 0.5\text{ cm}^3$ of volume as like as one used by VariSeedTM program.

2.4 Monte Carlo methods

Several methods are proposed to calculate the dose distribution in patient using Monte Carlo calculation. Dose rates calculated by Monte Carlo around one seed are referenced to the TG-43U1 reference point ($r=1\text{ cm}$, $\theta=90^\circ$), then doses are calculated using Eq. 6. A comparison using MATLAB program was done between all dose distribution matrices calculated by these MC techniques and VariSeedTM dose distributions.

2.4.1 MCOSST (Monte Carlo One-Seed Superposition Technique)

MCOSST calculates the dose distribution around one seed (e.g. IsoSeed, I25S06) using MCNP5 code, and then it superposes the dose distribution to each implemented seed to another in order to obtain the total dose deposited in the patient. We called this technique the superposition technique as it simply adds the single seed dose distributions identically as done by VariSeedTM. This technique is fast (1 second per calculation using Intel^(R) Core^(TM)2 Quad CPU 2.83 GHz) it does not, however take into account the interseed effect.

2.4.2 FMCT (Full Monte Carlo Technique)

FMCT calculates directly the total dose deposited in patient for the proposed seed distribution. It models all the implemented seeds using the MCNP5 code. As all implemented seeds are modeled as a whole, this method will take into account the interseed effect. It is however very slow (48hr per patient calculation) and therefore it can only be used for benchmarking purposes.

2.4.3 MCOSIT (Monte Carlo One-Seed Superposition Interseed Technique)

MCOSIT is comparable to MCOSST, but it takes into account the interseed effect by applying a mathematical correction matrix. In fact, the interseed effect is a complicated effect that is neglected in prostate brachytherapy dosimetry. The complexity of this effect is due to many variables e.g. seed's construction, seed positions, distances between seeds and the density of implanted seeds by volume unity (seed/cm^3). This effect is studied by using Monte Carlo calculations (Chibani and Williamson). In a previous paper we proposed a mathematical function complementary to the radial dose or anisotropy function. This function was called ISE_{DRFS} (InterSeed Effect on Dose Rate for Single seed) (Abboud *et al.*). It reflects the shadowing effect of the seed on the dose rate distribution of one seed only and varies with the position of the obstacle seed, its composition, and with the measured point positions. The mathematical correction matrix is based on this function ISE_{DRFS}. A combination of MC superposition calculation (MCOSST) and this mathematical algorithm developed in our institute is the basis of the MCOSIT model. It corrects the interseed effect as much as possible (first order correction "see chapter 4").

This MCOSSIT model is also very fast: 2 sec using one computer for a patient treatment model. (Intel^R Core^{TM2} Quad CPU 2.83 GHz). This technique will be detailed in patent in progress (see chapter 4).

3. Results

3.1 Symmetra source model validation (I25S06)

The I25S06 source (Symmetra) commercialized by IBt-Bebig group used for prostate Brachytherapy in our hospital was modeled using the drawings and data published by Hedtjärn *et al.* Benchmarking of our seed model was obtained by comparing calculated TG-43 dosimetric parameters with one in literature (Hedtjärn *et al.*). Differences between MC calculated and VariSeedTM calculated (TG-43U1-2D anisotropy function) dose distribution around a single seed vary between -5% and 5% for distances varying between 0.5 cm and 7 cm. This is within the TG-43U1 uncertainties. Close to the seed, at distances less than 5mm, this difference exceeds 5%. A map of dose differences for several planes is illustrated in figure 1. This difference larger than 5% is due to TG-43 mathematical approximation that is not accurate in regions less than 5 mm from the source (Nath *et al.*).

The clinical impact is however negligible of this uncertainty close to the source, but it will appear when analyzing average doses from DVH comparisons (see 3.5).

3.2 Comparison between VariSeedTM & MCOSSIT

The MC model of IsoSeed being validated, then the superposition algorithm was approved for different set of seeds with different positions. Therefore, the superposition method of the MC dosimetry planning system, MCOSSIT was compared with VariSeedTM program for 8 patients treated at our institute.

Figure 2 shows the difference between calculation of 2D anisotropy approximation (equation 1) used by VariSeedTM and MC calculations. Results ranging between -2% up to 2% except for regions near to seeds are observed, the differences close to the seed being discussed before (see 3.1). Due to the rapidity of MCOSSIT, which is comparable to VariSeedTM and due to a more accurate calculation method if compared to TG-43 makes it a good planning system for real-time clinical implant dosimetry in a near future.

3.3 Comparison between MCOSSIT & FMCT

The interseed effect for a real patient is clearly illustrated when comparing MCOSSIT and FMCT. Although, MCOSSIT is a fast and accurate planning system for real-time dosimetry it does not take into account the interseed effect as it only is making a superposition of single seeds. FMCT, however, is a model of the complete implant and can be used to investigate this effect. Comparison between MCOSSIT and FMCT (figure 3) shows the interseed effect in all planes for prostate, varying between 4% and 10%. These differences are comparable with published data where dose errors due to the absence of interseed attenuation effect for Symmetra seed vary between 2% and 10% with an average value of 4% (Chibani O. and Williamson J. F, 2005). Figure 3 however, presents a full multi-planar 2D view of the effect, which was found to be quite comparable for the 8 patients studied. It clearly illustrates the reduced dose especially behind coplanar/aligned seeds. Although the long calculation time spent by FMCT (48 h), it could be used for postimplant calculations too. This result could be obtained rapidly during 2 sec using MCOSSIT, which is derived from MCOSSIT by adding a

mathematical correction for the interseed effect based on MC calculation. Figure 4 illustrates the efficiency of MCOSSIT. It reduces error due to interseed effect from of 15% to 3-4%.

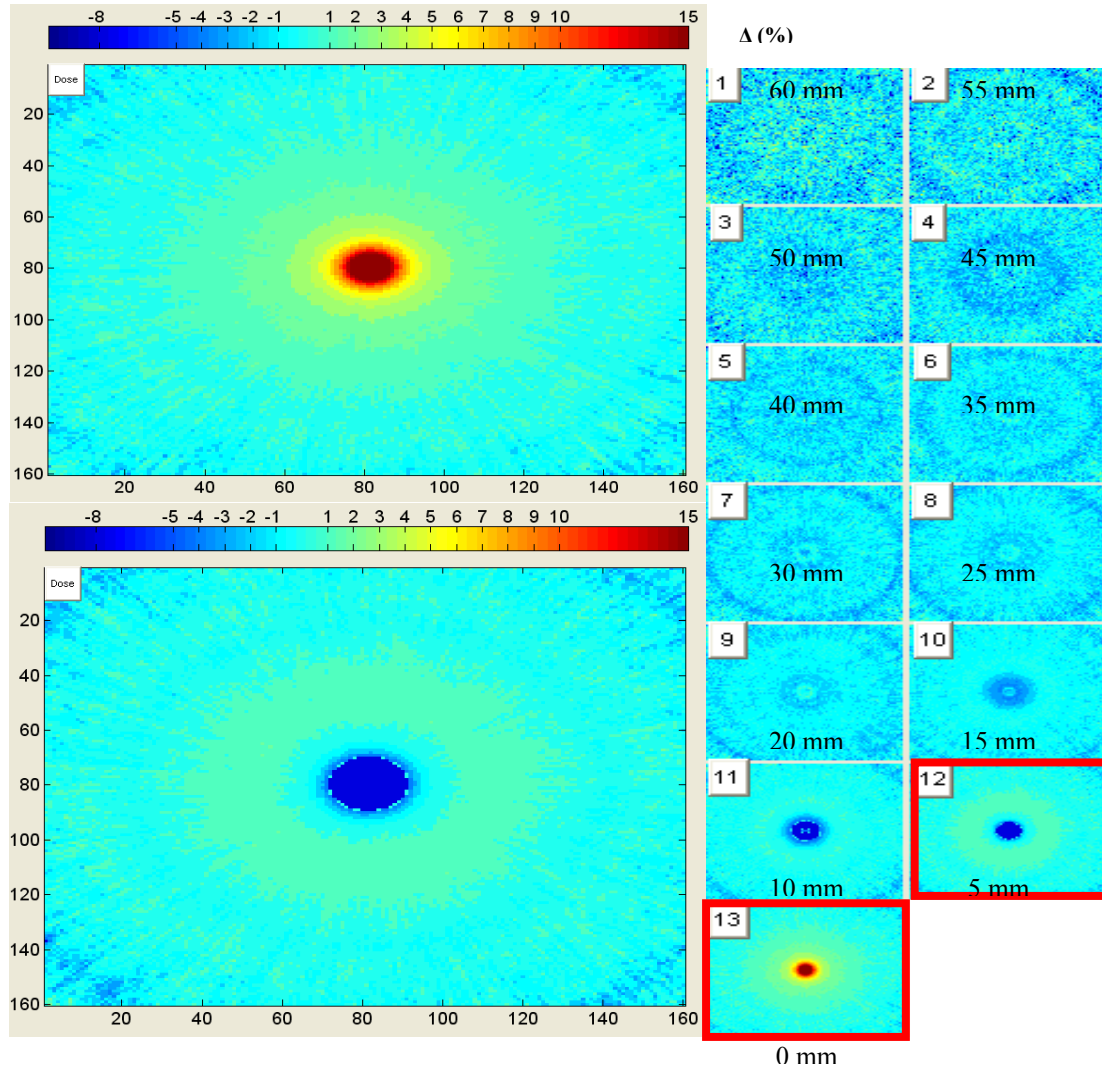


Figure. 1. Dose difference in % between VariSeedTM & MC ($\frac{VariSeed - MC}{VariSeed} \%$) for single seed illustrated in several plans taken each 5 mm. The difference ranges between -5% and 5%. Two planes with red squares are showed on the left side to show the limitation of TG-43 approximations

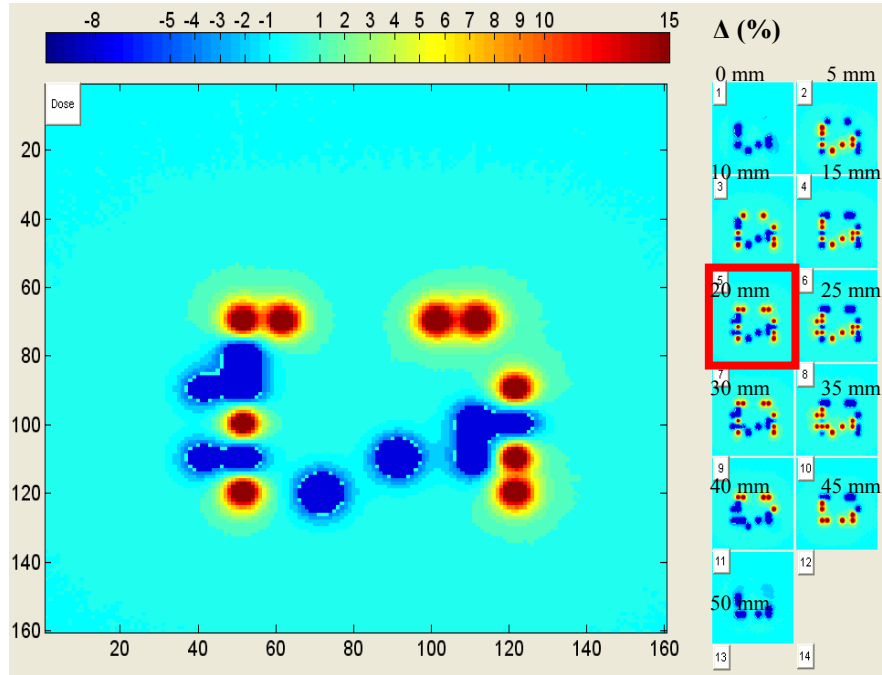


Figure. 2. Dose difference in% between VariSeedTM & MCOSST ($\frac{VariSeed - MCOSST}{VariSeed} \%$) in real patient illustrated in several planes taken each 5 mm. The difference ranges between -2% and 2% except close to seeds, Plan with red square is shown on the left side.

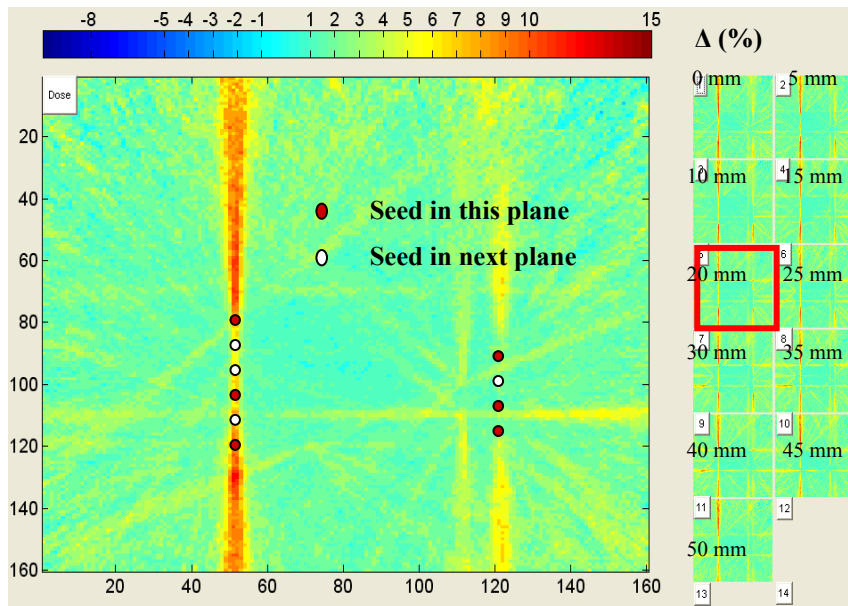


Figure. 3. Dose difference in% between MCOSST & FMCT ($\frac{MCOSST - FMCT}{FMCT} \%$) for a real patient illustrated in several plans taken each 5 mm. Interseed effect varies from 4% up to 10% especially behind coplanar/aligned seeds. Plane with red square is shown on the left side.

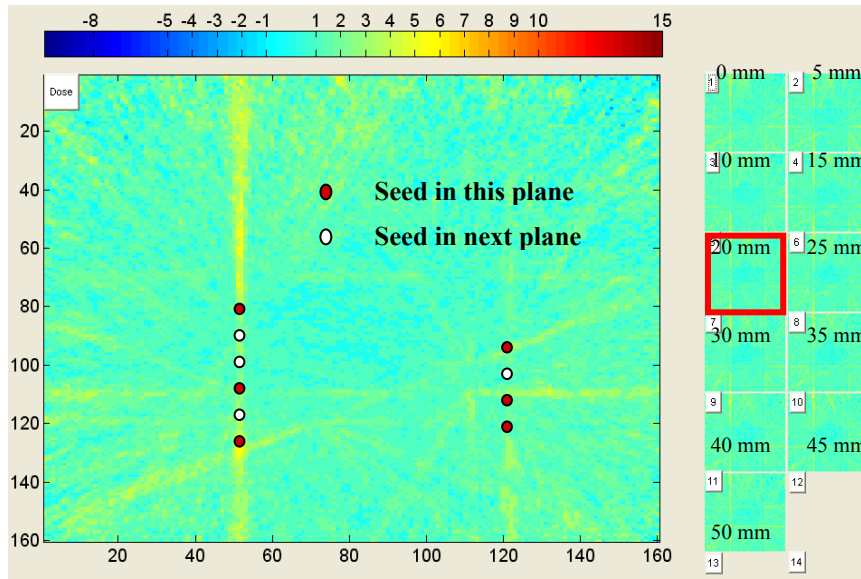


Figure. 4. Dose difference in% between MCOSSIT & FMCT ($\frac{MCOSSIT - FMCT}{FMCT} \%$) for a real patient illustrated in several plans taken each 5 mm (Interseed effect correct as much as possible to be less than 3%). Plane with red square is shown on the left side.

3.4 Comparison of DVH; influence of the use of the 1D & 2D anisotropy functions (TG-43U1 protocol)

The impact on the DVH (Dose Volume Histogram), in particular, for prostate organ was studied. For this goal, the prostate was modeled using US (ultra sound) images taken every 5 mm. The volumes were reconstructed using software developed at our institute. With this software, the prostate volume data obtained was comparable with one obtained from VariSeedTM for the same US images.

DVH comparison was performed for FMCT, MCOSSIT and MCOSSIT calculations and compared to TG-43U1 calculations at the level of D_{98} (Dose covered 98% of volume), D_{90} (Dose covered 90% of volume), minimum dose (D_{min}) and average dose (D_{mean}) (see Figure 5 for one typical patient implant). Moreover differences due to the 1D and 2D approximations of the anisotropy function in the TG-43U1 formalism are also presented.

Comparison between FMCT and MCOSSIT results in the interseed effect. Calculations for 8 patients implanted by IsoSeed seeds show an overestimation for D_{90} , D_{98} , D_{min} and D_{mean} with an average of 2%. D_{90} is the key factor that can be correlated with the probability of biochemical control (Stock *et al.* 1998). For the 8 patients studied, it varies from 1% up to 2.5%. D_{98} and D_{min} indicate the value and the volume of cold points used also for prescription. The values obtained for the 8 patients are ranging between -0.5% to 2% and -2% up to 10.3%, respectively. D_{mean} reflects the average dose delivered to prostate; this parameter is varying between 3% and 6.5%.

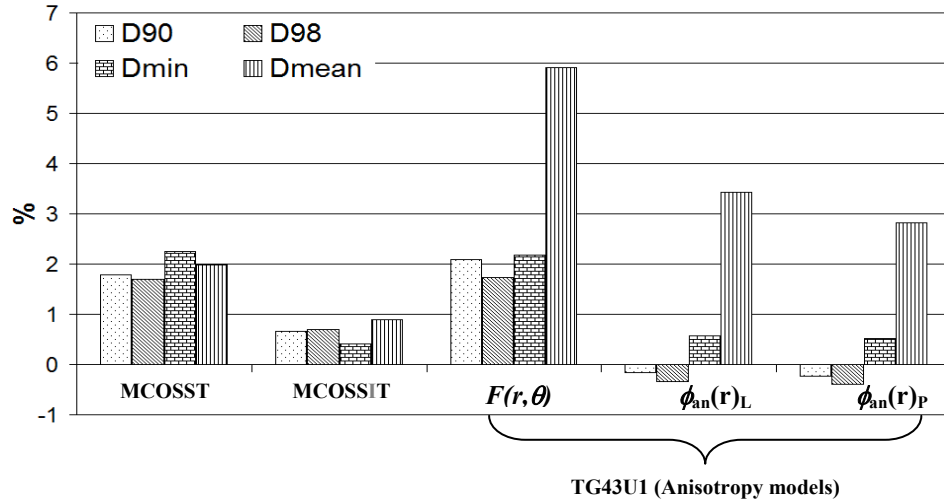


Figure. 5. D_{98} , D_{90} , D_{min} and D_{mean} difference in% between FMCT ($\frac{Technique - FMCT}{FMCT} \%$) and the other techniques (MC techniques & TG-43U1 approximations) for prostate (patient 1).

Similarly, Chibani O. and Williamson J. F estimated the interseed effect on D_{90} , D_{80} and D_{100} from 3% up to 5% depending on density of seeds per unity of volume (seed/cm³).

Consequently, DVHs do only indicate a dose average of the interseed effect. The influence on dose distributions is more clearly illustrated in figure 6, presenting a typical planar dose distribution with and without interseed effect. In fact a clear difference is observed at the level of the 116Gy isodose being more curved inside the prostate when the interseed effect is taken into account. Also this figure illustrates the same isodoses calculated with MCOSSIT, being close to the one calculated with FMCT, indicating that the correction method takes into account the interseed effect.

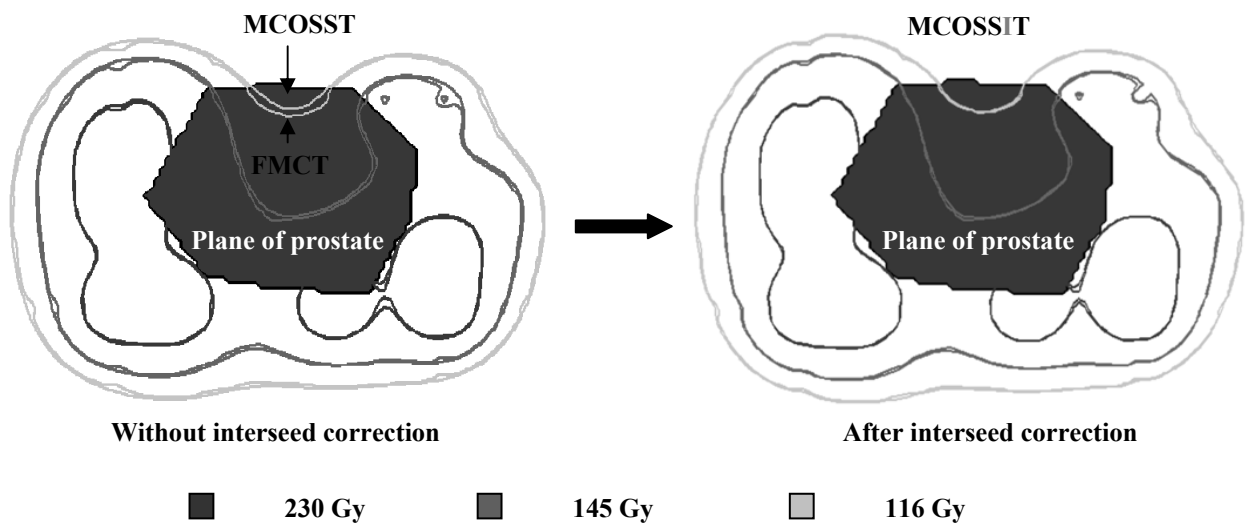


Figure. 6. Impact of interseed on isodose in plane before and after applying interseed correction: left hand side the isodoses for MCOOST and FMCT, illustrating the difference at the level of the 116Gy isodose; right hand side the isodoses calculated with MCOSSIT and compared to FMCT.

In order to illustrate the effect of the 1D and 2D anisotropy approximations in TG-43U1, D_{90} , D_{98} , $D_{\min}$ and D_{mean} calculations are presented for a second patient in figure 7. In general, TG-43U1 approximations will overestimate prostate average dose due to the over dosage near to the sources (see section 3.1.). 2D anisotropy function is in principle the most accurate approximation however from figure 5 (patient 1) an overestimation with more than 5% of the average dose is observed when comparing with FMCT. Figure 5 shows that the calculation using the 1D anisotropy function is closer to FMCT than the calculation using the 2D anisotropy function. This seems to be a contradictory observation. The difference, however between D_{90} , D_{98} , $D_{\min}$ and D_{mean} calculated by 2D approximation and FMCT is consistent for all patients, which is not the case when using 1D approximation. For example, figure 7 illustrates a difference for the 1D approximation at the level of the minimum dose of more than 10% when compared to FMCT. This was not seen in patient 1 (figure 5). To understand this inconsistency due to 1D approximation, we compared dose distribution calculated by 2D and 1D approximations (figure 8). We can see that 1D approximation overestimates the dose for about of 15% in planes situated at the two ends of implant containing no implanted seeds while it underestimates dose about 5% in the other planes. This yields a compensating effect in the resulting DVH's. These over dosage and under dosage must be attributed to an averaging effect between 2D and 1D anisotropy function.

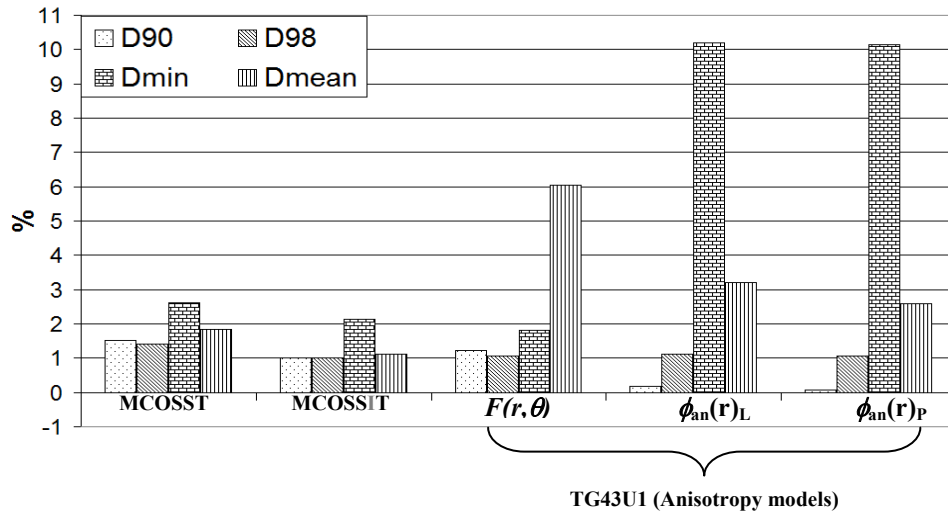


Figure. 7. D_{98} , D_{90} , $D_{\min}$ and D_{mean} difference in% between FMCT ($\frac{\text{Technique} - \text{FMCT}}{\text{FMCT}} \%$) and the other techniques (MC techniques & TG-43U1 approximations) for prostate (patient 2).

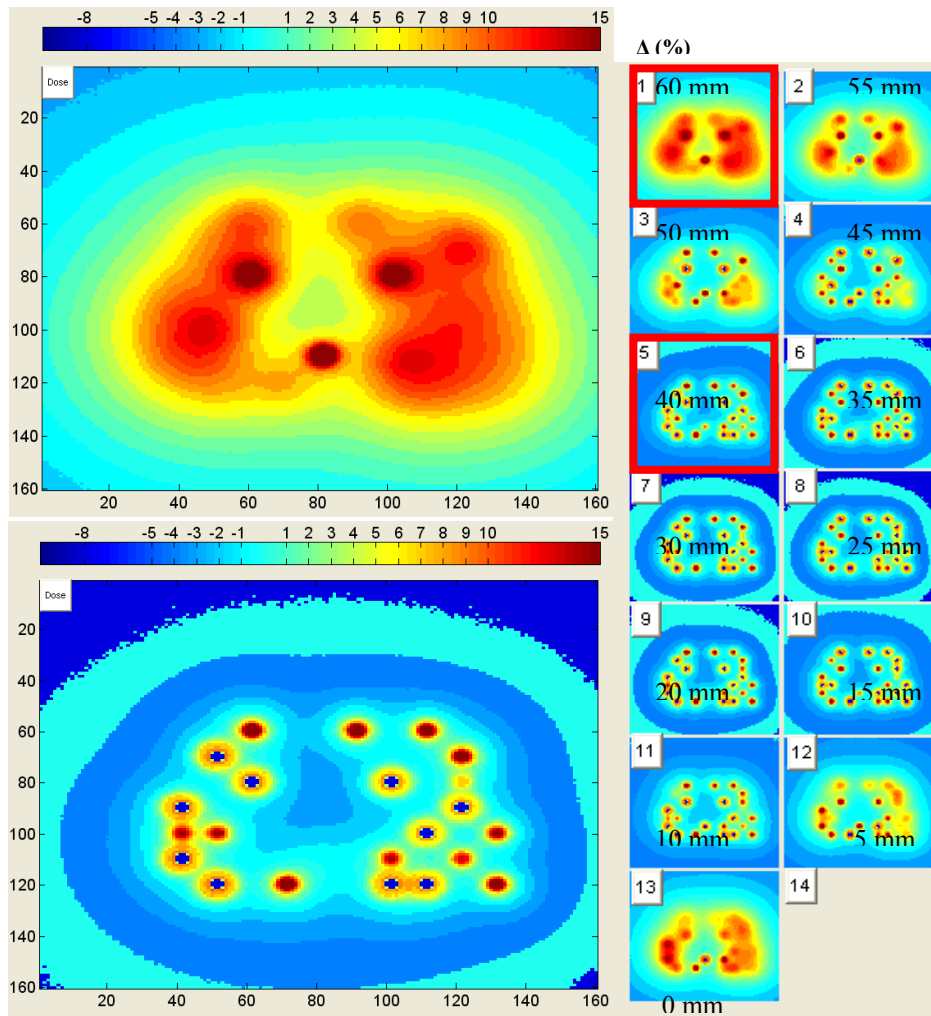


Figure. 8. Dose difference in % between 2D & 1D anisotropy function ($\frac{1D - 2D}{1D} \%$) in a real patient illustrated in several plans taken each 5 mm. planes with red squares are showed on the left side to show the limitation of 1D approximation.

4. Discussion

It was shown that the interseed effect on planar dose distribution varies from 4% up to 10%, especially behind coplanar/aligned seeds. This is comparable with published data by Chibani O. and Williamson J. F. They explained that dose errors due to the absence of interseed attenuation effect for Symmetra seed vary between 2% and 10% with an average value of 4%. The clinical influence of cold spots on the treatment quality is unknown, they may lead to prostate cancer recurrence. Therefore, when observing the 2D multi-planar difference maps, we would recommend avoiding as much as possible coplanar/aligned seeds for clinical applications.

In 1998, Stock et al. at Mount Sinai Hospital published the first report that quantitatively linked treatment outcome to implant quality. The key factor that correlated with probability of biochemical control was the D_{90} . It was shown that where the D_{90} exceeded 140 Gy (pre TG-43), biochemical control rates of 80% to 90% were achieved, whereas those patients with a D_{90} of less than 140 Gy had a 40% to 50% biochemical relapse rate by 5 years. Moreover, the effect on D_{90} is ranging from 5.8% to 12.8% when comparing clinically

approved TG-43 and MC simulations in prostate tissue (interseed effect and tissue heterogeneity) was shown by Carrier and Beaulieu in 2006.

Interseed effect on DVHs was performed at the level of the D_{90} , D_{98} , $D_{\min}$ and D_{mean} values. These values are overestimated with an average of 2% (~ 5 Gy comparing to prescribed dose of 145 Gy) in this study. Published data show that D_{90} , D_{80} and D_{100} vary from 3% up to 5% depending on density of seeds per unity of volume (seed/cm³) (Chibani O. and Williamson J. F, 2005). Therefore, attention has to be paid during implant to avoid as much as possible dose reductions due to the interseed effect.

Anisotropy approximations in the TG-43U1 formalism can have a significant effect on the dosimetric quality of prostate brachytherapy implants (over dosage of 5% for average dose) especially when using 1D anisotropy function. It was shown that the use of the 1D approximation might lead to inconsistent results at the level at least of $D_{\min}$ comparing to the 2D anisotropy function. Difference between the both approximations seems more important in planar dose distribution at the level of the 116Gy isodose position as was seen in figure 6. Such differences, ranging between -5% up to 15% are not easily discerned by DVHs. Although in first view the 1D approximation seems to be closer to our MC results, we could recommend using 2D anisotropy function in preference 1D anisotropy function as the first one yields much more consistent results. A comparable result was also reported by Lindsay et al. (2000).

Overall, cold spots may lead to prostate cancer recurrence while hot spots may lead to damage of the rectum or bladder. If a “cold spot” were judged (which is not precisely known using TG-43 clinical application) to be occurring in a clinically significant location and did not resolve after repeat CT dosimetry analysis, additional radiation treatment might be contemplated to correct this, particularly if the patient had an intermediate or unfavorable cancer characteristic. Therefore, the main reason for developing a fast Monte Carlo technique such as MCOSSIT is to account in a rigorous way, on line, for the effects of interseed attenuation and the influence of the different approximations of TG-43U1 protocol (e.g. 1D and 2D anisotropy) on the planned and delivered dose to the prostate and organs at risk.

5. Conclusion

This study showed that for clinical applications TG-43 systematically overestimates the deposited dose in the prostate. Due to the interseed effect, planar dose distribution is overestimated especially behind coplanar/aligned seeds up to 10%. D_{90} and D_{98} are overestimated by 2% while average dose is systematically overestimated more than 5% and minimum dose, in some cases, more than 10%.

Because of the significant overestimation and the variability among the patients, dose–outcome studies generated with TG-43–based dosimetry can potentially be problematic. MC based calculations yield much more accurate results. Calculation of a full MC based plan still is time consuming (+/- 48h) however our proposal (MCOSSIT) is a new, fast (2 sec) and accurate dosimetric technique for real-time permanent brachytherapy of the prostate, based on MC calculations (MCNP5). It can be used for all types of seeds and takes into account the interseed effect.

Although the long calculation time spent by FMCT it will be a good application for the post implant calculations, especially when our model includes the tissue heterogeneities.

With respect to the use of TG-43U1 approximations, the use of the 2D anisotropy function is preferred to the 1D anisotropy function yielding more consistent results for the 8 patients studied. The significant overestimation, the variability among the patients and dose–outcome inconsistent generated by TG-43U1 calculation, require a new and accurate dosimetric system to be able to evaluate these effects for real permanent prostate implants.

Therefore, MCOSSIT based on a Monte Carlo dose calculation engine has been developed for real-time dosimetry, taking into account the interseed effect. It is a fast and precise algorithm, which can be used on line.

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Chapter 7

Publication 4

European Society for Therapeutic Radiology and Oncology, September 2010

Is 1D anisotropy function recommended by TG-43U1 protocol good enough for clinical brachytherapy dosimetry?

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Abstract

Purpose

The effect of the anisotropy on dose distributions for real permanent prostate implants with ¹²⁵I seeds has been evaluated and compared with Monte Carlo (MC) calculations for 8 real patients. A dose overestimation and the variability among the patients have been observed that can lead to variations in dose–outcome studies.

Materials and Methods

Dose distribution of the prostate implants was calculated using MCNP5 code. First, the Monte Carlo model for a single seed “IsoSeed” (Bebig) was previously carefully validated by comparing the radial dose, anisotropy functions and dose rate constant with published data by Hedtj rn *et al.* (2000). A 3D voxel matrix of 0.5×0.5×5 mm was chosen to calculate the 3D dose distribution. TG43U1 approximations for 8 real patients implanted with “IsoSeed” seeds at our hospital was benchmarked by the 3D MC calculation. Thereafter, a DVH comparison between 2D and 1D approximation was performed for prostate, urethra and rectum for 20 patients

Results and discussion

In general, 2D approximation is the most accurate compared to full MC. It was benchmarked by the 3D MC calculation for 8 patients. Differences of 6% up to 10% due to interseed effect were observed whereas, 2D approximation does not take this effect into account. A comparison of DVHs for 1D & 2D anisotropy functions is presented in figure 1 for 20 prostates implants.

D_{mean} , D_{90} and D_{98} are underestimated, in average, by about 3%, 1.5% and 1%, while 1D anisotropy function leads to inconsistent results for D_{min} and D_{100} for prostate.

To understand this inconsistency, dose distribution calculated by 2D and 1D anisotropy functions were compared in different planes. It can be observed that 1D approximation overestimates the dose for about of 13% in planes situated at the two ends of implant containing no implanted seeds while it underestimates dose about 5% in the other planes (figure 2). This yields a compensating effect in the resulting DVH’s. These over-dosage and under-dosage must be attributed to an averaging effect between 2D and 1D anisotropy function.

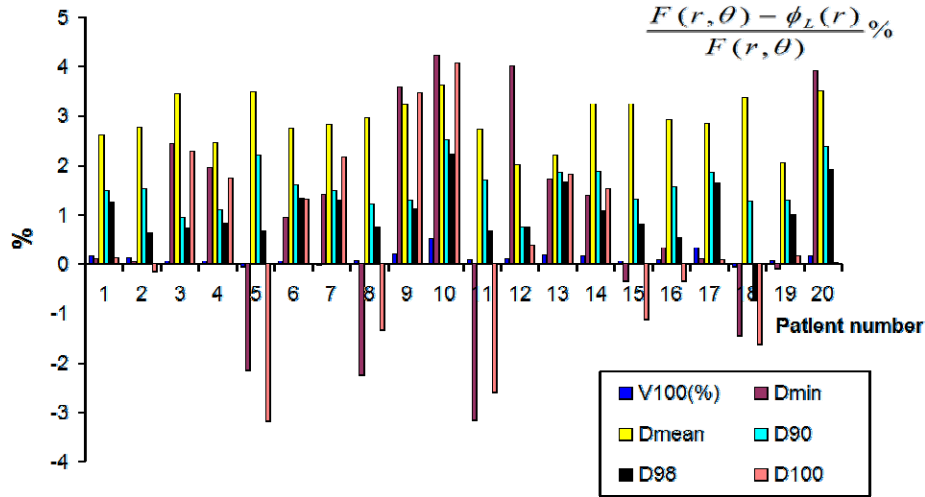


Figure 1. A DVHs comparison between the use of 1D & 2D anisotropy functions for 20 prostates implants.

We present the effect of the use of the 1D anisotropy function (Line factor $\phi_{L(r)}$ and point factor $\phi_{P(r)}$) on D_{98} , $D_{\min}$, D_{90} (for prostate), $D_{\max}$ (for urethra) and V_{100} (for rectum) these being the main parameters used during optimization of the implants. For the prostate contour it can be noticed that the effect of 1D approximation on D_{98} and $D_{\min}$ varies from one patient to the other (figure 3). This is due to the several factors, for example, prostate volume, number of seeds and seeds positions relative to prostate...etc. Moreover, D_{90} is always underestimated by 1D approximation whereas for 70% of the patients D_{90} exceeds 185 Gy. For the urethra, 1D approximation underestimates the $D_{\max}$ for 60% of the patients, their maximum dose for the urethra exceeds the limits (figure 3). Finally, 1D approximation underestimates V_{100} about 50% less than 2D approximation.

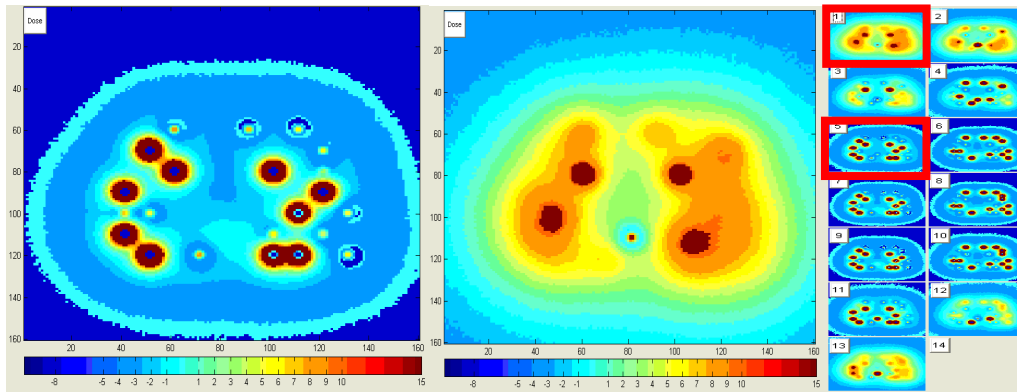


Figure 2. Dose difference in % between 2D & 1D anisotropy function in real patient showed in several plans taken each 5 mm. Planes with red squares show differences ranging between -5% (on the left side) and 13 % (on the right one)

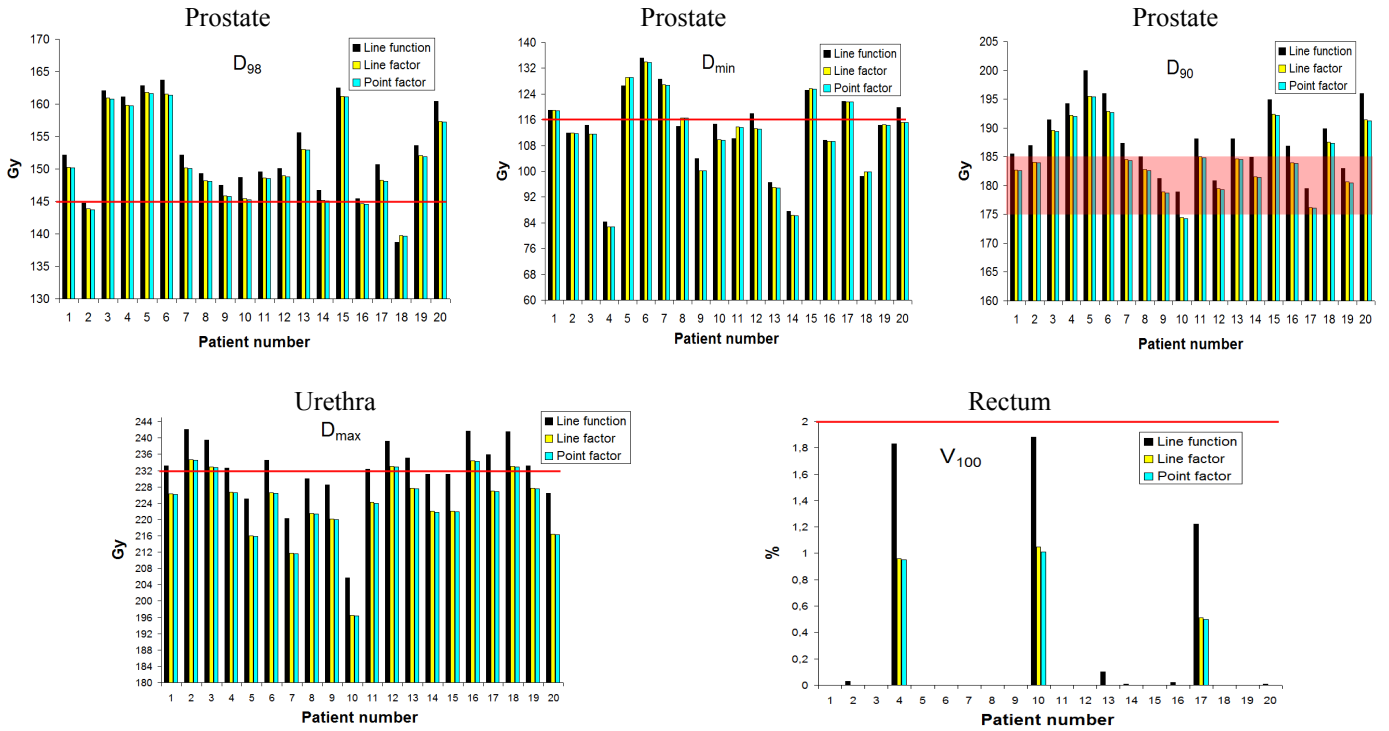


Figure 3. D_{98} , D_{min} , D_{90} (for prostate), D_{max} (for urethra) and V_{100} (for rectum) presented for 20 prostate implants. Comparison between the use of 2D anisotropy function (Line function $F(r,\theta)$) and 1D anisotropy function (Line factor $\phi_L(r)$ and point factor $\phi_P(r)$).

4. Conclusion: For TG43U1 calculations, the use of the 2D anisotropy function is preferred to the 1D anisotropy function as this approximation yields more consistent results for the 20 patients studied. The observed overestimation and the variability among the patients can influence dose–outcome. Therefore, a Monte Carlo dose calculation engine is useful as well for benchmarking studies as for evaluating the effect of the use of different anisotropy approximations in the TG43U1 formalism.

Reference

Hedtj rn H., Carlsson G. A. and Williamson J. F., ‘‘Monte Carlo-aided dosimetry of the symmetra model I25.S06 I–25, interstitial brachytherapy seed,’’ Med. Phys. 27(5), 1076–1084 (2000).

Chapter 8

Publication 5

Evaluation of the Dose Distribution Gradient in the Close Vicinity of Brachytherapy Seeds Using Electron Paramagnetic Resonance Imaging

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Electron paramagnetic resonance (EPR) spectroscopy has been successfully employed to determine radiation dose using alanine. The EPR signal intensity reflects the number of stable free radicals produced, and provides a quantitative measurement of the absorbed dose. The aim of the present study was to explore whether this principle can be extended to provide information on spatial dose distribution using EPR imaging (EPRI). Lithium formate was selected because irradiation induces a single EPR line, a characteristic that is particularly convenient for imaging purposes. ¹²⁵I-brachytherapy seeds were inserted in tablets made of lithium formate. Images were acquired at 1.1 GHz. Monte Carlo (MC) calculations were used for comparison. The dose gradient can be determined using two-dimensional (2D) EPR images. Quantitative data correlated with the dose estimated by the MC simulations, although differences were observed. This study provides a first proof-of-concept that EPRI can be used to estimate the gradient dose distribution in phantoms after irradiation. Magn Reson Med 61:1225–1231, 2009. © 2009 Wiley-Liss, Inc.

Key words: EPR; free radicals; dosimetry; dose distribution; brachytherapy

Low dose rate (LDR) brachytherapy via permanently implanted Iodine-125 or Palladium-103 seeds (~30 keV photons with a dose-reduction factor of about 10 for 1 cm of tissue) is frequently used to treat tumors, prostate cancer in particular, but also eye tumors. The advantages of low energy are that radioprotection for medical workers is easier and there is a confined volume of radiation dose from the implant. When performing a clinical treatment, it is mandatory to very precisely report various parameters that can impact patient treatment outcome. These parameters include the prescribed dose, the doses received by various organs, and the degree of dose uniformity that will

be achieved on the target and in the surrounding healthy tissues. It is clear that to achieve good precision in the treatment itself, the source dosimetry must be established with a maximum of accuracy. As dosimetric characteristics at these low energies are very dependent on the internal design of the implant, any new source design must undergo detailed evaluation (1). Generally, dosimetric characteristics are determined using Monte Carlo (MC) simulations. However, such calculations can give different results depending on the MC calculation codes used. These can differ in their basic data or in the approximations made in the underlying physics (2). Experimentally, dosimetry could be performed using thermoluminescent (TLD) dosimeters. However, to obtain data with a high spatial resolution is still challenging because of the large gradient of dose and the very LDR. In this context, there is still a need to develop experimental methods that allow estimation of the dose deposited in the proximity of brachytherapy seeds. The present study attempted to develop a new method based on the reconstruction of dose using electron paramagnetic resonance (EPR) imaging (EPRI).

EPR dosimetry (3) is the determination of dose by measuring radiation-induced free radicals in irradiated materials using EPR. The EPR signal intensity directly reflects the number of stable free radicals produced in a solid matrix, providing a quantitative measurement of the absorbed dose. The major advantages of an EPR dosimeter are its small physical size and that no cables or auxiliary equipment are required during the measurements. Further, the nondestructive readout allows repeated calibration and accumulated doses to be measured. Alanine is the best known dosimeter material, already suggested for this purpose more than 40 years ago and now formally accepted by the International Atomic Energy Agency (IAEA) as a standard for high-dose (0.1–100 kGy) and transfer dosimetry. The alanine response varies little with radiation energy, dose rate, temperature, and time between irradiation and readout. In brachytherapy, alanine pellets have been used to determine the dose at discrete points around ¹⁹²Ir and ¹³⁷Cs sources (4–6).

Formates (salts of formic acid, HCOOH) were suggested as alternatives to alanine a few years ago (7,8). Lithium formate shows great potential for accurately determining low radiation doses (9). Lithium formate is about six times more sensitive than alanine, shows a linear dose response up to 1 kGy, and is close to water in terms of absorption properties and scattering of radiation. It also has a high resistance to fading if it is kept in correct conditions (low humidity and dark) after irradiation. Moreover, the EPR

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spectrum of irradiated polycrystalline lithium formate consists of a single EPR line. This latter characteristic is particularly useful for imaging purpose with EPRI.

Using appropriate field gradients, EPRI can map the distribution of free radicals inside samples in two or three dimensions. This method is analogous to MRI, except that the generated image represents the distribution of electron spins instead of nuclear spins. EPRI has been used *in vivo* to investigate the distribution of stable free radicals, or to indirectly map important physiological parameters, such as oxygen (10), nitric oxide (11), or redox status (12). In the field of dosimetry, EPRI has been used to retrospectively reconstruct the dose after bone irradiation (13). To our knowledge, the present study is the first attempt to use EPRI as a tool to experimentally evaluate the spatial dose distribution and to apply proof-of-concept to the reconstruction of the gradient of doses surrounding brachytherapy seeds. For this purpose, we developed large cylindrical tablets of lithium formate, in which holes were drilled to allow the insertion of brachytherapy ^{125}I seeds. EPR images of pellets were obtained after irradiation by one or two seeds. Experimental data were compared to MC simulations using MCNP version 4 code (MCNP-4C) (14,15). MC simulation is a statistical solution for complex mathematical problems that uses random sampling. MC simulation of particle transport has become an essential tool for dose calculation in complex medical physics situations, as these calculations are a faithful simulation of physical reality, particularly in situations where measurements are difficult or impossible (16). MCNP, which stands for MC N-Particles, and its precursors, were developed at Los Alamos National Laboratory (Los Alamos, NM, USA) to analyze problems related to nuclear reactors. MCNP-4C is a general-purpose radiation transport code that can be used for coupled neutron/photon/electron transport (17). The code can handle any arbitrary three-dimensional (3D) configuration.

The spatial resolution of EPR images was assessed with a semiempiric method from the edge spread function (ESF).

MATERIALS AND METHODS

Phantoms

Cylindrical tablets (diameter = 22 mm, height = 10 mm) of polycrystalline lithium formate monohydrate (Aldrich, Steinheim, Germany) were made using a tablet press (type AC27, 50 kg/cm²; Ateliers Courtoy, Halle, Belgium). Lithium formate forms strong pellets without need of additional binding material. For brachytherapy studies using one seed, one hole (1.5-mm in diameter) was drilled in the center of the tablet to introduce the radioactive source. For studies with two brachytherapy seeds, two holes (8 mm between centers) were drilled in the tablets.

Irradiation

Some tablets were externally irradiated using an X-ray beam (Philips 250 RT, 250 kV) with a dose rate of 0.85 Gy/min. The samples were irradiated at different doses (25, 50, 100, 200, and 300 Gy) to study the linearity of response. Some of these samples were partially protected

with several layers of lead (triangular shape) to visualize the different nonirradiated shapes. For brachytherapy studies, Iodine-125 seeds (Oncoseed model; GE Healthcare) were used. These seeds consist of a welded titanium capsule (diameter = 0.8 mm, length = 4.5 mm) containing iodine-125 adsorbed onto a silver rod (diameter = 0.5 mm, length = 3 mm). The tablets were irradiated for 2 weeks at room temperature, protected from light and humidity, and kept in the same conditions before being imaged.

EPR Imaging

Since we were interested in radial dosimetry in the phantom, 2D images were acquired along the source perpendicular axis. This allows to build radial dosimetry curves as is commonly performed in similar studies using other methodologies such as film dosimetry. No other 2D orientation nor 3D images were necessary for this work.

The EPR images were acquired at room temperature using an EPR Elexsys E540 System with three orthogonal water-cooled cylindrical gradient coils. The irradiated pellets were placed in the center of an L-Band EPR cylindrical resonator (ER 6502 BC, 23-mm in diameter) operating at 1.1 GHz. The samples were positioned in the EPR resonator with the symmetry axis along the central axis of the cavity. The usual EPRI acquisition parameters were as follows: modulation frequency = 100 kHz, microwave power = 45 mW, modulation amplitude = 3.35 G, 512 points, 30 scans of 5.24 s each, pixel size = 0.5 mm, and spatial window = 30 mm (field of view). The magnitude of the magnetic field gradient was 300 mT/m. 2D images were reconstructed on a 128 × 128 matrix by filtered back-projection using a Shepp-Logan filter (18,19). Before reconstruction, each projection was deconvolved using fast Fourier transform with the measured zero-gradient spectrum to improve image resolution. To reduce noise amplification and avoid possible division by zero at high frequencies, a low-pass filter was used. The deconvolution parameters, including the maximum cutoff frequency and the width of the window in the Fourier space, were set up after viewing the shape of all projections. Data were smoothed using either a Fermi-Dirac or a Gaussian filter.

Spectral deconvolution and filtered backprojection were performed using the Xepi software package (Bruker).

MC Simulations

MCNP-4C was used to calculate the dose distribution around the source. The detailed photon physics option of MCNP was used in this work. This option includes Compton scattering, Rayleigh scattering, and photoelectric effect with emission of fluorescence photons. The cross-section data and the form factors for coherent and incoherent photon scattering were taken from Storm and Israel (14) or from the Evaluated Nuclear Data File (ENDF) (15) while the fluorescence data were taken from Everett and Cashwell (20). A new library of photoelectric cross-sections updated by Bohm et al. (21) was also used. Spheres with a diameter of 0.1 mm defined the acquisition cells (22) at different distances, from -1.1 cm to 1.1 cm. Dose calculations were obtained using the F6 tally card in the MCNP (describing the mean energy deposition per cell in MeV/g),

assuming that electron transport can be neglected at this low photon energy and, consequently, that all electron energy is deposited locally. We modeled the source using data from the literature, and the dosimetric parameters were compared to existing publications to validate our model.

Finally, the number (one billion) of simulation histories was chosen to reduce the maximum statistical uncertainty in the MC calculations to about 2% for a volume element situated at 1.1 cm from the source.

Resolution—ESF Determination

Two different methods were used to assess the resolution of the imaging system.

In the first set of experiments, holes of different diameters (ranging from 5 mm to 2 mm) were drilled in the center of tablets that were subsequently irradiated at 300 Gy with a 6-MeV X-ray beam generated by an Elekta SL75/5 Linac linear accelerator. Image acquisition was performed using the same settings as described in the EPR Imaging section above. The evaluation of the resolution was carried out by visual estimation of images. More formally, the signal falloff in the middle of each image was also measured from the intensity curve using the Xepr software from Bruker.

In the second experiment, the spatial resolution was obtained in terms of the ESF. The ESF was determined following a procedure modified from the classical method used in MRI (23) and from the work of Ahn and Halpern (24–26).

Briefly, a parallelepiped phantom was filled with irradiated (300 Gy) lithium formate. The size of the phantom was 1.0 cm × 1.0 cm × 4.0 cm. A 2D image of the phantom was reconstructed. The signal along a line perpendicular to the edge of the phantom was extracted from the image and the derivative was calculated. A nine-point smoothing algorithm was used to obtain the derivative curve, which was then fitted by a Gaussian function:

$$f(x) = \frac{1}{\sigma \sqrt{2\pi}} e^{-\frac{(x-\mu)^2}{2\sigma^2}}. \quad [1]$$

From the computed σ values, the full-width at half-maximum (FWHM) of the Gaussian curve was calculated from the following equation:

$$\text{FWHM} = 2. \sigma \sqrt{2 \ln 2}. \quad [2]$$

All calculations and fitting were carried out using Prism 4 (GraphPad Software, Inc., La Jolla, CA, USA).

RESULTS

The EPR spectrum of irradiated $\text{HCO}_2\text{Li} \times \text{H}_2\text{O}$ presented a single-line that was attributed to CO_2^- radicals (Fig. 1a). The EPR signal intensity increased linearly with the dose of external beam irradiation (Fig. 1b), as previously shown (8,9), making this material suitable for dosimetry purposes. Using appropriate field gradients, it was possible to map the distribution of the radiation-induced free radicals

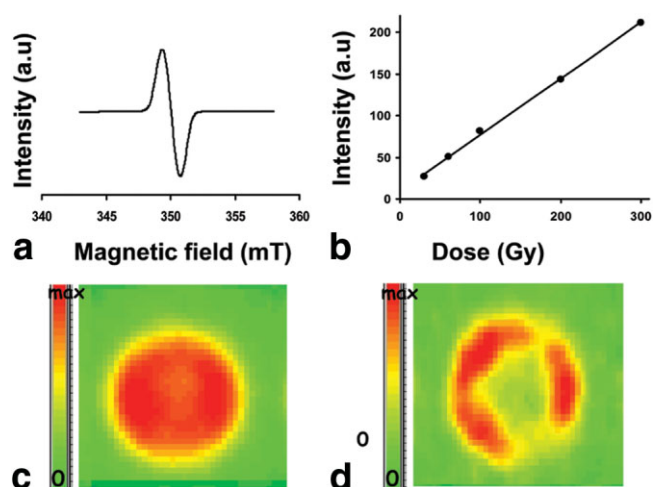


FIG. 1. EPR spectroscopy and imaging on lithium formate samples. **a:** EPR spectrum of externally irradiated lithium formate recorded at 9 GHz. **b:** Dose-response relationship. **c:** EPR image of an externally irradiated tablet of lithium formate. **d:** EPR image of an externally irradiated pellet partly protected by a triangle lead shielding.

in the tablets of lithium formate. The amplitude maps (reflecting the EPR signal intensity) of tablets irradiated by an external source of X-rays are shown in Fig. 1c and d, corresponding to tablets irradiated without lead protection and with a triangular lead protection, respectively. The irradiated zones can be easily visualized in the EPR images, which clearly reflect the known shape and dimensions of the object. The signal is homogenous in each considered zone.

Figure 2a shows the 2D projection of EPR signal intensity surrounding one ^{125}I brachytherapy seed. The shape of the lithium formate tablet is indicated by the black circle. As the EPR signal is proportional to the radiation dose, its variation, depicted by the color code, also reflects the variation of the dose distribution around the seed. Figure 2b is the corresponding wire-frame plot. This is a perspective view of the signal intensity variation inside the phantom. The intensity of the EPR signal reaches its maximum in the middle of the sample, where the seed was inserted, and decreases with distance toward the edges. The radial dose profile, normalized to its maximum, was obtained along the source perpendicular axis and is shown in Fig. 2c. The dose was measured approximately every 1 mm along the axis passing through the center of the tablet.

Figure 3a shows the dose distribution, estimated by the EPR signal intensity, around two ^{125}I radioactive seeds with the same activity, inserted in the phantom lithium formate dosimeter. The distance between two seeds, as measured on the image, is 10 mm. Figure 3b and c present perspective volumes of the doses, and estimated dose distributions (from EPR data) around the seeds.

In Fig. 4, the results of the MC calculations for one seed (Fig. 4a) and two seeds (Fig. 4b) are compared to the experimental data obtained by EPRI. For convenient comparison of EPR and MC curves, data were normalized to the values observed at 1 mm from the center. The first data point of the MC simulation was calculated at 1 mm from the center of the source because: 1) the seed itself was

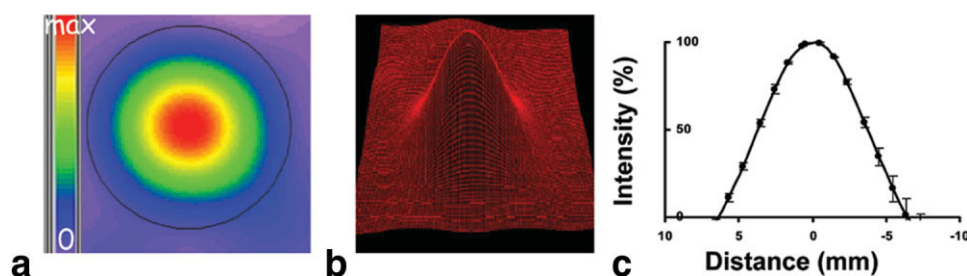


FIG. 2. EPR data obtained from a tablet of lithium formate irradiated by the insertion of one ^{125}I -iodine brachytherapy seed in the center of the tablet. **a**: 2D EPR image of the signal intensity. The color code directly reflects the gradient of dose received by this radiosensitive material. **b**: Wire-frame plot (or perspective view) of the signal intensity variation around the seed. **c**: Dose profile along the source perpendicular axis (error bars indicate mean $\pm$ standard deviation, $N = 3$).

0.8 mm wide, so it would not have made sense to compute a dose inside the source itself; and 2) the hole drilled to allow the insertion of the seed was 1.5 mm wide, so (in our model) the first meaningful dose was expected at 1 mm from the center of the phantom.

Although EPRI data generally correlated with MC simulation, several differences between these two curves can be observed.

First, the shape of the curves is different, the MC curve being narrower than the EPRI one, with a FWHM of 3.5 mm (vs. 7.2 mm for EPRI). The slope of the MC curve is very steep in the immediate vicinity of the radioactive source, becoming flatter with distance. According to the MC curve, the dose deposition at 1.7 mm is 50% and at 5.2 mm it is 90%. EPRI is a symmetric Gaussian-like curve, with 50% of dose deposition at about 3.9 mm and 90% at 5.8 mm (Fig. 4a).

Second, on the EPRI curve (Fig. 4b) it can be seen that the two maxima values are positioned at -5 mm and $+5$ mm (total distance between maxima is 10 mm) whereas the true location is -4 mm and $+4$ mm, respectively (real physical distance is 8.0 mm). This results in a shift of the two maxima points between the experimental and calculated curves.

Third, EPRI data are present even in areas where no signal would be expected, for example between -0.75 mm and $+0.75$ mm (Fig. 4a); these areas correspond to the holes drilled to insert the radioactive sources, and conse-

quently they do not contain any radiosensitive material (see Discussion).

Figure 5 shows the variation of the signal in externally irradiated phantoms with a central hole of decreasing size. This allows a semiquantitative estimation of the resolution based on a visual estimation of images. Calculation of signal intensity falloff in the center of the image gives a more formal approach. For a hole of 5 mm in diameter, the signal dip on the corresponding image is 93%, the two edges of the hole being almost perfectly separated. When the size of the hole decreases, the dip decreases accordingly and falls to 46% for a 2-mm hole.

Figure 6 shows the signal intensity response along a line perpendicular to the edge of the parallelepipedic phantom used for ESF measurement (black boxes, Fig. 6b), and its derivative (black curve, Fig. 6b and c). The first half of the curve was used for the Gaussian fitting (Fig. 6d). The σ value computed for the Gaussian fit of ESF was 1.879 ± 0.019 . The goodness of fit (r^2) was 0.993. The corresponding calculated FWHM was 4.4 mm.

DISCUSSION

Each radiation therapy intervention requires an accurate a priori estimation of the dose that will be delivered to the tumor and to the surrounding healthy tissues. In brachytherapy, estimation of the dose near the radioactive source is not easy. Estimation of the dose using MC calculations

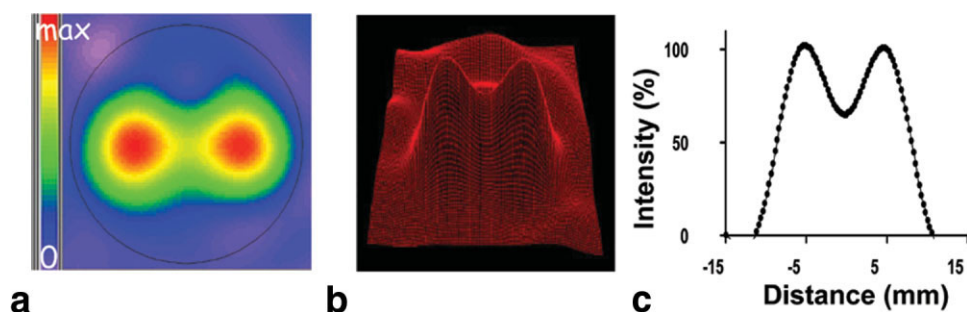


FIG. 3. EPR data obtained from a tablet of lithium formate irradiated by the insertion of two ^{125}I -iodine brachytherapy seeds. **a**: 2D EPR image of the signal intensity. The color code directly reflects the gradient of dose received by this radiosensitive material. **b**: Wire-frame plot (or perspective view) of the signal intensity variation around the seed. **c**: Distribution of dose in the plane perpendicular to the long axis of the seed, crossing the seeds in their center. The distance between the two maxima is 10 mm.

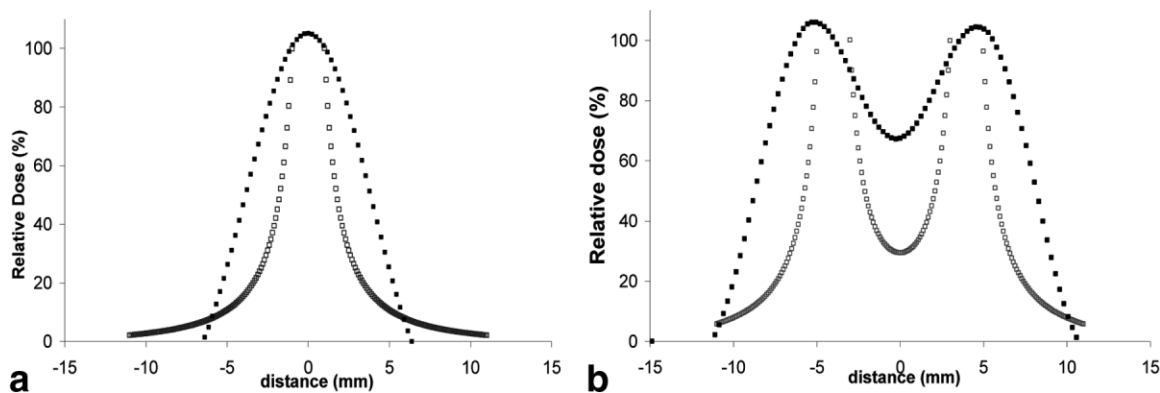


FIG. 4. **a:** Comparison of the dose distribution profiles in a tablet irradiated by one ^{125}I seed. EPRI data (black boxes) vs. Monte Carlo simulation (open boxes). **b:** Comparison of the dose distribution profiles in a tablet irradiated by two ^{125}I seeds. EPRI data (black boxes) vs. Monte Carlo simulation (open boxes).

in the close vicinity of the seeds (<1 cm) is dependent on the codes used and the underlying physics approximations. However, these estimations are particularly important for treatment planning and clinical outcome. Moreover, recent data showed that the evolution of the tumor microenvironment during brachytherapy is strongly dependent on the distance (in the first millimeters) between the irradiation seeds and the tumor tissue (27). In this work, we suggest a new experimental method based on the EPR imaging of free radicals induced by the irradiation in a solid matrix made of a radiosensitive material. Overall, the method offers linearity of response with increasing doses, high sensitivity, and reproducible homogeneity of signal in areas irradiated at the same dose.

Nevertheless, several differences are observed between EPRI experimental and MC simulated data. EPRI and MC intensity profiles have different shapes, the EPRI curve being broader than the MC curve. It is likely that the profile observed with the MC simulation is in closer agreement to the reality than the EPRI data. ^{125}I emits low-energy photons that are readily absorbed in tissue, and the dose

distribution pattern is expected to present a strong dose gradient. The data from the MC curve are more in agreement with this situation than those from the EPRI curve. Nevertheless, MC simulations are currently not fully validated for small distances (i.e., <5 mm).

It must also be remembered that the resolution reached with EPRI using lithium formate is definitely limited because of the rather large signal linewidth given by this particular material (~ 14 Gauss). Theoretically, the shortest distance (d) between two points that can be resolved in the EPR image is given by the equation

$$d = LW/G, \quad [3]$$

where LW (mT) is the linewidth of the EPR signal and G (mT/m) is the magnitude of the gradient field. In our study, the linewidth of the signal is 1.4 mT, gradient magnitude is 300 mT/m and applying Eq. [3] gives a theoretical resolution d of $1.4/300 = 4.7 \cdot 10^{-3}$ m (4.7 mm). The resolution calculated in terms of the ESF is 4.4 mm, and in close agreement with the theoretical value. However, it can be intuitively observed from Fig. 5 that resolution might be better. More quantitatively, the decrease in signal intensity in the dip reaches 35% for a 1-mm hole. Based on the Rayleigh's criterion used in the field of optics, Eaton et al. (28) have proposed as a working definition that two points are resolved if there is a 17% decrease in EPR signal intensity between them.

Whatever it may be, because of this finite resolution, the experimental curve is smoothed to some extent, and globally presents a different profile. This limited resolution could also explain some other features. In the “two-seed” experiment, the distance separating the sources was 8.0 mm, whereas the distance measured on the EPR image is 10 mm. This imprecision (around 1 mm for each peak position) is most probably due to the limited resolution imposed by the signal linewidth. Another unexpected result of the EPRI data is the presence of data even for points located immediately around the seeds; for example, between -0.75 and $+0.75$ mm around the zero position (Fig. 4a). A hole was drilled in that position in order to place the seed, so that there was no radiosensitive material (lithium

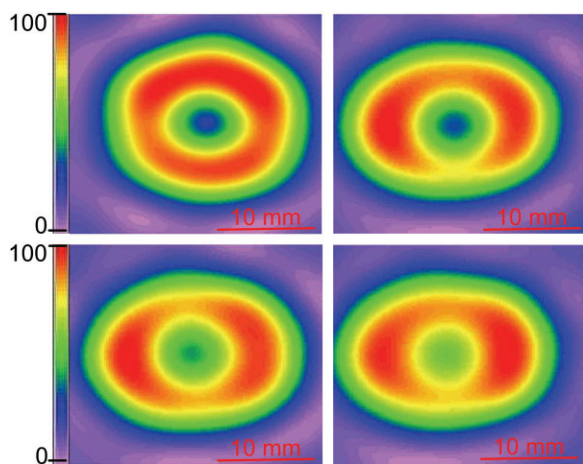


FIG. 5. 2D EPRI images of externally irradiated lithium formate phantoms. The size of the central hole is 5 mm (upper left), 4 mm (upper right), 3 mm (lower left), and 2 mm (lower right). Each image is normalized to its own maximum intensity.

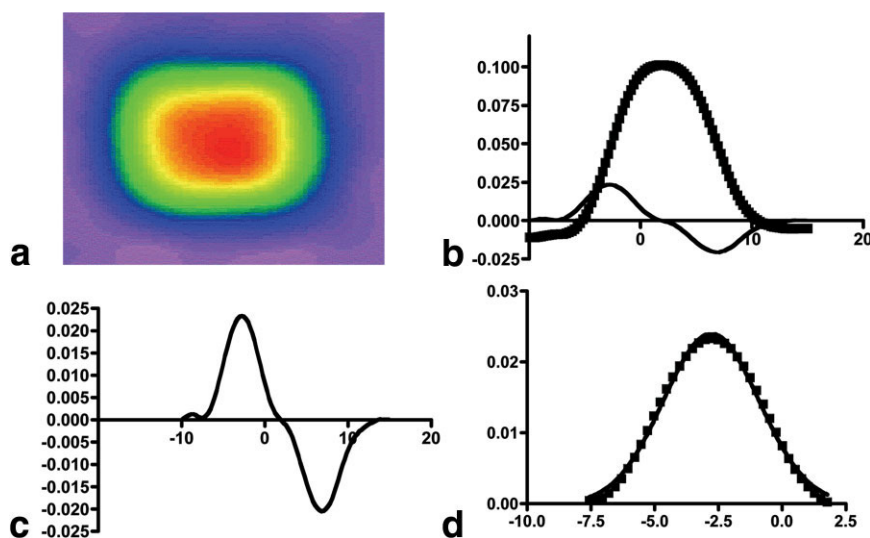


FIG. 6. **a:** 2D EPRI image using a square parallelepiped phantom. **b:** The signal response (black boxes) is obtained along a line perpendicular to the edges of the phantom. Derivative curve after smoothing (black curve). **c:** Derivative curve. **d:** First half of the derivative curve (black box) was used for Gaussian fitting (black curve).

formate) in that area. Consequently, there should not be any signal.

For this study, we used seeds containing ^{125}I . The low energy of the emitted photons is responsible for steep gradients of dose distribution. This is also the most challenging situation for EPRI since it requires accurate measurement over very small distances. Although the use of field gradients allowed evaluation of the continuous deposit of dose in the close vicinity of the seeds and the quantification of the dose gradient (Figs. 2 and 3), the resolution still requires further improvement. The accuracy of the method also has to be demonstrated.

The rationale for using lithium formate as a dosimetric material instead of alanine was based on the following considerations. First, the EPR spectrum of CO_2^- is single-lined (compared to the complex spectrum of irradiated alanine, which is not suitable for imaging purpose) (Fig. 1a), making the spectrum fairly simple and particularly convenient for imaging applications. CO_2^- radicals are also reported to be extremely stable, up to 10^9 years (29,30). Second, as the lithium formate EPR spectrum is a single line, Vestad et al. (9) reported that this material gives a higher peak-to-peak signal and is six times more sensitive than alanine. This material is also tissue equivalent: the Z_{eff} are 6.78, 7.31, and 7.51 for alanine, lithium formate, and water, respectively. Moreover, it exhibits no zero-dose signal (8,9), and shows a linear dose response (Fig. 1b). Finally, lithium formate can be pressed into tablets without the need for a binding agent. Other materials known to have a narrower EPR linewidth signal could be used but have several disadvantages, such as being very highly hygroscopic or not being commercially available. A high spatial resolution of 1 mm would be desirable for applicability of EPRI for clinical purpose, as radiotherapists need an accurate dosimetry in the range of 1 mm. Several different strategies could be considered. First of all, images could be acquired using a higher magnitude of the gradient field. With a gradient up to 2000 mT/m the theoretical resolution would be 0.7 mm. Enhancement of the resolution could also be achieved by using another radiosensitive material with a more narrow linewidth. On

our system, the maximum field gradient is 490 mT/m. In order to reach a resolution of 1 mm, the maximum linewidth of the material should be, according to Eq. [3], 0.49 mT (490 mT/m * 0.001 m). Ammonium formate gives a ~ 0.65 mT (6.5 G)-width EPR signal (8), and could be investigated as a radiosensitive material for EPR imaging allowing a better theoretical resolution. Finally, it has been demonstrated that an optimized mathematical treatment of the signal before reconstruction could also greatly improve the resolution (31).

In conclusion, the present study should be considered as a first proof-of-principle that gradients of dose in the vicinity of brachytherapy seeds can be estimated using EPRI. With the present material used as a dosimetric phantom, some discrepancies were observed between MC simulations and EPRI. This is likely due to the limited resolution imposed by the signal linewidth of the material used. Better resolution would be expected with radiosensitive materials with narrower linewidths. No gold standard method is currently available to evaluate the dose distribution pattern in areas around brachytherapy sources. As there is a growing need for new methods, EPRI appears to possess interesting characteristics that demonstrate its potential in this field of investigation. The perspectives of the present study could be the development of absolute 2D and 3D quantification of doses, for example by using internal or external references. It is also likely that the present concept could be applied to evaluate the distribution of doses in other forms of radiotherapy with steep gradients in dose distribution, such as the ones that are used in intensity-modulated radiation therapy (IMRT).

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Chapter 9

Publication 6

Experimental determination of the radial dose distribution in high gradient regions from a low dose rate iridium-192 wire sources using EPR imaging

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Abstract– Electron paramagnetic resonance imaging (EPRI) dosimetry is an experimental method for performing relative dosimetry in brachytherapy at proximal distances from radioactive sources, where the dose gradient is steep and difficult to measure. This method is based on an EPRI of free radicals induced by irradiation in a solid matrix made of a radiosensitive material. The goal of this study is to determine the relative radial dose distributions for a low dose rate (LDR) Iridium-192 wire sources. Ammonium formate (HCO_2NH_4) was chosen as an EPR dosimeter material. It was found to have an atomic composition close to tissue (density 1.27 g/cm^3). The radical signal in irradiated ammonium formate is contained in a single narrow EPR line. The linearity of dose response and stability of the signal intensity with time were verified experimentally. The radial dose distribution was measured for distances between 0.1 and 0.5 cm. Monte Carlo (MC) simulation using MCNP4C2 software code was utilized as a tool to provide an analytical method against which EPRI results can be compared. Furthermore, an additional experimental measurements were performed, using Gafchromic EBT films. The coincidence between film study measurements and MC calculations are within 1%, while comparison of EPRI data with other methods show discrepancies. Our results suggest that EPRI data can be used to determine the relative radial dose distribution at proximal distances from a LDR ^{192}Ir wire sources within an experimental error.

Key words– brachytherapy, radial dose distribution, EPRI, Iridium-192 wires, EBT films

I. INTRODUCTION

Platinum encapsulated 0.3 mm diameter ^{192}Ir wires have been widely used as interstitial sources in a low dose rate brachytherapy. Due to the steep dose gradient in the millimeters distance range, it is difficult to perform an accurate dose measurements in high spatial resolution. It leads to a search for improved dosimetry techniques [1].

Guidelines for dosimetry of brachytherapy sources in the cm distance range are presented in a report published by the AAPM Radiation Therapy Committee Task Group 43 and

by the AAPM Task Group 60 (TG-60) in the millimeters distance range [2-4]. Analytical Monte Carlo calculations provide essential data on dose distribution around such clinical sources [5-9].

Several dosimetry experiments were performed to obtain the dose distribution using ionization chambers of different sizes and by use of LiF thermoluminescence dosimeters (TLD) [10-12].

Films also offer a high spatial resolution in a single, 2D-plane and provide the relative dose information and absolute dose measurements when appropriately calibrated [13,14]. Gafchromic EBT film has a near-tissue equivalence and shows low energy dependence of its sensitivity (response/dose). The effective atomic number of EBT film ($Z_{\text{eff}}=6.98$) is close to water [15].

Solid-state dosimetry by means of EPR spectroscopy, usually with the amino acid L- α -alanine as a dosimeter has been proven for high doses (kGy region) [16,17]. For dose determination in high gradient regions there is a need for a high spatial resolution. Therefore, a more sensitive material than alanine is needed. Ammonium formate material was found to have an atomic composition close to tissue (density 1.27 g/cm^3). The radical signal in irradiated ammonium formate is contained in a single narrow EPR line [18-20].

The intensity of the EPR signal is proportional to the concentration of free radicals generated by radiation in the dosimeter. It is important to know the spatial location of these radicals using EPRI method. The first attempt to use EPRI dosimetry was applied to alanine irradiated with electrons from a 4 MeV linear accelerator [21]. 2D EPRI experiments were performed using alanine dosimeters irradiated with a 10 MeV electron beam or 10 MeV gamma-photons [22]. Alanine dosimeters irradiated with beta (β) particles to a maximum dose of 6 kGy were examined by EPRI.

Finally, evaluation of the dose distribution was obtained using 2D EPRI with lithium formate dosimeters irradiated with Iodine-125 (I^{125}) and potassium dithionate dosimeters irradiated with C^{6+} and N^{7+} Ions [23,24].

In the present study, EPRI dosimetry has been used to investigate the radial dose distributions around a LDR ^{192}Ir

brachytherapy wire sources in the millimeters distance range.

II. MATERIALS AND METHODS

A. EPRI dosimetry

The phantoms were made of an ammonium formate powder pressed into small cylinders with a diameter of 22 mm and a height of 10 mm using a tablet press (Ateliers Courtoy, type AC27, Halle, Belgium, 50 kg/cm²). Ammonium formate phantoms were externally irradiated using X-ray beam (Philips 250 RT, 250 keV) with a dose-rate 0.85 Gy/min in the dose range of 25-200 Gy to study the linearity of dose response. EPR spectra were collected using L-band Eleksys 540 spectrometer operating at 1.1 GHz and with 100 kHz magnetic field modulation. The signal intensity (measured as the peak-to-peak height) in EPR spectra reflects the number of stable free radicals produced in the irradiated phantoms and provides a quantitative measurement of the absorbed dose. All measurements were performed with a continuous flow of a dry argon gas through the cavity in order to keep the samples completely dry.

For brachytherapy dosimetry one or two holes (0.4 mm in diameter) were drilled inside cylinders. ¹⁹²Ir wire sources (BEBIG, GmbH, Berlin, Germany) were inserted for irradiation during two weeks. Each wire had an outer diameter of 0.3 mm and a length of 1 cm.

Images were obtained using Bruker L-band Eleksys 540 EPRI system and L-band EPR cylindrical resonator (ER 6502 BC, 25 mm diameter). In continuous wave (CW) EPRI, the data were acquired in the form of projections, which are the absorption signal detected by sweeping the main magnetic field in the presence of a linear static magnetic field gradient. Applied magnetic field gradient 250 mT/m was generated by three orthogonal water-cooled cylindrical gradient coils. EPRI acquisition parameters were as follows: applied modulation frequency of 100 kHz, a microwave power of 36 mW, a modulation amplitude of 0.25. The measured projection is the convolution of the true spatial profile of an ammonium formate material and the spectral shape function, which is the absorption signal measured in the absence of magnetic field gradient. The intrinsic line width of used material affects on the image resolution. A spectrum with large line width results in blurring of the projection data. The effect of image blurring can be reversed by deconvolving each projection [25]. Spectral deconvolution and filtered back-projection were performed using Xepr software package (Bruker, Germany).

Using the software code, the radial intensity profile from each image was extracted. An average radial intensity profiles from images were obtained and presented.

B. Gafchromic film dosimetry

EBT films sheets were cut into 2.2x2.2 cm² squares with a small line drawn on along the edge and parallel to the long axis of the film sheet. This was done to ensure consistent film orientation on the scanner. The calibration data set was obtained by exposing films at following dose levels: 0, 1, 2, 4, 6 and 8 Gy with a 250 keV X-ray beam using 7x7 cm² field size at distance of 33.5 mm. One set of EBT films was not irradiated to define a background reading. After irradiation EBT films were scanned using a Vidar film scanner 2 h after irradiation along portrait direction to allow the saturation of color growth, as recommended by the film manufacturer and processed using a dosimetry film software VXR-16 Dosimetry Pro. The pixel intensity (gray level) of exposed films was acquired with the software. Measured relative intensity values were plotted as a function of absorbed dose. The films were scanned at 7 days to verify the post-irradiation color stability with time.

In order to prevent saturation at short radial distances, different irradiation time was employed in the experiment. The Gafchromic films were placed between two pieces of ammonium formate phantoms of equal size and stacked together for different exposure time: 5, 20 and 30 minutes, 1, 2 and 18 hours, air gap between pieces was avoided. One or two holes (0.4 mm in diameter) were drilled inside films for insertion of ¹⁹²Ir wires. The pieces of films were exposed sequentially. Each exposure was designed to measure the radial dose distribution for distances between 0.1-0.5 cm. The exposed films were digitized using a Vidar film scanner and analyzed in order to determine the radial dose distributions in 0.36 mm steps. The films were always digitized in the same orientation and read out at the same time as calibration films [26]. Radial dose distributions in the vicinity of radioactive sources ¹⁹²Ir were mapped. Pixel values were taken across a radial line profile from the center of the source.

C. Monte Carlo calculations

Monte Carlo N-particles transport calculations are accepted as the most efficient method of detailed 3D geometry in the field of brachytherapy. The general purpose Monte Carlo N-particle transport code, MCNP4c2, (Los Alamos National laboratory, USA) has been utilized to model ¹⁹²Ir wires with surrounding geometry [27]. The simulated sources are ¹⁹²Ir wires of 1 cm length and 0.3 mm in diameter. The central core is 0.1 mm in diameter,

composed of about 20% Ir and 80% Pt, encased in a 0.1 mm Pt sheath. Radioactive source wire was located in the center of the phantom with its long axis coincident with the phantom central axes. The ^{192}Ir wires were modeled as cylinders: an inner cylindrical core 0.1 mm in diameter encased in a 0.1 mm Pt cylindrical sheath with the same height. Radial dose distributions were determined by placing concentric cylinders about the ^{192}Ir core and Pt encapsulation in 0.1 mm radial increments up to the 11 mm radius phantom. F6 tallies were used in order to obtain the radial dose determinations. The cutoff energy for photons was taken at 10 keV. The ^{192}Ir gamma spectrum used in this study was taken from the published data [6]. One-billion initial source particles were followed.

RESULTS

An EPR image directly reflects the known shape and the size of irradiated phantoms. The color code depicts the dose gradient around radioactive wire source, as shown in Fig.1.

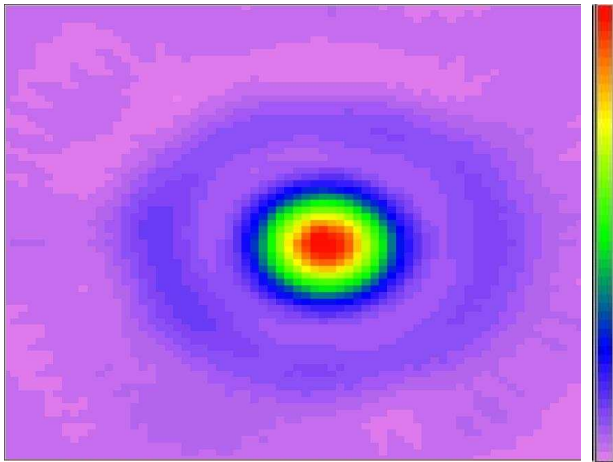


Fig.1 2D EPR image of ammonium formate phantom irradiated by ^{192}Ir wire source

Three 2D EPRI data sets were collected and used to numerically analyze the relative dose distributions. The dose measurements were made along the axis passing through the center of the tablet in 0.25 mm steps. The radial intensity profile from each image was extracted and normalized at 1 mm from the center of the source. The ^{192}Ir wire source and its surrounding phantom were simulated, and the dose distributions were calculated for radial distances, using MC software code. Radial dose distributions were measured, using EBT films in 0.36 mm steps, taken across a radial line profile from the center of the source. The results from three methods (EPRI data, MC

calculations and films study measurements) were compared and presented in Fig.2.

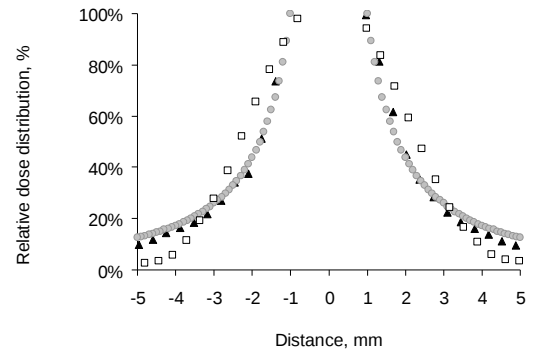


Fig.2 Radial dose profiles, EPRI data, white boxes, MC calculation, grey circles, EBT film results, black small triangles

The radial dose gradient from the source out to 2 mm is still steep, it decreases up to 44%, while levels off more smoothly from 2 mm to 3 mm up to 28%. The coincidence between film study measurements and MC calculations are within 1%, but comparison of EPRI data with other methods show some discrepancies.

III. DISCUSSION

EPRI dosimetry has been presented as an experimental method for relative dosimetry in brachytherapy. The use of ammonium formate dosimeters in EPRI provides both long term stability of the EPR signal and linearity of response over a large range of radiation doses. The two-dimensional reconstructions produced an image that is a projection of the whole volume of the phantom on planes selected by the gradient. The radial dose distribution profile from each image was obtained. Monte Carlo simulation using the MCNP4C2 software code was used as analytical method to derive the radial dose profiles for comparison with obtained EPRI data. The dose distributions were also measured, using EBT films as an additional experimental method. The discrepancies between measured EPRI data and other comparable methods were observed. Experimental EPR profile presents a different shape due to experimental resolution limit. It can be explained as follows. In this study, the spatial resolution imposed by the signal line width of the material used was approximately 2-2.5 mm, it still requires further improvement to achieve a spatial resolution within 1 millimeter. It depends on intrinsic line width of used material, signal-to-noise ratio, and the

effectiveness of the deconvolution procedure, which was applied to suppress the effects of system blurring. The resolution can be enhanced by using the material with narrow spectrum and by applying high gradient strength. However, increasing the gradient strength may result to broadening the spectrum and lowering the signal intensity. One of the possibilities is to improve the postprocessing algorithm for enhancing spatial resolution in 2D EPR images [28].

IV. CONCLUSIONS

EPRI data provided a quantitative information about the relative radial dose distributions around ^{192}Ir wire sources. We concluded that EPRI method with ammonium formate allows the relative radiation dose mapping in two dimensions at short distances within an experimental error of measured data. The perspective of EPRI technique is to perform 3D- dosimetry in the millimeters distance range.

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Chapter 10

Publication 7

Experimental determination of the radial dose distribution in high gradient regions around ^{192}Ir wires: Comparison of electron paramagnetic resonance imaging, films, and Monte Carlo simulations

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Purpose: The experimental determination of doses at proximal distances from radioactive sources is difficult because of the steepness of the dose gradient. The goal of this study was to determine the relative radial dose distribution for a low dose rate ^{192}Ir wire source using electron paramagnetic resonance imaging (EPRI) and to compare the results to those obtained using Gafchromic EBT film dosimetry and Monte Carlo (MC) simulations.

Methods: Lithium formate and ammonium formate were chosen as the EPR dosimetric materials and were used to form cylindrical phantoms. The dose distribution of the stable radiation-induced free radicals in the lithium formate and ammonium formate phantoms was assessed by EPRI. EBT films were also inserted inside in ammonium formate phantoms for comparison. MC simulation was performed using the MCNP4C2 software code.

Results: The radical signal in irradiated ammonium formate is contained in a single narrow EPR line, with an EPR peak-to-peak linewidth narrower than that of lithium formate (~ 0.64 and 1.4 mT, respectively). The spatial resolution of EPR images was enhanced by a factor of 2.3 using ammonium formate compared to lithium formate because its linewidth is about 0.75 mT narrower than that of lithium formate. The EPRI results were consistent to within 1% with those of Gafchromic EBT films and MC simulations at distances from 1.0 to 2.9 mm. The radial dose values obtained by EPRI were about 4% lower at distances from 2.9 to 4.0 mm than those determined by MC simulation and EBT film dosimetry.

Conclusions: Ammonium formate is a suitable material under certain conditions for use in brachytherapy dosimetry using EPRI. In this study, the authors demonstrated that the EPRI technique allows the estimation of the relative radial dose distribution at short distances for a ^{192}Ir wire source. © 2010 American Association of Physicists in Medicine. [DOI: [10.1118/1.3488913](https://doi.org/10.1118/1.3488913)]

Key words: EPR, EPR imaging, brachytherapy, dosimetry, ^{192}Ir , Gafchromic EBT films, Monte Carlo

I. INTRODUCTION

Platinum encapsulated 0.3 mm diameter ^{192}Ir wires have been widely used as interstitial sources in low dose rate (LDR) brachytherapy. Due to the steep dose gradient in the millimeter distance range, it is difficult to perform accurate dose measurements with a high spatial resolution. This limitation has stimulated research for improved 2D and 3D dosimetry techniques.¹ The guidelines for dosimetry of brachytherapy sources in the centimeter distance range are presented in a report published by the American Association of Physicists in Medicine (AAPM) Radiation Therapy Committee Task Group 43 and can be extended to the millimeter range using the report of the AAPM Task Group 60.^{2–4} Analytical Monte Carlo (MC) calculations provide reliable data

on dose distribution.^{5–9} Dose distribution can also be measured using ionization chambers of different sizes or LiF thermoluminescence dosimeters.^{10–12} Films offer a high spatial resolution in a single 2D plane and provide relative dose information and absolute dose measurements when appropriately calibrated.^{13,14} Gafchromic EBT (EBT) films are becoming increasingly popular due to their advantageous properties: They are nearly tissue equivalent (the effective atomic number of EBT film is $Z_{\text{eff}}=6.98$, this value is close to the Z_{eff} of water, which is 7.3); they have very low energy dependency, with not more than 5% difference between MeV and keV photons,¹⁵ and they can be used to record the incidence of radiation at closely spaced points simultaneously and close to the source.

Electron paramagnetic resonance (EPR) spectroscopy represents a powerful tool for qualitative and quantitative analysis of radiation-induced stable free radicals. Solid-state dosimetry by means of EPR spectroscopy, usually with the amino acid L- α -alanine as a dosimeter, has been shown to be accurate at high doses (kGy region).^{16,17} EPR measurements using alanine as a dosimetric material is internationally recognized as a standard method for reliable dose measurements.¹⁸ Despite its wide use in reference laboratories, alanine is not routinely used in clinic where ionization chambers and diode detectors are more often preferred.

Polycrystalline formates and dithionates have been proposed recently as new materials for EPR dosimetry because the irradiation produces a large yield of stable free radicals with a linear dose response. Moreover, these compounds give a single-lined EPR spectrum, resulting in a higher peak-to-peak value of the central line as compared to the complicated alanine spectra.^{19–22} The radiation energy dependency of ammonium formate is low above ~ 80 keV.²² While EPR dosimetry can determine the concentration of free radicals, which is a function of the absorbed dose in whole samples, the distribution of radicals along two dimensions can be visualized by electron paramagnetic resonance imaging (EPRI). The first attempt to use EPRI in dosimetry was performed using alanine irradiated with electrons from a 4 MeV linear accelerator.²³ Other 2D EPRI experiments have been performed using alanine dosimeters irradiated with a 10 MeV electron beam or 10 MeV gamma photons.²⁴ Alanine dosimeters irradiated with beta (β) particles with high doses (up to 6 kGy) have also been examined by EPRI.²⁵ More recently, the evaluation of the dose distribution was obtained using potassium dithionate dosimeters irradiated by C^{6+} and N^{7+} ions.²⁶

In a previous study, we demonstrated for the first time that 2D EPRI could be useful to determine the dose distribution around brachytherapy seeds using lithium formate (LiFo) as a dosimetric material.²⁷ Although we demonstrated that this approach was feasible, we concluded that the spatial resolution of the method was hampered by the large EPR linewidth of the lithium formate. The spatial resolution, which is the ability to distinguish two points in space, depends on the magnetic field gradient, the EPR linewidth of the material, and the deconvolution processing.²⁸ To overcome this possible limitation, we chose to study ammonium formate (HCO_2NH_4 , AmFo). The radical signal in irradiated ammonium formate is contained in a single narrow EPR line, with an EPR linewidth narrower than that of lithium formate (~ 0.64 and 1.4 mT, respectively). Although EPR spectroscopy is a well established technology used for dosimetry studies, EPR imaging is yet to be validated. In this validation process, we explore the performances of EPR imaging, which is not yet a quantitative technique, to study the relative distribution of dose around brachytherapy sources (LDR ^{192}Ir) using a better dosimetric material, ammonium formate, compared to the previously used lithium formate. In the second part of the study, we compare the experimental relative EPRI dose distribution profiles for short distances, from 1.0

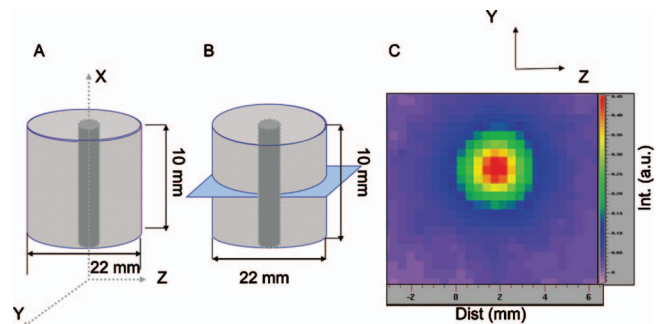


FIG. 1. Experimental setups used in the present study. (a) The setup for 2D EPR image reconstruction and the geometry used in the MC simulations. (b) The setup used for EBT film measurements and the geometry of the MC simulations including the film. (c) 2D reconstructed EPR image of the ammonium formate phantom irradiated by a ^{192}Ir wire source. Image directions relative to the EPR magnet are shown. Intensity integral is along the X-direction.

to 4.0 mm from the center of the source, to a validated experimental method using Gafchromic EBT films and to a theoretical method using MC simulations performed using the MCNP4C2 software code.

II. MATERIALS AND METHODS

II.A. Iridium wire sources

^{192}Ir wire source emits a spectrum of relatively low gamma energies with an average value of 360 keV; its half-life is 73.83 days.⁶ The beta component of the ^{192}Ir spectrum has 180 keV average energy; however, the contribution of the beta particles was less than 0.01 (1%) even at the radial distance of $r=0.5$ mm.⁹ Secondary electrons are also generated from platinum (Pt) encapsulation, but, at radial distances greater than about 1.0 mm, the dose rates including and excluding secondary electrons from the Pt encapsulation coincide with each other.^{29,30}

The ^{192}Ir wire source (air kerma at 1 m: $2.52 \mu\text{Gy h}^{-1} \text{cm}^{-1}$, BEBIG GmbH, Berlin, Germany) had a length of 10.0 mm and a diameter of 0.3 mm. The central core was 0.1 mm in diameter, composed of about 20% Ir and 80% Pt, encased in a 0.1 mm Pt sheath. A radioactive wire was located at the center of the phantoms with its long axis coinciding with the phantom's central axis [cf. infra, EPR imaging section, and Fig. 1(a)].

II.B. Phantoms

The phantoms were made of polycrystalline lithium formate monohydrate or ammonium formate (Aldrich, Steinheim, Germany) powder pressed into small cylinders with a diameter of 22.0 mm and a height of 10.0 mm using a tablet press (Ateliers Courtoy, type AC27, Halle, Belgium, 50 kg/cm^2). For brachytherapy dosimetry, a hole (0.4 mm in diameter) was drilled at the center of all cylindrical phantoms. ^{192}Ir wires were inserted in the phantoms and were removed after 2 weeks of irradiation. Imaging was performed as soon as possible after the irradiation. As ammo-

nium formate is very hygroscopic, all samples were kept dry during the imaging process with a continuous flow of dry argon gas through the EPR cavity.

II.C. EPR Imaging

EPR spectra were collected using an L-band bridge Elexsys 540 spectrometer with a cylindrical cavity (ER 6502 BC, 25 mm in diameter) operating at 1.1 GHz and with 100 kHz magnetic field modulation. The signal intensity (measured as the peak-to-peak height) of the EPR spectra reflects the number of stable free radicals produced in the irradiated phantoms and provides a quantitative measurement of the absorbed dose.

2D EPR images were obtained using the same system. Planar (ZY plane) spatial images were acquired, where each pixel is the intensity integral of the spin density along the x dimension. The coordinate system has the longitudinal and transverse axes of the source as the z and y axes, respectively [Fig. 1(a)].

The applied magnetic field gradient was 450 mT/m and was generated by three orthogonal water-cooled cylindrical gradient coils. Other EPRI acquisition parameters were as follows: Applied modulation frequency of 100 kHz, microwave power of 28.6 or 57.6 mW, modulation amplitude of 0.25 mT, field of view of 25 mm, pixel size of 0.7 mm, and the number of pixels is 35. All imaging parameters were kept constant for all the irradiated phantoms.

II.C.1. Deconvolution: Image reconstruction

2D images were reconstructed on a 128×128 matrix by filtered backprojection using a Shepp–Logan filter. Before reconstruction, each projection was deconvolved using fast Fourier transform with the measured zero-gradient spectrum in order to improve image resolution.^{31–34} To reduce noise amplification and avoid possible division by zero at high frequencies, a low pass filter was used. The deconvolution parameters, including the maximum cut-off frequency and the width of the window in the Fourier space, were set up after viewing the shape of all projections. Data were smoothed using either a Fermi–Dirac or a Gaussian filter. Spectral deconvolution and filtered backprojection were performed using the XEPR software package (Bruker GmbH, Rheinstetten, Germany).

Three 2D EPRI data sets were collected for each phantom and used to numerically analyze the relative radial dose distributions. All the relative radiation doses were doses to ammonium formate since ammonium formate was chosen as the reference material in this work. The dose measurements were made across the radial line profile from the center of the tablet in 0.35 mm steps. When the signal-to-noise ratio was greater than 2, the measured signal intensity was considered to be significant. The noise was measured in regions outside the area of the phantoms of 22 mm in diameter, where there were no signal sources.

The radial intensity profile extracted from each image was normalized to 100% at 1 mm from the center of the source as for other dosimetric methods. The results are given as the mean of three independent measurements.

II.D. EPRI resolution: Determination of the edge spread function

The theoretical spatial resolution, which represents the shortest distance (d) between two points that can be resolved in an EPR image, was calculated as follows:

$$d = \text{LW}/G, \quad (1)$$

where LW (mT) is the linewidth of an EPR signal and G (mT/m) is the magnitude of the magnetic field gradient. The linewidths of the signal were 1.4 mT (LiFo) and 0.64 mT (AmFo), the magnetic field gradient was 450 mT/m, and the theoretical spatial resolutions were calculated as 3.1 and 1.4 mm, respectively.

The spatial resolution was also experimentally evaluated in terms of the edge spread function (ESF). ESF was determined following a procedure modified from the classical method used in MRI³⁵ and from the work of Halpern's group,^{36–38} as previously published by our laboratory.^{27,39} Briefly, a parallelepiped phantom made of AmFo or LiFo was homogeneously irradiated (300 Gy) with an external 250 kVp x-ray beam. The size of the phantom was $1.0 \times 1.0 \times 4.0$ (cm). A 2D image of the phantom was reconstructed. The image was acquired at 300 mT/m. The signal along a line perpendicular to the edge of the phantom was extracted from the image and the derivative was calculated. A nine-point smoothing algorithm was used to obtain the derivative curve, which was then fitted by a Gaussian function,

$$f(x) = \frac{1}{\sigma\sqrt{2\pi}} e^{-(x-\mu)^2/2\sigma^2}. \quad (2)$$

From the computed σ values, the full width at half maximum (FWHM) of the Gaussian curve was calculated from the following equation:

$$\text{FWHM} = 2 \cdot \sigma\sqrt{2 \cdot \ln 2}. \quad (3)$$

All calculations and fitting were carried out using Prism 4 from GraphPad Software, Inc. (La Jolla, CA).

II.E. Gafchromic film dosimetry

Additional experimental measurements were performed using Gafchromic EBT films. Gafchromic EBT film (International Specialty Products, Wayne, NJ) sheets were cut into 2.2×2.2 (cm) squares. The calibration data set was obtained by exposing films at the following dose levels: 0, 1, 2, 4, 6, and 8 Gy with a 250 kVp x-ray beam using a 7×7 (cm) field size at a source surface distance of 33.5 mm.^{15,40,41} EBT film was placed on top of a Plexiglas phantom during irradiations in full scatter conditions [phantom size of $30 \times 3 \times 30$ (cm)]. The effective measurement points were assumed to be at the center of the active emulsion layer, hence at 0.02 mm (half thickness of the active layer). EBT

films were selected because of their weak energy dependence dose response in the 50 kVp–10 MVp x-ray range.⁴⁰

One set of EBT films was not irradiated to provide a background reading. EBT films were scanned in the portrait direction using a Vidar film scanner 2 h after irradiation to allow the saturation of color growth, according to the recommendations of the manufacturer, and processed using a dosimetry film software VXR-16 Dosimetry Pro. The pixel intensity (gray level) of exposed films was acquired with the software. The radial dose profiles were expressed as doses to the film and determined from EBT film data in 0.36 mm steps (the spatial resolution of the Vidar scanner). The films were also scanned at 7 days to verify postirradiation color stability over time. No significant variation was observed between both readings, a result that is consistent with that previously published data.⁴²

For brachytherapy dosimetry, EBT films were placed between two ammonium formate phantoms of equal size (22.0 mm in diameter, 4.9 mm thick) and stacked together to prevent any air gap between them. A hole (0.4 mm in diameter) was drilled at the center of the films for the insertion of ¹⁹²Ir wires. A scheme of the experimental setup is shown in Fig. 1(b). Different exposure times (5, 20, and 30 min; 1, 2, and 18 h) were used in our experiments to prevent saturation at short radial distances. Each exposure was designed to measure the radial dose distribution for distances between 1.0 and 4.0 mm from the center of the source. The exposed films were digitized and analyzed as described above. The films were always digitized in the same orientation and read at the same time.

II.F. Monte Carlo calculations

The MCNP4C2 Monte Carlo code (Los Alamos, National Laboratory, USA) was used in this work. The code is utilized to model ¹⁹²Ir wires with surrounding geometry,⁴³ and the materials used in the MC calculations and their composition, density, and effective atomic number are presented in Table I. The photon interaction cross-section file used in this study was the DLC-200 library. The dose distribution (expressed as dose to ammonium formate) was calculated for short radial distances using the MC software code. A total of three different simulations was performed to provide comparisons with real measurements.

A first calculation was made for comparison with the EPRI results. The ¹⁹²Ir wires were modeled as cylinders with an inner cylindrical core of 0.1 mm in diameter encased in a 0.1 mm Pt cylindrical sheath with the same height. Cylindrical cells in the phantom were modeled with the same geometry as that used in the EPRI postprocessing. The radial dose distributions were modeled by placing concentric cylinders around the ¹⁹²Ir core and Pt encapsulation in 0.1 mm radial increments up to the 11 mm radius phantom.

The second simulation was performed for comparison with EBT film experimental data, including modeling of Gafchromic EBT films, placed between two cylindrical ammonium formate phantoms of equal size. Gafchromic EBT films were modeled for radial symmetry by placing concen-

TABLE I. The materials used in the Monte Carlo calculations and their composition, density, and effective atomic number.

Material	Element	Composition (% by weight)	Density (g/cm ³)	Z _{eff}
Ir	...	...	22.39	77
Pt	...	...	21.41	78
Ir(20%)	Ir	20	21.613	78
Pt(80%)	Pt	80	...	...
Air (dry)			0.001205	8
	C	0.0124	...	...
	N	75.5267	...	...
	O	23.1781	...	...
	Ar	1.2827	...	...
Ammonium formate			1.26	7.03
	N	22.21	...	...
	C	19.05	...	...
	H ₅	7.99	...	...
	O ₂	50.75	...	...
EBT film			1.1	6.98
	H	39.7	...	...
	C	42.3	...	...
	O	16.2	...	...
	N	1.1	...	...
	Li	0.3	...	...
	Cl	0.3	...	...

tric rings (0.234 mm high and with a thickness of 0.1 mm) around the wire source in the middle of phantoms. The energy deposition of the particles was scored within all films. We calculated the dose deposition using MC simulations for phantoms with or without insertion of Gafchromic EBT film. The insertion of EBT film did not affect the radial dose distribution.

Finally, the third simulation was implemented, where the energy deposited in the medium was scored within the cylindrical rings with a thickness of 0.1 mm and a height of 1.0 mm along the longitudinal axis of the source. Photon doses were calculated from 0.3 to 11.0 mm from the source center in the radial direction, in 0.1 mm increments. In the longitudinal direction, 1 mm intervals were scored from the center of the source to 5.0 mm. It was observed that the dose gradients obtained from the two planes of different thicknesses were almost superimposed.

F6 tallies were employed for gamma calculations, measuring the photon track length traversing a voxel. The cutoff energy for photons was set at 10 keV⁵ and used a minimum of 1×10^8 histories, which yielded the average standard error of 1% for all radial distances for the cases with and without the secondary electrons from Pt encapsulation.

III. RESULTS

Each reconstructed 2D EPR image reflected the known shape of phantoms. The color code directly depicts the radial dose distribution around the radioactive wire source, as shown in Fig. 1(c). The EPR signal intensity increased linearly with the delivered dose, as previously observed by others.^{20,22}

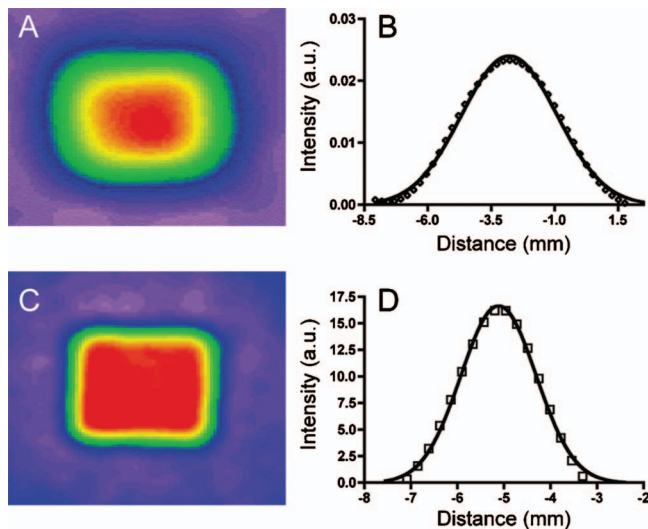


FIG. 2. Calculation of the edge spread function for the determination of the spatial resolution. (a) 2D EPRI image of a square phantom made of LiFo and (b) ESF (diamonds) derived from the image and the fitted Gaussian curve. (c) 2D EPRI image for AmFo phantom. (d) ESF (boxes) and the corresponding fitted Gaussian curve.

Figure 2 shows the spatial resolution improvement due to ammonium formate at 300 mT/m. For lithium formate, the σ value computed from the Gaussian fit of ESF was 1.86 ± 0.03 with a corresponding resolution (FWHM) of 4.4 mm. The σ value for ammonium formate was 0.81 ± 0.02 and the computed resolution (FWHM) was 1.9 mm. The theoretical values were 4.6 mm (AmFo) and 2.1 mm (LiFo), respectively. In other words, the experimental resolution was increased by a factor of 2.3 when using AmFo vs LiFo at a gradient of field of 300 mT/m. When ammonium formate was used at a higher value of gradient (450 mT/m), the resolution was further increased up to 1.4 mm.

Figure 3(a) shows the radial dose profile measured with Gafchromic EBT films, as the average of three sets of data taken across a radial line from the center of the source. The comparison with MC calculations is shown in Fig. 3(b).

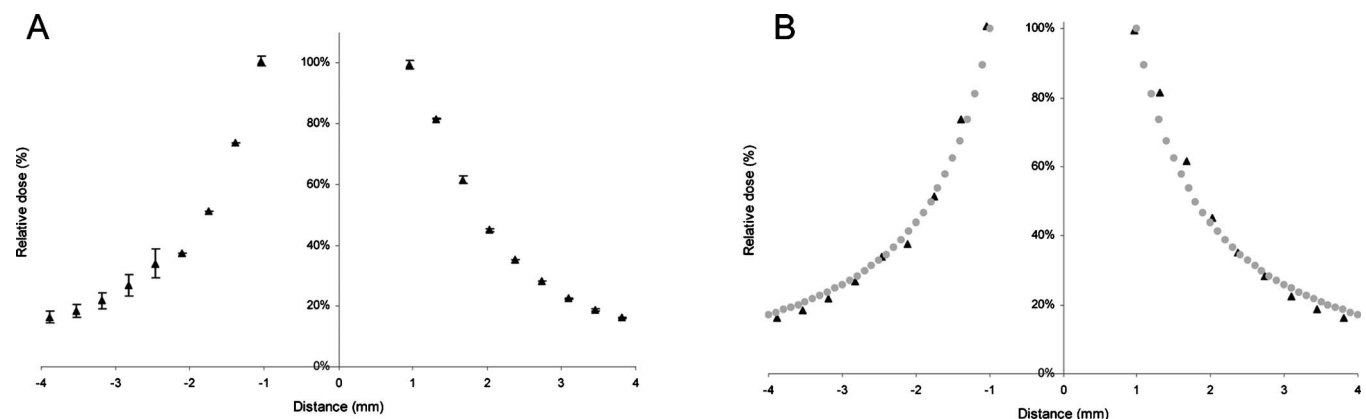


FIG. 3. (a) EBT film dosimetry profile using the setup presented in Fig. 1. The results are the average of three different data sets. Values are normalized at 1 mm from the center of the iridium wire. (b) Comparison of EBT film (black triangles) and Monte Carlo simulation (open squares) radial dose distributions for ammonium formate phantom irradiated by a ^{192}Ir wire source.

The comparison of EPRI results using different types of deconvolution (Gaussian or Fermi-Dirac) with MC simulations is presented in Fig. 4. It can be observed that the dose profile obtained with Gaussian filtered deconvolution is closer to the MC profile than the Fermi-Dirac filtered curve.

With a cylindrical ^{192}Ir wire source, the radioactive material is uniformly distributed throughout the wire, and the relative dose distribution in-plane is comparable to the average relative dose distribution from all planes in a full phantom. The relative radial dose values in-plane and for full phantoms, using the MCNP4C2 software code, were almost superimposed, and the insertion of EBT film did not affect the radial dose distribution from Gafchromic EBT films (data not shown).

Figure 5 shows the comparisons of the radial dose profiles obtained with the three different methodologies (film, EPRI, and MC). At distances ranging from 1.0 to 2.9 mm from the center of the phantom, the results of the EPRI data were consistent to within 1% with those of Gafchromic EBT films and MC simulations. At distances from 2.9 to 4.0 mm, the radial dose values obtained by EPRI were about 4% lower than those determined by MC simulations and EBT film dosimetry.

IV. DISCUSSION

The present study explores the ability of EPRI to estimate the relative dose distribution from low dose rate brachytherapy ^{192}Ir wire sources. The dosimetric properties of ammonium formate were previously described by Lund, Vestad, and co-workers using EPR spectroscopy.^{20-22,44} They pointed out a linear dose-response relationship and a low radiation energy dependence, which are very desirable properties. Moreover, the lineshape of the EPR spectrum was simple and narrow, a very favorable feature for EPR imaging.

We ourselves previously demonstrated that 2D EPRI could be useful to determine the steep dose gradient around the brachytherapy ^{125}I seeds.²⁷ In that previous study, LiFo was used as the dosimetric material. The main limitation of the method was a poor spatial resolution because of the large

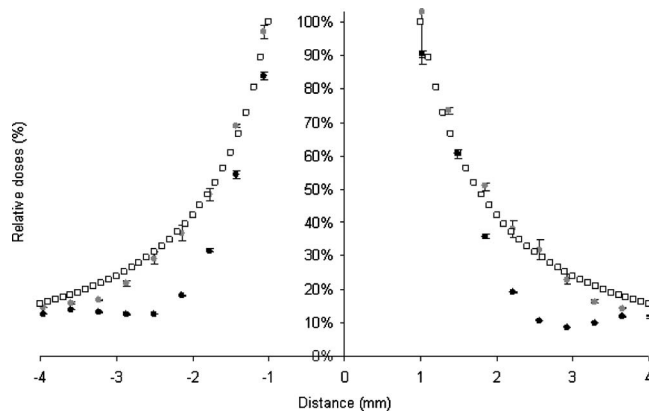


FIG. 4. Comparison of the Monte Carlo (open squares) and EPRI radial dose distributions obtained after Fermi-Dirac (black circles) or Gaussian (gray circles) deconvolution. EPR images were acquired with a gradient of field of 450 mT/m.

linewidth ($LW=1.4$ mT) of LiFo. As the spatial resolution is inversely proportional to the EPR linewidth, in the present study, we investigated the possible usefulness of ammonium formate ($LW=0.64$ mT) as a dosimetric material in EPR imaging. The ultimate goal is to get reliable spatial dosimetric information, which is not achievable using EPR spectroscopy.

In the present work, we have demonstrated that it is possible to improve the spatial resolution by a factor of 2.3 using ammonium formate instead of lithium formate. We are now approaching a spatial resolution compatible with the range of dose distribution observed with brachytherapy sources.

Because of the relatively low signal-to-noise ratio in our EPR images, we found that a Gaussian filter was more adequate for the deconvolution process and gave results closer to the MC or film data than those obtained with Fermi-Dirac filtering. FD filtering uses a sharp cut-off frequency in the Fourier space, leading to theoretically sharper images, but it requires a very good signal with low noise. Gaussian filter is smoother and avoid high frequency artifacts with noisy data.

To verify the potential of EPRI as a tool to measure the dose distribution around brachytherapy ^{192}Ir wires, we compared this method to the theoretical Monte Carlo simulations and to the experimental data obtained with a standard reference method (film dosimetry). Our final results from the EPRI data were consistent within 1% with those from Gafchromic EBT films and MC simulations at short distances ranging from 1.0 to 2.9 mm from the center of the source. The radial dose values obtained by EPRI were lower by about 4% at distances from 2.9 to 4.0 mm than those determined by MC simulations and EBT film dosimetry. These differences can partially be explained by the presence of noise in the reconstructed 2D EPR images and by the still somewhat limited spatial resolution.

Because our data are normalized and expressed as relative doses, we can compare the profiles obtained with the three methodologies. The energy dependence of the dosimeters used can be quite different, but as our data are normalized,

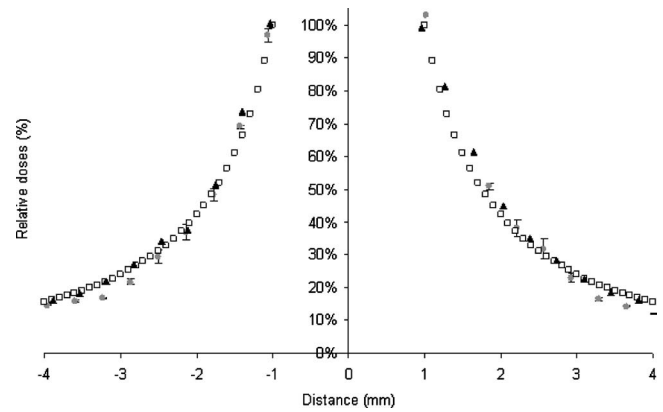


FIG. 5. Comparison of Monte Carlo (open squares), Gafchromic film (black triangles), and EPRI (gray circles) radial dose distributions for ammonium formate phantom irradiated by a ^{192}Ir wire source. Error bars for Gafchromic film are not plotted for more clarity but are available in Fig. 3(a).

the effect of the energy dependence vanishes and comparisons are possible without further correction. Nevertheless, it must be mentioned that this energy effect will be of major importance for absolute dosimetry. Films and EPR dosimeters are calibrated according to the NCS dosimetry protocol⁴⁵ and are consequently expressed as dose to water. Monte Carlo simulations are computed as doses to dosimeter. For kV photons, a correction should be applied for the energy dependence of the dosimeter material. For high energy photons and electrons, the energy dependence is very low both for alanine and lithium formate.^{46–50} Nevertheless, in the kV energy range, a substantial energy dependence has been demonstrated for alanine. A smaller dependence is observed for lithium formate⁵¹ and ammonium formate,²² so this point should be carefully investigated for future accurate absolute dosimetry.

We performed Monte Carlo simulations including different geometries. With a cylindrical ^{192}Ir wire source, the radioactive material is uniformly distributed throughout, and the relative dose distribution in-plane is comparable to the average relative dose distribution from all planes in a full phantom. The relative radial dose values in-plane and for full phantoms, using the MCNP4C2 software code, were almost superimposed, and the insertion of EBT film did not affect the radial dose distribution from Gafchromic EBT films.

This work provides a new experimental approach that completes the available range of techniques commonly used for dosimetry of low dose rate brachytherapy sources. They encompass theoretical Monte Carlo simulations^{5,52} or experimental procedure such as MR Imaging using gel dosimeters,⁵³ optical detection with plastic scintillator⁵⁴ or solid polyurethane,⁵⁵ or even MOSFET dosimeter.⁵⁶

V. CONCLUSIONS

Overall, ammonium formate is a suitable material, under certain conditions, for use in brachytherapy dosimetry and allows a marked improvement of the true spatial resolution achievable using EPRI. Nevertheless, it should be reminded that ammonium formate is a very hygroscopic material,

which limits its practical day-to-day use. In this study, we developed 2D EPRI dosimetry but 3D dosimetry is likely to be achieved with the EPRI approach in the future. Another interesting future perspective of the present study will be the development of absolute 2D and 3D quantification of the deposited absorbed doses.

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Chapter 11

Discussion

Discussion

In this discussion, we will elaborate on several points presented in the preceding chapters (chapter 2 to chapter 10). This discussion is divided into parts; first one focus on the dosimetry of new brachytherapy sources commercialized by IBt Bebig group and the second one discuss the accuracy of dose calculation performed by commercialized treatment planning systems which are based on TG-43U1 report.

Chapters 2 and 3 were dedicated to the dosimetry study of low energy photons emitted by ^{103}Pd and ^{125}I seeds used for prostate brachytherapy. These chapters covered the determination of dosimetric data, recommended by the TG-43U1 protocol, of two new seeds (OptiSeed-103 and SmartSeed-125), which are made totally in polymer for use in clinical applications.

Suspension of the production of OptiSeed-103 by the company led us to consider the seed as experimental and to focus on its marker effect to quantify its influence on dosimetric parameters. This was obvious in the title (An experimental palladium-103 seed (OptiSeed^{exp}) in a biocompatible polymer without a gold marker: characterization of dosimetric parameters including the interseed effect) of the first published paper presented in chapter 2.

Accurate determination of dose distribution in the patient is a critical part of treatment planning. Treatment planning systems for prostate brachytherapy with seeds generally use the TG-43 algorithm (Nath 1995) and its update, TG-43U1 (Rivard 2004), for dose calculations. This algorithm consists of mathematical equations that calculate approximately the dose distribution around single seeds based on dosimetric data extracted from Monte Carlo calculations. In treatment planning systems, the dose distributions of the individual seeds are superposed to determine the dose distribution for the whole implant.

However, one can debate the accuracy of TG-43U1 based dosimetry methods and errors related to superposing dose distributions of individual seeds. In this work we investigated two aspects:

1. Are the 1D & 2D anisotropy functions recommended by the TG-43U1 protocol good candidates for clinical brachytherapy dosimetry?
2. How can the errors which are due to assumptions related to superposition of the dose distributions of each seed independently be quantified to calculate the total dose distribution for a multi-seed implant and correct it for real-time dosimetry? In other words, how can we correct for the quantified interseed effect with an acceptable speed (less than a second) to enable dose optimization to be performed in parallel with the insertion of the seeds into the area to be irradiated?

Chapters from 4 up to 10 discuss the above-mentioned questions and give some recommendations and new methodology to take into account the interseed effect during real time dosimetry. This will, therefore, improve the accuracy of dose calculation for real time prostate brachytherapy.

1. Dosimetry study of a new iodine-125 and palladium-103 brachytherapy seeds

Dosimetric parameters for OptiSeed-103 and SmartSeed-125 from IBt Bebig group were obtained by measurements using LiF TLD detectors and by Monte Carlo calculations using MCNP code version 4 and 5.

The decision to use LiF TLD detectors was made taking into account the following points:

- They are widely used for dosimetric studies in brachytherapy and are recommended by the TG-43U1 protocol.
- The high dose gradient occurring as a result of the high attenuation of low energy photons affects special resolution of measurement, which makes TLDs an ideal choice because of their high spatial resolution.
- Our considerable experience with this technique, inherited from the studies of Reniers *et al.* (2005), who established dosimetric protocols using TLDs in brachytherapy dosimetry in our institution.

Measurements were performed in solid water (WT1) phantom instead of the liquid water recommended by the TG-43U1 protocol to obtain high precision TLDs and source positions. However, solid water is not adapted for low energy photons and can cause differences in the radial dose function of up to 10% for ^{125}I (Reniers *et al.* 2005). Correction factors therefore have to be applied to obtain data for liquid water. No correction for the use of liquid water as a tissue substitute has been applied to TG-43U1 equations because of the complexity of representing tissue heterogeneity using a mathematical function. In chapter 2, measurements in solid water for OptiSeed^{exp} were only used to check the Monte Carlo calculations and validate the seed model. The dosimetric parameters of OptiSeed^{exp} were therefore, directly derived from Monte Carlo calculations in liquid water. In contrast, in chapter 3, because SmartSeed-125 will be commercialized for clinical use and the TG-43U1 protocol recommends that dosimetric parameters must be the mean of measurements and Monte Carlo calculations, corrections taken from Williamson's Monte Carlo calculations (Williamson 1991) were applied to measurements in solid water in order to obtain measurements for liquid water. The goal of using Williamson's water-to-tissue correction was to apply an independent calculation. Moreover, Williamson's corrections were verified using the MCNP5 code.

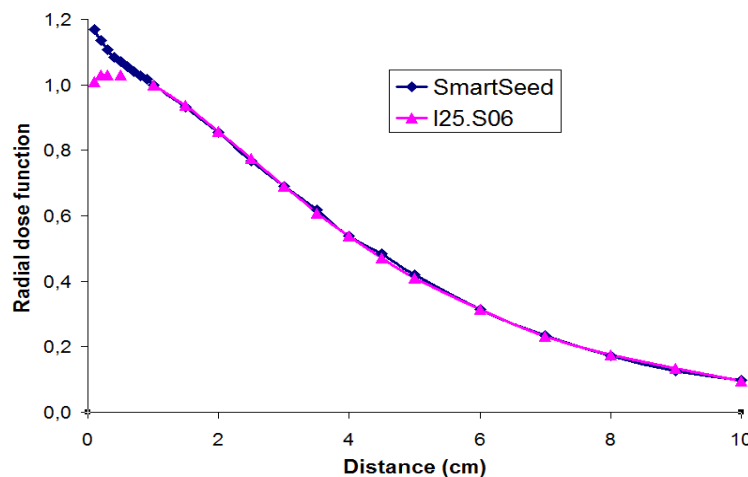


Figure 5. Comparison of the radial dose function calculated in water of two seed models: The SmartSeed (Abboud *et al.* 2010), Symmetra I25.S06 (Hedjtärn 2000).

Radial dose function, anisotropy function and dose rate constant were therefore, calculated in liquid water for these plastic seeds. The radial dose function accounts for dose fall-off on the transverse-plane due to photon scattering, attenuation and absorption in medium; it can also be influenced by filtration of photons by the encapsulation and source materials, especially at short distances in which low-energy photons can penetrate the

polymer encapsulation and contribute to the dose. Therefore, the presence of a polymer instead of a titanium shell did not affect the radial dose functions of OptiSeed^{exp} -103 and SmartSeed-125 calculated in liquid water compared to those of the commercialized seeds. A comparison of two sources, SmartSeed-125 and I25.S06 seeds, with polymer and titanium shell, respectively, is shown in figure 5.

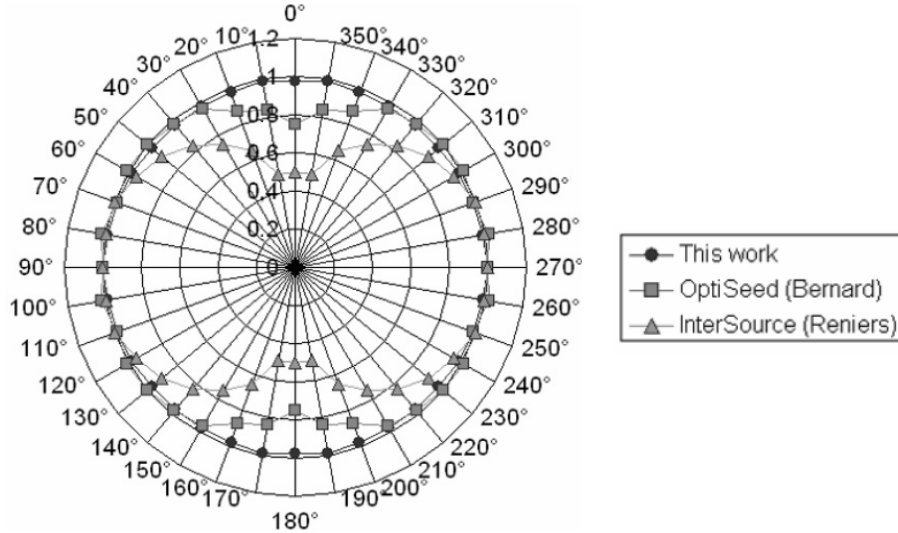


Figure 6. Comparison of anisotropy function measured at 3 cm in a solid water phantom for different Pd-103 sources: OptiSeed-exp (Abboud *et al.* 2008), OptiSeed-103 (Bernard *et al.* 2005) and InterSource-103 (Reniers *et al.* 2002)

The anisotropy function, $F(r, \theta)$, describes the variation in dose as a function of polar angle relative to the transverse plane. Its value typically decreases as r decreases, θ approaches 0° or 180° , encapsulation thickness increases, photon energy decreases and composition and density of encapsulation material change. In present study, we can notice the gain for the anisotropy function of the polymer seed compared to the metallic one (less attenuation at 0°), which is almost isotropic. For example, the variation in the 2D anisotropy function of OptiSeed^{exp} -103 (Abboud 2008) at 3 cm and 0° was less than 8% compared to about 60% for the titanium-encapsulated InterSource-103 (Reniers 2002) (see figure 6) and that of SmartSeed-125 (Abboud 2010) was less than 18% compared to about 32%, 39%, and 47% for the InterSource-125 (Reniers 2001), Symmetra I25.S06 (Hedjtärn 2000), and Amersham model 6702 (Rivard 2004), respectively (see figure 7).

The large value (closer to unity) for the polymer seed anisotropy function at small angles is attributed to the polymer encapsulation, which absorbs low-energy photons much less than the titanium encapsulation in the other sources. The magnitude of this effect is also appreciated when one considers that the path length through the shell increases significantly when the scoring dose is near the axis and attenuation of photons follows exponential behavior. Consequently, a variation in seed orientation will highly affect dose calculation using metallic seed while it will be minimal using the plastic one.

Furthermore, using a polymer shell may substantially reduce the artifacts that can occur with traditional medical imaging techniques when using metallic shells. This effect should, however, be quantified using different imaging modalities (CT, MRI, ultrasound, and mammography) and was not part of the investigations in this thesis.

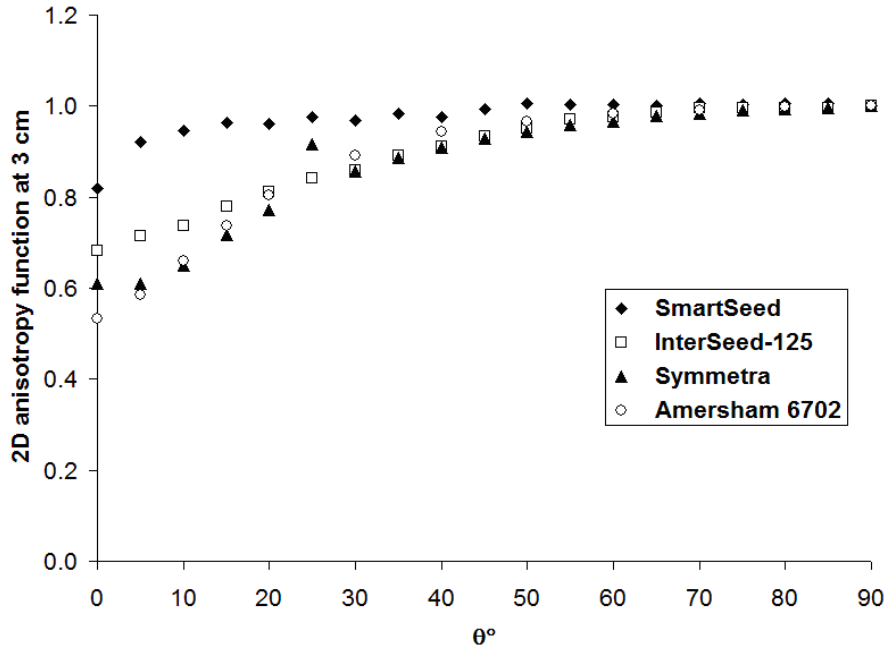


Figure 7. Comparison of the 2D anisotropy function calculated in water at 3 cm for several seed models: The SmartSeed, InterSeed-125 (Reniers *et al.* 2001), Symmetra (Hedjtärn *et al.* 2000) and Amersham 6702 (Rivard *et al.* 2004).

All new seeds have to be precisely calibrated in such a manner that there is direct traceability to either the NIST or an AAPM ADCL (Accredited Dosimetry Calibration Laboratory) before clinical application as described by the AAPM Report TG-43U1. This calibration is performed in air so requires a transformation factor from air to water, the dose rate constant (see chapter 2). Because measurement in air is performed at distances long enough to consider the source as a point and since most seeds have nearly the same cylindrical shape, the dose rate constant will depend only on the energetic spectrum of emitted photons. Dose rate constants are, therefore, comparable for the same radioactive source (Pd-103 or I-125), as we reported for OptiSeed^{exp}-103, but not for SmartSeed-125. The dose rate constant for SmartSeed-125 is about $0.895 \pm 7.3\%$ cGy h⁻¹ U⁻¹ which is less than other commercialized seeds, such as InterSource-125 (Reniers 2001) for which $\Lambda = 1.020 \pm 6\%$ cGy h⁻¹ U⁻¹ and I25.S06 seed (Hedjtärn 2000) for which $\Lambda = 1.002 \pm 1\%$ cGy h⁻¹ U⁻¹.

This result is due to the influence of the 12 keV X-ray on the NIST measured air-kerma (see chapter 3 sec. III C). The major X-rays (~12 keV at 12.3%, ~5 keV at 1.5%, and ~3 keV at 0.2%) are emitted by the lead glass and xenon components of the seed (see figure 8). The polymer capsule is less attenuating than typical titanium so the low-energy X-rays are visible in the emission spectrum. The lead X-rays at 12 keV, therefore, affect the air-kerma strength value but do not contribute to the dose rate at the reference point (see figure 9), thus decreasing the dose rate constant value by about 15%. As mentioned, when Kubo (1985) called attention to contaminant photons from Ti X-rays, NIST adopted a new measurement standard using an aluminum sheet filter. By after, the updated TG-43U1 guidelines implemented a cut-off energy parameter to aid in the MC calculations of air-kerma. NIST, however, cannot be expected to change their measurement methods for each new product, such as the SmartSeed; therefore, we present both values for the dose rate constant, Λ , of $0.895 \pm 7.3\%$ cGy h⁻¹ U⁻¹ at a cut-off of 5 keV (as recommended by TG-43U1 for clinical applications) and $1.024 \pm 2.7\%$ cGy h⁻¹ U⁻¹ at a cut-off of 14 keV.

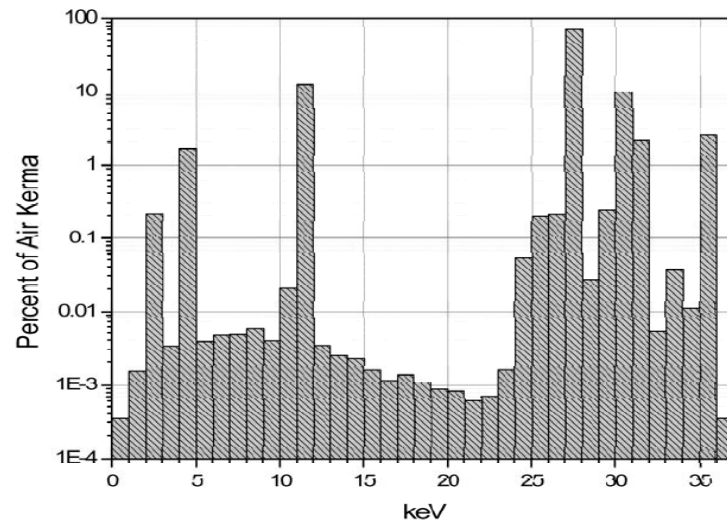


Figure 8. The full energy-fluence spectrum expressed as percent of total air kerma versus photon energy bin

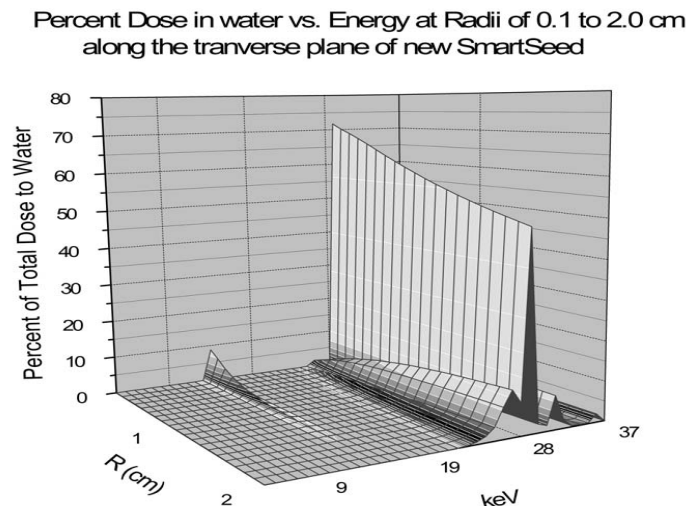


Figure 9. Percent dose in water versus energy along the transverse plane of a new SmartSeed.

These new types of seeds are a new generation of brachytherapy sources that have several advantages compared with conventional metallic ones. Polymer encapsulation absorbs low-energy photons much less than the titanium encapsulation in the other sources that permits a reduction in the quantity of isotope implanted in every seed, leading to a reduction in production costs. Dose calculation error due to variation in seed orientation will be minimal using the plastic seed. Plastic seeds may have future clinical applications; however we need to update and adapt our dosimetric methods to these new products.

2. Accuracy of dose calculation based on TG-43U1 algorithm

The American Association of Physicists in Medicine (AAPM) Task Group No. 43 published a protocol (TG-43) introducing a new brachytherapy dose calculation formalism.

By after, TG-43U1 had been published to accommodate the significant advances which have taken place in the field of permanent source implantation and brachytherapy dosimetry, to develop guidelines for the determination of reference-quality dose distributions by both experimental and Monte Carlo methods, and to promote consistency in derivation of parameters used in TG-43 formalism. Since, it became the standard of treatment planning system used in brachytherapy. However, one can debate the accuracy of TG-43U1 based dosimetry methods, approximations and errors related to superposing dose distributions of individual seeds.

2.1 Errors due to using 1D & 2D approximation (see introduction section 2.2.1)

TG-43U1 protocol presents the 2D approximation as the true complex 2D dose distribution and the most accurate compared to full MC (see chapter 7). However, it does not take into account the interseed effect that induces differences of 6% to 10% (It will be discussed later). 1D isotropic point-source approximation only approximates the 2D dose distribution, therefore, why should have to use the 1D approximation?

The advantage of using 1D approximation compared to 2D approximation is:

- The speed of calculation, for example, using the same processor at Saint-Luc hospital, we noticed that 1D calculation was at least five times faster than 2D calculation.
- It simplifies source localization procedures by eliminating the need to determine the orientation of the source longitudinal axis from imaging studies.

Our investigation focused on the dosimetric error arising because of the 1D approximation in which seeds are straightly implemented.

A DVH comparison of 1D and 2D anisotropy functions is presented in figure 10 for 20 prostate implants. For the prostate, using the 1D anisotropy function, D_{mean} , D_{90} and D_{98} were underestimated by about 3%, 1.5%, and 1%, respectively, and the results of D_{min} and D_{100} were inconsistent.

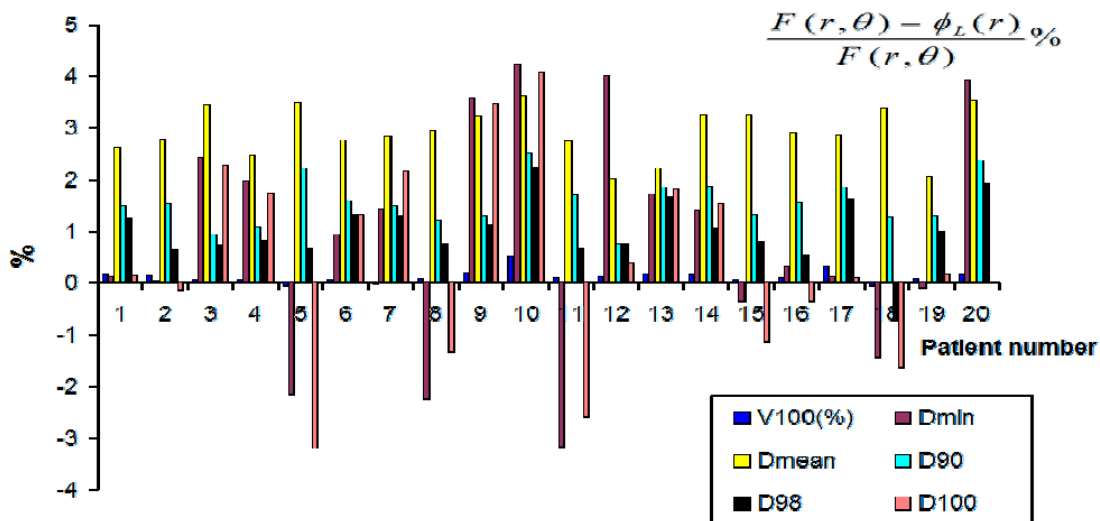


Figure 10. A DVH comparison of 1D and 2D anisotropy functions for 20 prostate implants.

Figure 11 presents the effect of use of the 1D anisotropy function (Line factor $\phi_{L(r)}$ and point factor $\phi_{P(r)}$) on D_{98} , D_{min} , D_{90} (for prostate), D_{max} (for urethra) and V_{100} (for rectum), these being the main parameters used during optimization of the prostate implant in our institute.

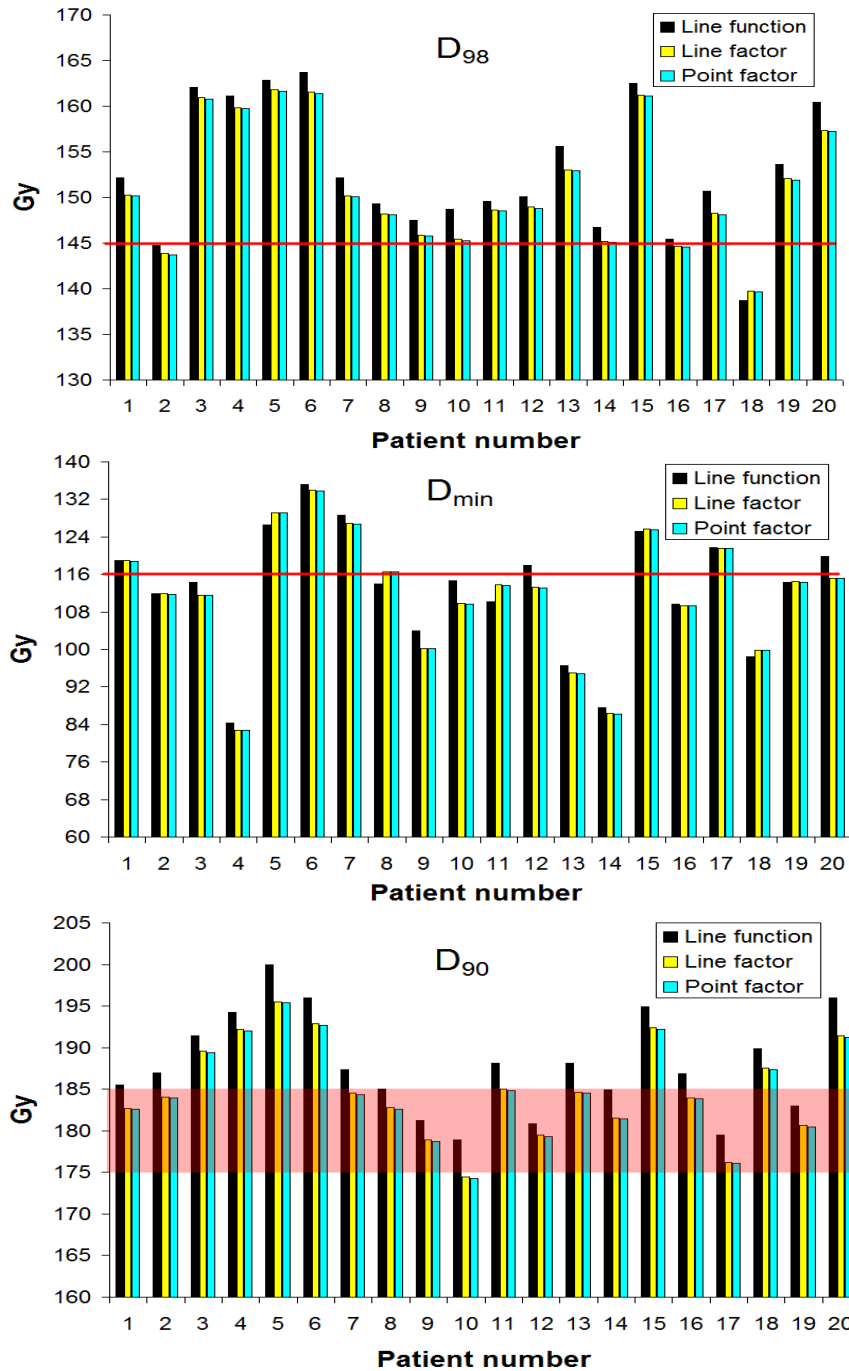


Figure 11. D_{98} , D_{min} , D_{90} for prostate presented for 20 prostate implants. Comparison of the use of 2D anisotropy function (Line function $F(r,\theta)$) and 1D anisotropy function (Line factor $\phi_{L(r)}$ and point factor $\phi_{P(r)}$). The red lines and the red range reflect the recommended parameters limit.

For the urethra, 1D approximation underestimates the $D_{\max}$ for 60% of the patients; their maximum dose for exceeded the limit of 232 Gy accepted in our optimization (figure 12).

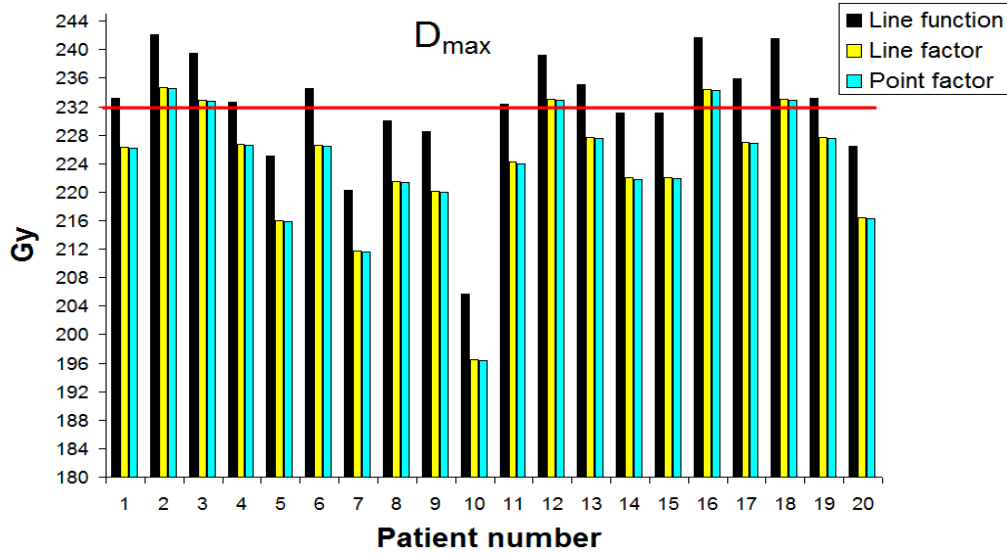


Figure 12. $D_{\max}$ for urethra presented for 20 prostate implants. Comparison of the use of 2D anisotropy function (Line function $F(r,\theta)$) and 1D anisotropy function (Line factor $\phi_{L(r)}$ and point factor $\phi_{P(r)}$). The red line reflects the recommended parameter limit.

Moreover, 1D approximation underestimates V_{100} about 50% less than 2D approximation for the rectum (figure 13). Fortunately, all studied patients have V_{100} , calculated by 1D approximation, less than 1%, if not it will exceed the limit (2%) accepted in our optimisation.

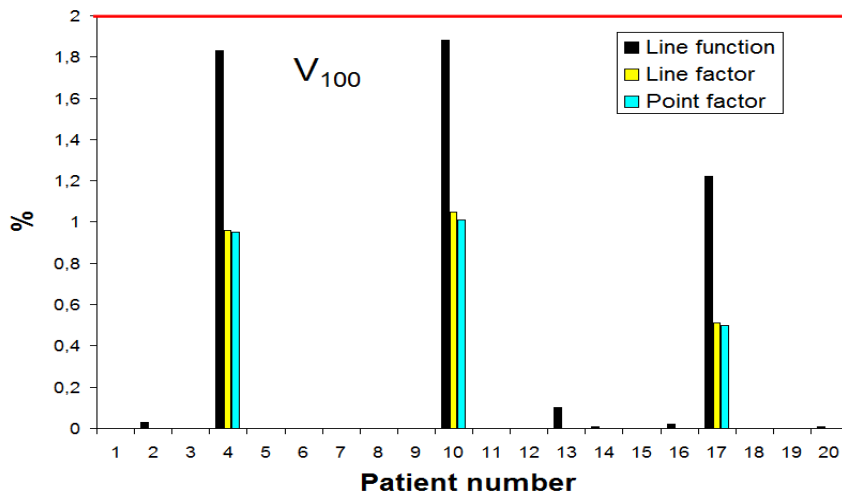


Figure 13. V_{100} for rectum presented for 20 prostate implants. Comparison of the use of 2D anisotropy function (Line function $F(r,\theta)$) and 1D anisotropy function (Line factor $\phi_{L(r)}$ and point factor $\phi_{P(r)}$). The red line reflects the recommended parameter limit.

To understand these difference and inconsistency, dose distributions in planes calculated by 2D and 1D anisotropy functions were compared (figure 14). 1D approximation overestimates the dose by about 15% in planes situated at the two ends of the implant containing no implanted seeds whereas it underestimates the dose by about 5% in the other planes. This yields a compensating effect in the resulting DVHs. These over- and under-dosages can be attributed to an averaging effect of 2D and 1D anisotropy functions (figure 15).

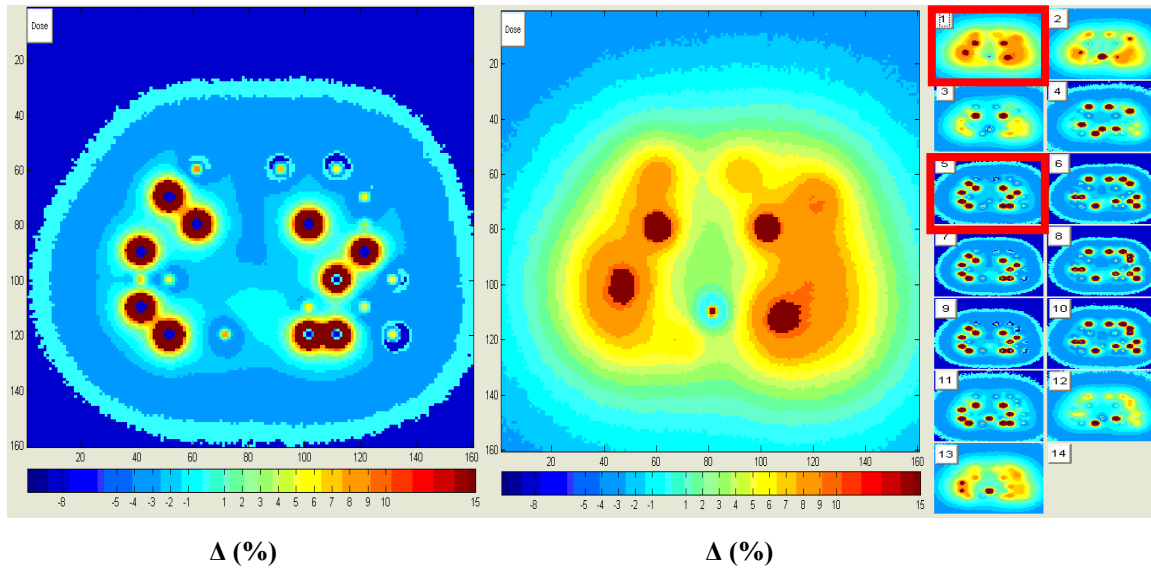


Figure 14. Dose difference in % between 2D and 1D anisotropy function in a patient shown in several planes taken at 5 mm intervals. Planes with red squares show differences ranging between -5% (left side) and 13% (right side)

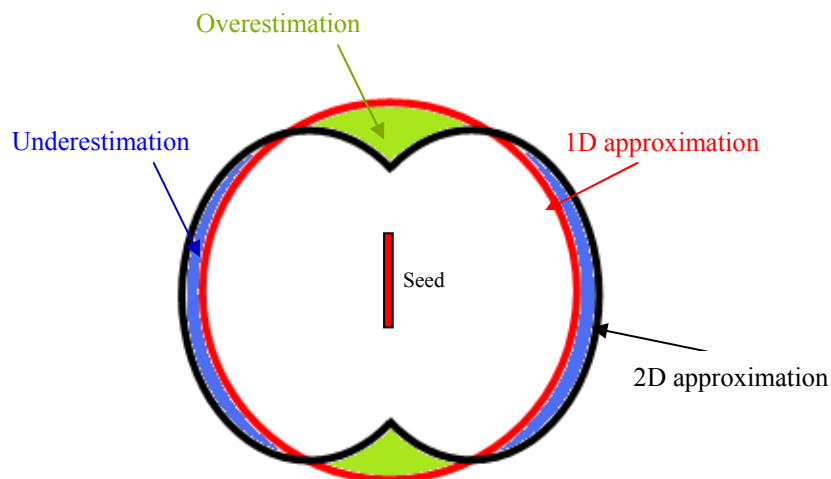


Figure 15. Differences in 2D and 1D anisotropy functions around one seed

Therefore, for TG43U1 calculations, the 2D anisotropy function is preferred to the 1D anisotropy function because this approximation yielded more consistent results for the 20 patients studied. The observed overestimation and variability among the patients can influence the dose–outcome. The clinical effect of the error dose calculation due to 1D approximation has to be deeply investigated taking into account error resulting from seed orientation and interseed effect.

2.2 Errors due to interseed effect

The interseed effect is the attenuation effect of one seed on the dose distribution of all other implanted seeds. Chapters 2, 4, 5 and 6 investigated in depth the second point, i.e., concerning quantification of the interseed effect and development of an effective solution to correct for it for real-time dosimetry.

Indeed, as we explained before, one of the assumptions is that the total dose distribution for a multi-seed implant is merely the superposition of the dose distributions from each seed individually. Hence, TG-43U1 based methods do not take into account interseed effect.

Figure 16 shows that the interseed effect on planar dose distribution varied from 4% to 10%, especially behind coplanar/aligned seeds. This result is comparable with data published by Chibani O. and Williamson J. F. (2005). These authors explained that, for Symmetra seeds, dose errors occurring as a result of the absent interseed attenuation effect vary between 2% and 10%, with an average value of 4%. The influence of cold spots on treatment quality is unknown, but they may lead to prostate cancer recurrence, highlighting the need for dosimetry to be as precise as possible.

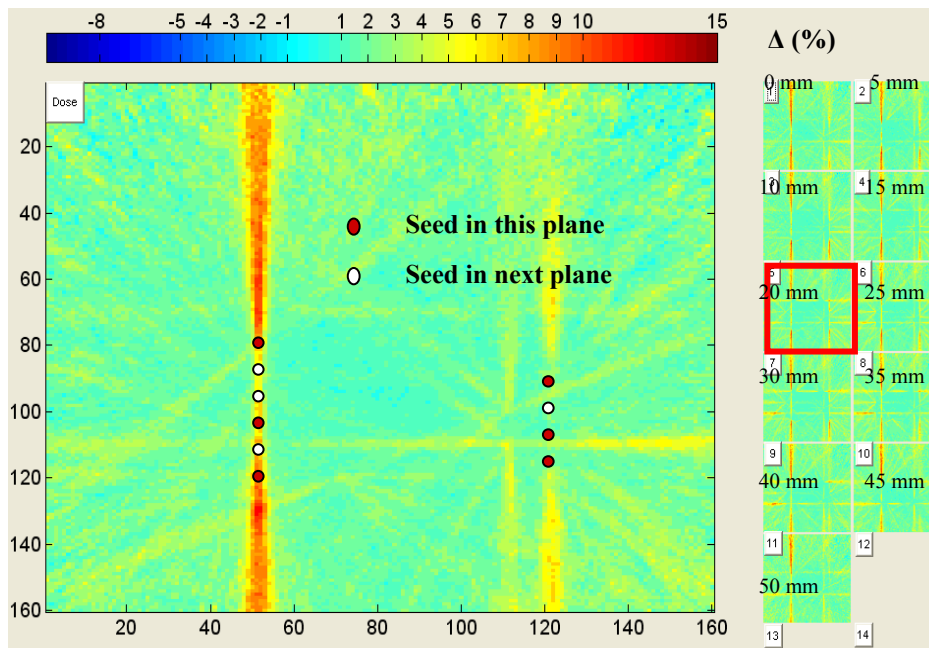


Figure 16. Illustration of the interseed effect that decreased dose estimation by about 4% to 10%, especially behind coplanar/aligned seeds. Data from a patient are shown in several planes taken at 5 mm intervals.

A new method was developed to quantify the interseed effect and include it in real-time dosimetry. First, the attenuation effect of the marker was quantified in chapter 2 by comparing OptiSeed^{exp} (without marker) with the same seed but with a gold marker (Bernard and Vynckier 2005). For this purpose two attenuation factors were defined: ISETDR (InterSeed Effect on the Total Dose Rate), which is similar to the interseed definition, and ISEDRFS (InterSeed Effect on the Dose Rate of the First Seed). The ISETDR of the gold marker was 4.2% and increased to 14% when using a titanium shell instead of a polymer one. ISEDRFS reflects the shadowing effect of the non-active seed (obstacle seed) on the dose rate distribution of a single active seed; it is a function of the position of the obstacle seed, its composition, and the distance of the point of measurement from the obstacle seed. This factor may be easier to insert in the current TPS calculations than the ISETDR because it can be calculated for a single seed as can the radial dose and anisotropy functions.

Moreover, our investigations on the ISEDRFS showed that the attenuation of one seed on the dose distribution of another decreased as the distance between the two seeds increased. As a result, depending on the level of accuracy that is desired, not all the neighboring seeds of each seed in an implant need to be considered in order to evaluate the interseed effect.

Because of the complexity of fitting the ISEDRFS factor to a mathematical function and inserting it in the current TPS algorithm, it was then transformed into a 3D matrix correction using MC simulation (see chapter 4 “patent”). An effective and adequate correction for the interseed effect was obtained by applying this correction matrix for only the nearest seeds (See figure 17 and compare it with figure 16, see also figure 18). Our methodology was divided into several steps. First, 3D MC dose data were calculated for a single seed; the superposition algorithm was then used to calculate the total dose for the multi-seed implant, in what we called MCOSST (Monte Carlo One Seed Superposition Technique). 3D MC interseed correction matrices, called MCOSSIT (Monte Carlo One Seed Superposition Interseed Technique), were applied for the neighboring seeds. This technique provides more rapid calculations and reduces time to 2 sec compared with 16 hours for the full MC calculation (FMCT [Full Monte Carlo Technique]). Figure 18 shows the impact of the interseed effect on isodose for a patient and the efficacy of MCOSSIT compared with FMCT and MCOSST. Therefore, this methodology is currently the most accurate for use in TPS for real-time dosimetry taking the interseed effect into account.

Correction for tissue heterogeneity is not easy to include in real-time dosimetry because ultrasound (US) imaging does not give any information about prostate composition. However, it is important for post-implant dosimetry. Quantification of this effect and trials to include it in both real-time and post-implant dosimetry will be the subject of future investigations.

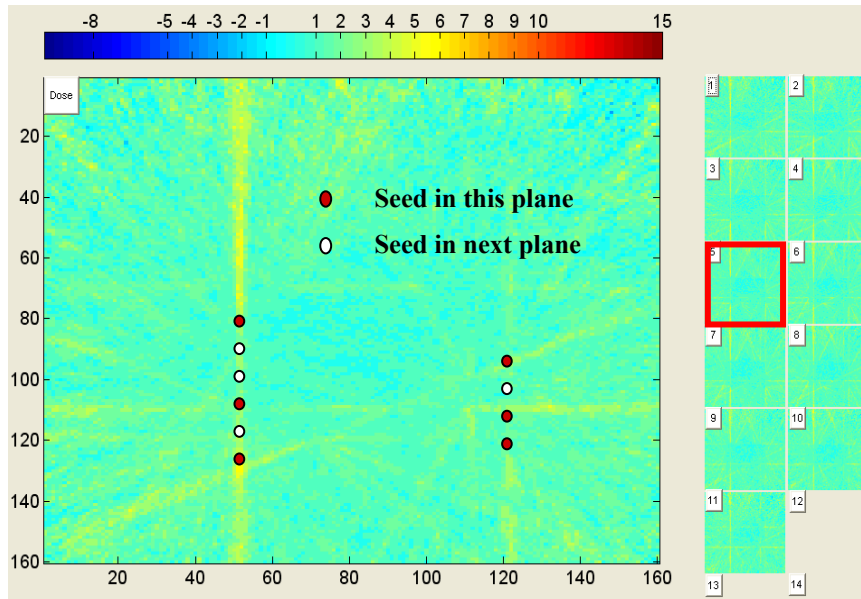


Figure 17. Illustration of the interseed effect after applying the correction matrix, showing the efficacy of our method. Data from a patient are presented for several planes taken at 5 mm intervals.

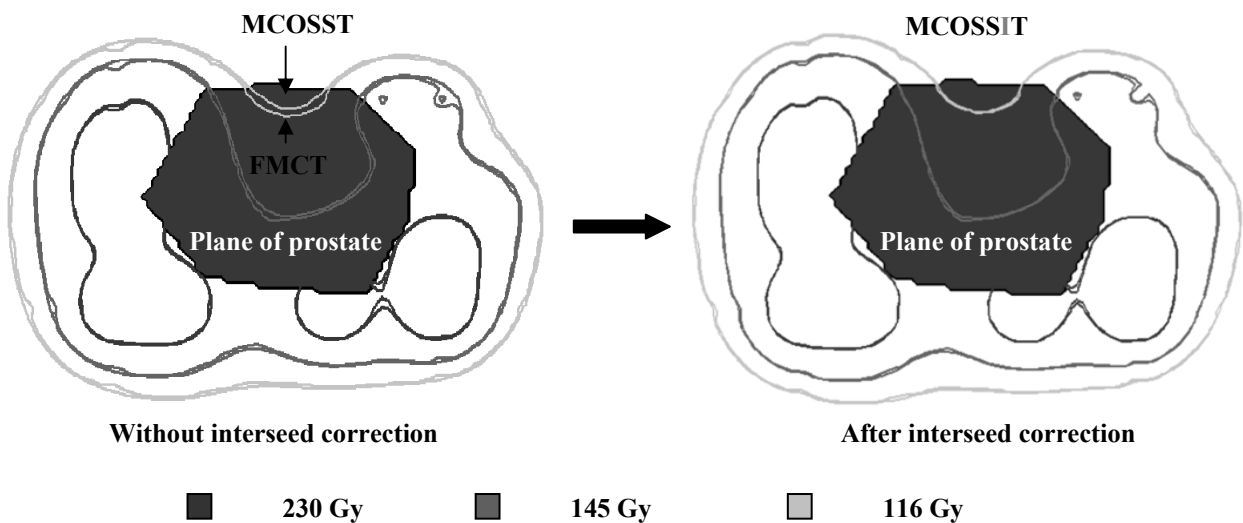


Figure 18. Impact of interseed effect on isodose in planes before and after applying the interseed correction: left hand side the isodoses for MCOOST and FMCT, illustrating the difference at the level of the 116 Gy isodose; right hand side the isodoses calculated with MCOSSIT.

3. Uncertainty analysis

The uncertainty associated with a measurement is a parameter that characterizes the dispersion of the values. This parameter is normally an estimated standard deviation. An uncertainty, therefore, has no known sign and is usually assumed to be symmetrical. It is a

measure of our lack of exact knowledge, after all recognized systematic effects have been eliminated by applying appropriate corrections.

Uncertainties of measurements are expressed as relative standard uncertainties and the evaluation of standard uncertainties is classified into type A and type B. The method of evaluation of type A standard uncertainties is by statistical analysis of a series of observations, whereas the method of evaluation of type B standard uncertainties is based on means other than statistical analysis of a series of observations. The standard uncertainty of Type A is identified with the standard deviation of the mean value of n measured or calculated values. The standard uncertainty of Type B includes not only unknown, although suspected, influences on the measurement process, but also little known effects of influence quantities (pressure, temperature, etc.), application of correction factors or physical data taken from the literature, etc. Some experimenters claim that they can estimate directly this type of uncertainty, while others prefer to use, as an intermediate step, some type of limit. It is often helpful to assume that these uncertainties have a probability distribution which corresponds to some easily recognizable shape (Andreo *et al.* 2000).

The measured and calculated uncertainties are presented in Table 4. The uncertainties estimated here are standard uncertainties, coverage factor $k=1$, approximating a 68% level of confidence. The combined standard uncertainty ($k=1$) on the absorbed dose obtained by TLD measurement was 6.6%. Since relatively little has been published on estimation of systematic (type B) uncertainties of Monte Carlo-based dose estimation, we apply the principles of uncertainty analysis, as outlined in NIST Technical Note 1297 (Taylor *et al.* 1994), to estimation of total uncertainty of Monte Carlo dose-rate constants, $_{MC}\Lambda$, Monte Carlo radial dose functions $_{MC}g(r)$, consensus dose-rate constants, $_{CON}\Lambda$, and absolute transverse-axis dose, Table 4, as evaluated by the dosimetric parameters recommended by TG-43U1 report (Rivard *et al.* 2004).

To estimate the total uncertainty of dosimetric parameters recommended by TG-43U1 protocole, NIST Report 1297 recommends using the Law of Propagation of Uncertainty (LPU) to estimate the uncertainty of a quantity y , that has a functional dependence on measured or estimated quantities $x_1, \dots, x_N$, as follows:

$$y = f(x_1, \dots, x_N),$$

$$\sigma_y^2 = \sum_{i=1}^N \left(\frac{\partial f}{\partial x_i} \right)^2 \sigma_{x_i}^2 + 2 \sum_{i=1}^{N-1} \sum_{j=i+1}^N \frac{\partial f}{\partial x_i} \frac{\partial f}{\partial x_j} \sigma_{x_i x_j}, \quad (1)$$

where σ_{x_i, x_j} (assumed zero here “uncorrelated variables”) represents the covariance of the two variables. For each dosimetric quantity, $Y(\Lambda, g(r), \text{etc.})$, the total percent uncertainty, $\% \sigma_Y$, is considered to be composed of three sources: type B systematic uncertainty due to uncertainty of the underlying cross sections, $\% \sigma_{Y/\mu}$; type B systematic uncertainties arising from uncertainty of the seed geometric model, $\% \sigma_{Y/geo}$; and the type A statistical uncertainty, $\% \sigma_{Y/s}$ inherent to the Monte Carlo technique.

Applying the equation 1 obtains:

$$\% \sigma_Y = \sqrt{\% \sigma_{Y/\mu}^2 + \% \sigma_{Y/geo}^2 + \% \sigma_{Y/s}^2}$$

$$= \sqrt{\left(\% \frac{\delta Y}{\delta \mu} \right)^2 \% \sigma_{\mu}^2 + \left(\% \frac{\delta Y}{\delta geo} \right)^2 \% \sigma_{Y/geo}^2 + \% \sigma_{Y/s}^2} \quad (2)$$

where the relative uncertainty propagation factor is defined as

$$\% \frac{\delta Y}{\delta \mu} \equiv \frac{x}{Y} \frac{\delta Y}{\delta x} \quad (3)$$

The variable x denotes either the cross-section value, μ , or geometric dimension, geo , of interest. The uncertainties estimated here are standard uncertainties, having a coverage factor of unity, approximating a 68% level of confidence.

Table 4. Generic uncertainty assessment for experimental measurements using TLDs, and Monte Carlo methods for radiation transport calculations. Type A and B uncertainties correspond to statistical and systematic uncertainties, respectively. All values provided are for $k=1$.

TLD uncertainties		
Component	Type A	Type B
Repetitive measurements	1.5%	
TLD dose calibration (including linac calibration and TLD reader)	1.8%	1.7%
LiF energy correction ^a		5%
Measurement medium correction factor ^a		3%
Seed/TLD positioning		1%
Quadrature sum	2.3%	6.2%
Total measurements uncertainty		6.6%
<i>S_K uncertainty (including NIST and Capintec CRC-15-R well chamber)</i>		1.7%
<i>Total combined uncertainty in A</i>		6.8%
Monte Carlo uncertainties		
Component	r = 1 cm	r = 5 cm
Statistics	0.2%	1.3%
Ionization cross-sections ^a	1.5%	4.5%
Seed geometry (provided by IBt-Bebig company)	1%	1%
Source energy spectrum	0.1%	0.3%
Total MC calculations uncertainty (quadrature sum)	1.8%	4.8%
<i>S_K uncertainty</i>	2%	
<i>Total combined uncertainty in A</i>	2.7%	

^a As suggested in the TG-43U1 report (Rivard *et al.* 2004).

The measured and calculated uncertainties are presented in Table 4. The uncertainties estimated here are standard uncertainties, coverage factor $k=1$, approximating a 68% level of confidence. The combined standard uncertainty ($k=1$) on the absorbed dose obtained by TLD measurement was 6.6%. Since relatively little has been published on estimation of systematic (type B) uncertainties of Monte Carlo-based dose estimation, we apply the principles of uncertainty analysis, as outlined in NIST Technical Note 1297 (Taylor *et al.* 1994), to estimation of total uncertainty of Monte Carlo dose-rate constants, $_{MC}\Lambda$, Monte Carlo radial dose functions $_{MC}g(r)$, consensus dose-rate constants, $_{CON}\Lambda$, and absolute transverse-axis dose, Table 4, as evaluated by the dosimetric parameters recommended by TG-43U1 report (Rivard *et al.* 2004).

Calculation of the consensus dose rate ($_{CON}\Lambda$) uncertainty is presented as an example. TG-43U1 defines the consensus dose-rate constant as:

$$_{CON}\Lambda = \frac{_{TLD}\Lambda + _{MC}\Lambda}{2} \quad (4)$$

that could be written in another form as:

$$_{CON}\Lambda = \alpha \cdot _{TLD}\Lambda + (1 - \alpha) \cdot _{MC}\Lambda \quad (5)$$

where $\alpha=0.5$ Applying the LPU law, equation 3, obtains

$$\% \frac{\delta _{CON}\Lambda}{\delta _{TLD}\Lambda} \equiv \frac{_{TLD}\Lambda}{_{CON}\Lambda} \cdot \alpha \quad (6)$$

$$\% \frac{\delta _{CON}\Lambda}{\delta _{MC}\Lambda} \equiv \frac{_{MC}\Lambda}{_{CON}\Lambda} \cdot (1 - \alpha) \quad (7)$$

then using equations 2, 6, and 7 we find

$$\% \sigma^2_{_{CON}\Lambda} = \alpha^2 \cdot \left(\frac{_{TLD}\Lambda}{_{CON}\Lambda} \right)^2 \% \sigma^2_{_{TLD}\Lambda} + (1 - \alpha)^2 \cdot \left(\frac{_{MC}\Lambda}{_{CON}\Lambda} \right)^2 \% \sigma^2_{_{MC}\Lambda} + (\% \sigma_B)^2 \quad (8)$$

$\% \sigma_B$ is an additional component of uncertainty in $_{CON}\Lambda$ due to the possible bias in the average of the results of experimental and Monte Carlo methods, and is modeled by a Type B rectangular distribution, bounded by $_{EXP}\Lambda$ and $_{MC}\Lambda$ (Levenson *et al.* 2000). The bias B is assumed to be equal to zero, with standard uncertainty given by

$$\% \sigma_B = 100 \frac{|_{TLD}\Lambda - _{MC}\Lambda|}{2\sqrt{3} _{CON}\Lambda}$$

Therefore, using data from table 4, $\% \sigma_B$ for SmartSeed is about 0.6% and $\% \sigma_{_{CON}\Lambda} = 3.7\%$

4. Future of EPRI (a collaboration study)

In brachytherapy, estimation of the dose near the radioactive source is not easy. This estimation is particularly important for treatment planning and clinical outcome. Moreover, recent data showed that evolution of the tumor microenvironment during brachytherapy is strongly dependent on the distance (in the first millimeters) between the irradiation seeds and

the tumor tissue (Crout *et al.* 2005). Estimation of the dose in the close vicinity of the seeds (<1 cm) using MC calculations is dependent on the codes used and the underlying physics' approximations. An accurate measurement method is required to confirm the MC result at these short distances. However, despite improvements in dosimetry using TLDs, some limitations and difficulties remain, so it is important to investigate new dosimeters and methods for brachytherapy dosimetry. Collaboration with the REMA laboratory using EPRI dosimetry showed the ability of EPRI to estimate the relative dose distribution from low dose rate brachytherapy sources, such as Iodine-125 and Iridium-192 wires (see chapters 7, 8, and 9). Initially, lithium formate (LiFo) was used as the dosimetric material. The main limitation of the method was poor spatial resolution because of the large line-width (LW=1.4 mT) of LiFo. This limitation was solved by using ammonium formate (LW=0.64 mT) as a dosimetric material in EPR imaging. Figure 19 shows the good agreement among EPR imaging, Monte Carlo calculation and Gafchromic film of radial dose distributions for an ammonium formate phantom irradiated by a ^{192}Ir wire source.

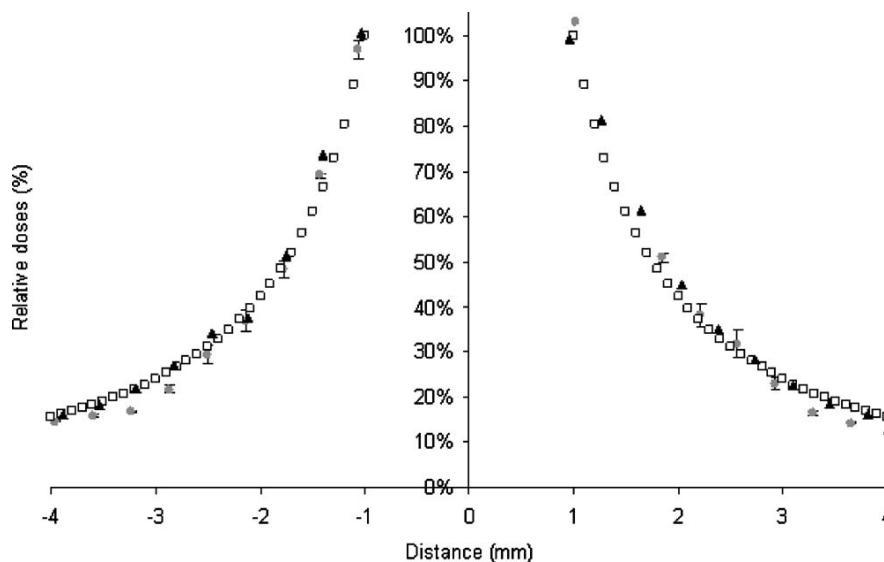


Figure 19. Comparison of Monte Carlo (open squares), Gafchromic film (black triangles), and EPRI (gray circles) radial dose distributions for ammonium formate phantom irradiated by a ^{192}Ir wire source.

We, therefore, demonstrated that the EPRI technique allows estimation of the relative radial dose distribution at short distances for brachytherapy sources.

1D and 2D relative dosimetry were performed; however further investigation is needed to improve the technique, especially its spatial resolution. Another interesting future perspective will be the development of absolute 2D and 3D quantification of the deposited absorbed doses.

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Chapter 12

Conclusion

Conclusion

Brachytherapy began at the turn of the 20th century, contemporary with external-beam radiotherapy. Physicists and physicians developed the field together and it has since seen continuous innovation and progress. The pace of change in the field has never been more rapid than at the present time, particularly in image-guided brachytherapy and the development of unconventional sources and treatment techniques.

The technological advance that probably had the largest impact in the last half century was the introduction of artificial radionuclide sources into clinical brachytherapy. This advance was associated with significantly reduced costs, reduced personnel exposure, and increased technical flexibility. This was highlighted by the new polymer sources studied in this work, in which we have detailed the advantages of new polymer seeds compared with conventional metallic ones. Polymer encapsulation permits a reduction in the quantity of isotope implanted in every seed, leading to a reduction in production costs. Moreover, we noticed the gain in the anisotropy function of the polymer seed compared to the metallic one. Furthermore, using a polymer shell may substantially reduce the artifacts that can occur with metallic shells in traditional medical imaging techniques. This effect should, however, be quantified using different imaging modalities (CT, MRI, ultrasound, and mammography) and was not investigated in this thesis; however, it will be the subject of future research.

We presented a detailed dosimetric study of this new generation of brachytherapy sources (SmartSeed-125 and OptiSeed-103 seeds) to be used for clinical application. However, we need to update our dosimetric methods and adapt them to the newer polymer seeds for future clinical applications.

Other important advances, reviewed elsewhere, have been computer-assisted treatment planning/dose evaluation and advances in dosimetry. Together, these advances set the stage for the dramatic shifts in clinical indications and technical practice that have occurred in the last 15 years. However, dose evaluation based on dosimetric evaluation still has a significant error rate of about 10 to 20%. This error is the result of mathematical approximation in the dose calculation algorithm, neglected interseed attenuation and a heterogeneity effect.

Most of these effects are quantified using MC simulation with high precision, however, there are difficulties correcting them for real-time dosimetry because of the prolonged times needed for MC calculations. In this work, we presented an effective methodology (patent presented in chapter...) to accelerate dose calculation while still preserving the high precision and taking into account the interseed effect.

However, the improvement in dosimetry using TLDs still has several unresolved limitations, so it is important to investigate new dosimeters and methods for brachytherapy dosimetry. A collaborative work on EPRI with the REMA laboratory showed the ability of EPRI to estimate the relative dose distribution from low dose rate brachytherapy sources, such as Iodine-125 and Iridium-192 wires (chapters 8, 9, and 10). 1D and 2D relative dosimetry were performed; however, further investigation is needed to improve the technique, especially in terms of its spatial resolution, and to move towards 3D dosimetry.

Finally, despite improved dose calculations for brachytherapy a reliable implantation technique that ensures the desired positions of seeds and avoids seed displacement is still needed to be able to consider accurate dosimetry as an ideal choice. These observations should also encourage researchers to make efforts to correct for tissue heterogeneity in real-time dosimetry.

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Index

SYSTEM AND METHOD FOR DETERMINING RADIATION DOSE DISTRIBUTION

TECHNICAL FIELD

[0001] The present invention relates to a method, an apparatus, a program and a computer readable medium for determining the radiation dose distribution created by a set of radioactive seeds placed in a volume.

DESCRIPTION OF RELATED ART

[0002] Brachytherapy represents an effective treatment option for different types of cancer. In contrast to external beam radiotherapy in which high-energy particles are directed at the tumor from outside the body, brachytherapy involves the precise placement of radiation sources directly at the site of the cancerous tumor. As an example, for the treatment of the prostate cancer, ^{125}I or ^{103}Pd isotopes are encapsulated in small seeds (typically 5 mm long and 0.5 mm in diameter) that are inserted into the volume to be irradiated.

[0003] A critical part of treatment planning is an accurate determination of dose distribution in the patient. Treatment planning systems for prostate brachytherapy with seeds generally use the TG-43 algorithm and its update, TG-43U1 for dose calculations. The TG-43 algorithm is discussed in article by R. Nath et al., entitled "Dosimetry of interstitial brachytherapy sources: Recommendations of the AAPM Radiation Therapy Committee Task Group No. 43", Med. Phys. 22(2), 209-234 (1995); the TG-43U1 protocol is discussed by M.J. Rivard et al. in "Update of AAPM Task Group No. 43 report: A revised AAPM protocol for brachytherapy dose calculation," Med. Phys. 31(3), 633-674 (2004).

[0004] In TG-43 based dosimetry methods, the dose distributions of the individual seeds are superposed to determine the dose distribution for the whole implant. The calculations of the TG-43 protocol can be made with a treatment planning system at an acceptable speed (less than a second). This allows one to perform the dose optimization in parallel to the insertion of the seeds into the area to be irradiated. Because of tissue heterogeneities and/or positioning errors, some seeds do not locate at their predicted and desired positions. These deviations can be viewed 'on-line', which means during the insertion of the seeds, by using ultrasound-based imaging techniques as an example. A rapid calculation of the dose distribution with these new seed positions is then particularly interesting for placing the following seeds.

[0005] However, one might discuss the accuracy of TG-43 based dosimetry methods. Indeed, one of the assumptions is that the total dose distribution for a multi-seed implant is merely the superposition of the dose distributions due to each seed independently. That means that TG-43 based methods do not take into account the interseed attenuations, known as the interseed effect. The interseed effect is illustrated in figure 1. A seed that is assumed to be non-active, 50, attenuates the radiation dose distribution created by the active seed 40. Studies have shown that the influence of the interseed effect on dose distribution can be large and that it increases with the seeds density. Typically the interseed effect varies between 2 % and 10 %, inducing that the average dose deposited in the prostate is overestimated when using a

TG-43 based method. The influence of the interseed effect on dose distribution is notably discussed in the articles by S. G. Burns et al., entitled “The accuracy of single-seed dose superposition for I-125 implants” Med. Phys. 16, 627-631 (1989); J. F. Carrier et al. entitled “Impact of interseed attenuation and tissue composition for permanent prostate implants”, Med. Phys. 33 (3), 595-604 (2006); O. Chibani et al., entitled “Dosimetric effect of seed anisotropy and interseed attenuation for ^{103}Pd and ^{125}I prostate implants”, Med. Phys. 32(8), 2557-66 (2005).

[0006] Full Monte Carlo Simulations (FMCS) techniques directly calculate the total dose of a given seed distribution. One of such methods uses the Monte Carlo N-Particles (MCNP) code (J.F. Briesmeiter, “MCNP general Monte Carlo N-particle transport”, Los Alamos National Laboratory, Report No. LA-12625, 2004). These techniques take into account the interseed effect but are very slow because of the large number of seeds (greater than fifty). With computers commonly used in medical applications having a processor such as Intel Core Duo 2.83 GHz, the time of calculation reaches 16 hours per patient. Such a method is discussed in the article by O. Chibani et al., entitled “Dosimetric effect of seed anisotropy and interseed attenuation for ^{103}Pd and ^{125}I prostate implants”, Med. Phys. 32(8), 2557-66 (2005). Because of the long calculation time, one cannot use the FMCS method simultaneously with the placement of the seeds.

[0007] An accelerated Monte Carlo code, named MCPI, has been developed for dose calculation in prostate brachytherapy (O. Chibani et al., “MCPI: A sub-minute Monte Carlo dose calculation engine for prostate implants”, Med. Phys. 32(12), 3688-3698). The MCPI calculation method takes into account the interseed effect and is faster than FMCS techniques. However, the calculation time is about one minute for 83 ^{103}Pd -based seeds if one uses a single Pentium 4 PC, 2.4 GHz. Moreover, the MCPI technique requires a deep modification of the used Monte Carlo algorithms inducing new complex computational steps.

[0008] In response to the concerns discussed above, what is needed is a method, an apparatus, a program or a computer readable medium for quickly determining the radiation dose distribution created by a set of radioactive sources and that takes into account the interseed effect. The word “quickly” means in an acceptable time for the patient and the therapist during the insertion of the seeds, which represents a time of few seconds.

SUMMARY OF THE INVENTION

[0009] The object of the present invention is to provide a calculation method and a calculation apparatus that quickly determine the dose distribution created by a set of radioactive sources placed in a volume and which take into account the interseed effect, a program for allowing computer to execute the dose calculation method, and a computer readable medium where such program is recorded. The present invention is applicable to many problems in which energy or dose calculations are required.

[0010] According to a first aspect of the invention, a method for determining the radiation dose distribution created by a set of radioactive seeds placed in a volume is provided. This method includes three stages, T01, T02, and T03 (but T02 is optional), each stage comprising different steps.

[0011] The steps of the first stage that are called preliminary steps are: assuming (S01) that seeds are positioned at nodes of a three-dimensional periodic lattice; determining (S02)

the unit radiation dose distribution, $D_{Single}(x, y, z)$, created by one seed SE_0 when said seed SE_0 is alone in the volume and when its centre is positioned at (x_0, y_0, z_0) ; choosing (S03) in the lattice X neighboring seeds of SE_0 ; choosing (S04) among these X neighboring seeds of SE_0 , SE_k seeds, $k = 1 \dots P$, $P \leq X$; determining (S05) the basic individual attenuations $BIE_k(x, y, z)$, $k = 1 \dots P$, by subtracting from $D_{Single}(x, y, z)$ the radiation dose distribution created by the same seed SE_0 in the presence of one of the SE_k seeds that is assumed to be non active; when $P < X$, determining (S06) the individual attenuations $OIE_m(x, y, z)$, $m = 1 \dots X - P$, created by the neighboring seeds of SE_0 of step S03 and that are not considered in step S05, from the basic individual attenuations $BIE_k(x, y, z)$ and by applying to them one or more mathematical operations selected from the list of rotation, reflection with respect to a plane or a point.

[0012] The second stage is optional and comprises the steps of: loading the unit radiation dose distribution $D_{Single}(x, y, z)$ (S07) and the X individual attenuations (S08) determined in steps S05 and S06.

[0013] The steps of the last stage are: inputting (S09) the actual positions (x_n, y_n, z_n) of the S_n seeds that are placed in the volume, $n = 1 \dots N_s$; determining (S10) the total radiation dose distribution without the interseed effect by adding all the unit radiation dose distributions created by each seed S_n , said unit radiation dose distributions being obtained from $D_{Single}(x, y, z)$ and to which spatial translations are applied; determining (S11) for each seed the attenuation $IE_n(x, y, z)$ that represents the total attenuation created by the neighboring seeds of each said seed S_n , by adding for each said seed S_n , the individual attenuations created by its neighboring seeds that are closer from said each seed S_n than one or two predetermined distances, the individual attenuations being obtained from $BIE_k(x, y, z)$ and $OIE_m(x, y, z)$ and to which spatial translations are applied; adding (S12) all the attenuations $IE_n(x, y, z)$, and finally, determining (S13) the radiation dose distribution created by a set of radioactive seeds by subtracting the result of step S12 from the result of step S10.

[0014] Preferably, the three-dimensional periodic lattice of step S01 of the method of the invention is a primitive cubic lattice, wherein six neighboring seeds of SE_0 are chosen in step S03, these six neighboring seeds being located at the closest neighboring nodes of SE_0 .

[0015] In a more advantageous embodiment, the three-dimensional periodic lattice of step S01 is a primitive cubic or tetragonal lattice, wherein twenty-six neighboring seeds of SE_0 are chosen in step S03 and where five seeds are chosen in step S04 among them.

[0016] In another embodiment, the three-dimensional periodic lattice of step S01 is a prism with a regular hexagonal base, wherein twenty neighboring seeds of SE_0 are chosen in step S03 and where three seeds are chosen in step S04 among them.

[0017] The unit radiation dose distribution $D_{Single}(x, y, z)$ can be obtained from a calculation using the method of Monte Carlo.

[0018] The predetermined distance of step S11 of the method of the invention can be chosen equal to 10 mm for neighboring seeds that do not lie along the same $\vec{z}$ axis as each said seed S_n , and equal to 20 mm for neighboring seeds that lie along the same $\vec{z}$ axis as each said seed S_n , the $\vec{z}$ axis being parallel to the direction of insertion of the seeds.

[0019] According to a second aspect of the invention, an apparatus adapted for calculating the radiation dose distribution created by a set of radioactive seeds placed in a volume is provided. This apparatus comprises: means (M01) for virtually positioning the seeds at nodes of a three-dimensional periodic lattice; means (M02) for determining the unit radiation dose distribution, $D_{Single}(x, y, z)$, created by one seed SE_0 when said seed SE_0 is alone in the volume and when its centre is positioned at (x_0, y_0, z_0) ; means (M03) for choosing in the lattice X neighboring seeds of SE_0 ; means (M04) for choosing among these X neighboring seeds of SE_0 , SE_k seeds, $k = 1 \dots P$, $P \leq X$; means (M05) for determining the basic individual attenuations $BIE_k(x, y, z)$, $k = 1 \dots P$, by subtracting from $D_{Single}(x, y, z)$ the radiation dose distribution created by the same seed SE_0 in the presence of one of the SE_k seeds that is assumed to be non active; means (M06) for determining when $P < X$ the individual attenuations $OIE_m(x, y, z)$, $m = 1 \dots X - P$, created by the neighboring seeds of SE_0 chosen by means M03 and that are not considered with means M05 from the basic individual attenuations $BIE_k(x, y, z)$ and by applying to them one or more mathematical operations selected from the list of rotation, reflection with respect to a plane or a point; optional means (M07) for loading the unit radiation dose distribution $D_{Single}(x, y, z)$; optional means (M08) for loading the X individual attenuations determined by means M05 and M06; means (M09) for inputting the actual positions (x_n, y_n, z_n) of the S_n seeds that are placed in the volume (30), $n = 1 \dots N_s$; means (M10) for determining the total radiation dose distribution without the interseed effect by adding all the unit radiation dose distributions created by each seed S_n , said unit radiation dose distributions being obtained from $D_{Single}(x, y, z)$ and to which spatial translations are applied; means (M11) for determining for each seed the attenuation $IE_n(x, y, z)$ that represents the total attenuation created by the neighboring seeds of each said seed S_n , by adding for each said seed S_n , the individual attenuations created by its neighboring seeds that are closer from said each seed S_n than one or two predetermined distances, the individual attenuations being obtained from $BIE_k(x, y, z)$ and $OIE_m(x, y, z)$ and to which spatial translations are applied; means (M12) for adding all the attenuations $IE_n(x, y, z)$; means (M13) for determining the radiation dose distribution created by a set of seed by subtracting the result obtained by means M12 from the result obtained by means M10.

[0020] An example of three-dimensional periodic lattice used by means M01 is a primitive cubic lattice. In such a case, six neighboring seeds of SE_0 can be chosen by means M03, these six neighboring seeds being located at the closest neighboring nodes of SE_0 . In another embodiment using a primitive cubic lattice or a tetragonal lattice, twenty-six neighboring seeds of SE_0 are chosen by means M03, and five seeds are chosen by means M04 among these twenty-six neighboring seeds. A last example of lattice used by means M01 is a prism with a regular hexagonal base. Then, twenty neighboring seeds can be chosen by means M03 and three seeds among them can be chosen by means M04 as an example.

[0021] The unit radiation dose distribution $D_{Single}(x, y, z)$ can be determined by a calculation unit that uses the method of Monte Carlo.

[0022] The predetermined distance used with means M11 can be chosen equal to 10 mm for neighboring seeds that do not lie along the same $\vec{z}$ axis as each said seed S_n , and equal to 20 mm for neighboring seeds that lie along the same $\vec{z}$ axis as each said seed S_n , the $\vec{z}$ axis being parallel to the direction of insertion of the seeds.

[0023] According to a third aspect of the invention, a computer program is proposed. This computer program comprises software code adapted to cause the apparatus described above to perform steps of the method covered by claims 1-7.

[0024] According to a fourth aspect of the invention, a computer readable medium is proposed. This computer readable medium comprises a computer program (typically stored thereon) comprising software code adapted to cause the apparatus described above to perform steps of the method covered by claims 1-7.

BRIEF DESCRIPTION OF THE DRAWINGS

[0025] Fig.1 is a representation of the interseed effect.

[0026] Fig.2 shows a two-dimensional representation of a set of radioactive seeds in a volume.

[0027] Fig.3 shows a sketch of a template that is used for the insertion of radioactive seeds for treating the prostate cancer.

[0028] Fig.4 shows a cross-section parallel to $\vec{z}$ of a primitive cubic lattice, some nodes of the lattice being occupied by a seed.

[0029] Fig.5 shows a plane of a primitive cubic or tetragonal lattice, each node being occupied by a seed.

[0030] Fig.6 shows three planes of a primitive cubic lattice. A seed is represented alone in its plane and two other planes are shown, one above and one below this seed.

[0031] Fig.7 shows a seed with two neighboring seeds along the same $\vec{z}$ axis.

[0032] Fig.8 shows a lattice that is a prism with a regular hexagonal base.

[0033] Fig.9 shows a block diagram of a computer apparatus for performing the present invention.

[0034] Fig.10(a) shows a cross-section of a prostate with iso-dose curves calculated by the Full Monte Carlo method and by a TG-43 based algorithm. Fig.10(b) shows a cross-section of a prostate with iso-dose curves calculated by the Full Monte Carlo method and by the method of the invention.

[0035] Figure 11(a) shows in a plane iso-value curves for the absolute value of the difference in percent between the dose distribution calculated by a method that does not take

into account the interseed effect (superposition of unit radiation dose distributions) and by the full Monte Carlo technique. Figure 11(b) shows in a plane iso-value curves for the absolute value of the difference in percent between the dose distribution calculated by the method of the invention and by the full Monte Carlo technique.

DETAILED DESCRIPTION OF THE INVENTION

[0036] Explanation will be given below in detail with reference to the drawings.

[0037] Figure 2 shows an exemplary two-dimensional representation of a set of radioactive seeds 20 that are placed in a volume 30. In this figure, the seeds are assumed to form a square lattice. Typically, the volume 30 represents a structure, such as a tumor of a patient cancer, which is to receive a radiation dose. Figure 2 is a two-dimensional representation for simplicity. However, a real target volume 30 is three-dimensional extending in the $\bar{x}$, $\bar{y}$, and $\bar{z}$ directions. Therefore, the present invention is discussed in three-dimensions. When the radiation dose distribution has to be determined in a volume 30, this said volume 30 is often divided in voxels (see for instance EP 1 128 873). Rectangular parallelepipedic voxels are also defined in Computed Tomography (CT) or Magnetic Resonance Imaging (MRI) scans. Then, the radiation dose distribution is a discretized function and is represented by a matrix extending in the three spatial dimensions, each element of the matrix being equal to the radiation dose in each voxel. The method of the invention can be used with continuous or discretized radiation dose distributions.

[0038] The method of the invention includes three stages, T01, T02, and T03, each stage comprising different steps. The first stage T01 includes preliminary steps that have to be carried out only once and whose results can be used for subsequent dose distribution calculations if two conditions are fulfilled. First, the seeds 20 that are in the volume 30 or that are going to be inserted in the volume 30 must be positioned at the nodes of a periodic lattice or at some of them, this lattice being of the same type as the one used in steps of stage T01. Second, the seeds 20 that are in the volume 30 or that are going to be inserted in the volume 30 must be of the same type as the seeds used in the steps of stage T01. These two conditions are detailed below. The second stage T02 includes steps consisting of loading some results obtained in the preliminary steps of stage T01. The third stage T03 comprises different steps which have to be performed each time that a dose distribution is wanted. The different steps are now described in details.

[0039] First (step S01), the seeds 20 are assumed to be positioned at the nodes 15 of a three-dimensional periodic lattice 10. Figure 4 shows a cross-section along the $\bar{z}$ axis of an example of periodic lattice 10. The axis $\bar{z}$ is typically chosen parallel to the direction of insertion of the seeds. The assumption that seeds are positioned at the nodes of a periodic lattice 10 is made because the seeds are typically inserted following a periodic pattern. Figure 3 shows a sketch of a template 80 that is used for the insertion of radioactive seeds 20 for treating the prostate cancer. Needles carrying the seeds 20 are inserted along the $\bar{z}$ direction of figure 3, through the holes 85 and into the volume 30 that has to be radiated. The $\bar{z}$ direction is perpendicular to the plane formed by the holes 85 of the template 80. The distance 70 between each hole along the $\bar{x}$ and $\bar{y}$ directions defined in figure 3 is typically equal to 5 mm. Along the third direction, $\bar{z}$, the seeds 20 are typically placed each 5 or 10 mm. As a consequence of the use of the template 80 shown in figure 3, the inserted seeds form a three-dimensional periodic lattice that is a primitive cubic lattice if the seeds are placed each 5 mm along the $\bar{z}$ direction and a primitive tetragonal lattice if the seeds are positioned each 10 mm

along the same $\vec{z}$ direction. Other templates having a periodic pattern of holes 85 can be used for the insertion of the needles. A template imposing a different spacing of the needles in the $\vec{x}$ and $\vec{y}$ directions results in a positioning of the seeds at the nodes of an orthorhombic lattice whereas a template presenting an hexagonal pattern of holes leads to a positioning of the seeds at the nodes of a prism with a regular hexagonal base. Actually, all the nodes 15 of the lattice 10 are not necessarily occupied by a radioactive seed 20. This is illustrated in figure 4 where each seed is assumed to have the form of a cylinder with an axis parallel to $\vec{z}$. In this figure the distance between each node of the lattice is assumed to be equal to 5 mm and only some of them are occupied by a seed 20. In the preliminary steps of the stage T01, the assumption that all the nodes 15 of the lattice 10 are occupied is nevertheless made to deal with a general case whose results will be used partially or totally in stage T03 depending on the actual implementation of the seeds.

[0040] To obtain the radiation dose distribution created by a set of radioactive seeds 20, it is necessary to know the unit radiation dose distribution created by one seed that is alone in the volume 30. This is the aim of step S02. The unit radiation dose distribution created by one seed SE_0 when said seed is alone and when its centre is assumed to be positioned at (x_0, y_0, z_0) is referred as $D_{Single}(x, y, z)$ in the following. As stated above, $D_{Single}(x, y, z)$ can be a continuous function or a matrix. As the seed SE_0 is assumed to be alone, $D_{Single}(x, y, z)$ represents the unit radiation dose distribution without taking into account the attenuation created by the other seeds, i.e. without taking into account the interseed effect. The unit radiation dose distribution $D_{Single}(x, y, z)$ can be determined experimentally or from a calculation. In the second case, one can use the method of Monte Carlo with the MCNP5 code as an example. The unit radiation dose distribution $D_{Single}(x, y, z)$ is different for each type of radioactive seed. As a consequence, it has to be determined each time that a new type of seed is used. One of the advantages of the invention is that $D_{Single}(x, y, z)$ corresponding to one type of seed has to be determined only once. When $D_{Single}(x, y, z)$ is saved, it can be used for determining the radiation dose distribution created by different sets of seeds if these seeds are of the same type as the seed used to determine $D_{Single}(x, y, z)$. One example of seeds that are used for the treatment of prostate cancers is the seed I25.S06 commercialized by IBt Bebig.

[0041] The interseed effect is the attenuation carried out by each seed on the radiation dose distribution created by the other ones. The attenuation carried out by one seed on the radiation dose distribution created by another one decreases as the distance between these two seeds increases. As a consequence, depending on the level of accuracy that is desired, it is not necessary to consider all the neighboring seeds of each seed to evaluate the interseed effect. In step S03, neighboring seeds of SE_0 that are used to evaluate the interseed effect around (x_0, y_0, z_0) are chosen. Such neighboring seeds constitute a group of X neighboring seeds of SE_0 ($X \geq 1$).

[0042] When the lattice 10 is a primitive cubic lattice and when the seeds have a cylindrical shape, one possible choice of the X neighboring seeds of SE_0 is shown in figures 5, 6 and 7. Figures 5 and 6 show three planes of such a lattice where the distance between two closest nodes is assumed to be equal to 5 mm. Figure 5 shows a first plane that includes the seed SE_0 and where each node of the plane is occupied by a seed 20. Figure 6 shows the planes above and below SE_0 . For clarity reasons, the seeds positioned in the same plane as

SE_0 are not shown in figure 6. Figure 7 shows the seed SE_0 with its two chosen neighboring seeds along the $\bar{z}$ axis. From these figures, we see that twenty-six ($X = 8 \times 3 + 2 = 26$) neighboring seeds of SE_0 are chosen. Such a choice results from the evaluation of the importance of the interseed effect by the inventors when I25.S06 seeds are used. For the neighboring seeds that do not lie along the same $\bar{z}$ axis, the inventors have found that the interseed effect mainly results from the presence of neighboring seeds that are closer than a given distance which is equal to 10 mm for I25.S06 seeds. If one uses the template 80 of figure 3 to insert the seeds 20 in the volume 30, a distance of 10 mm represents two times the distance between two closest nodes of the three-dimensional lattice formed by the seeds 20. So, among the neighboring seeds of SE_0 that do not lie along the same $\bar{z}$ axis, only the seeds such that the distance between their centre and the centre of SE_0 is strictly smaller than two times the distance between two closest nodes of the lattice 10 are considered in the calculation of the interseed effect (seeds depicted in figures 5 and 6). Seeds that have a cylindrical shape such as I25.S06 seeds are typically not positioned at all the nodes of the lattice 10 along the $\bar{z}$ direction. Generally, the distance along $\bar{z}$ between the centers of such seeds is equal to two times the distance between two closest nodes of the lattice 10. The closest neighboring seeds of SE_0 along $\bar{z}$ are then actually placed at the second neighboring nodes of SE_0 along $\bar{z}$. The inventors have found that such neighboring seeds significantly contribute to the interseed effect. That is why such seeds are typically chosen to evaluate the interseed effect when I25.S06 seeds are used and when the lattice 10 is a primitive cubic lattice.

[0043] If the lattice 10 were a primitive cubic lattice and if spherical seeds were used, one could again choose twenty-six neighboring seeds of SE_0 in step S03 but in this case, those along the same $\bar{z}$ axis as SE_0 would be chosen as seeds positioned at the closest nodes of SE_0 along $\bar{z}$. By using the template of figure 3, this means to choose neighboring seeds along $\bar{z}$ whose centers are positioned at a distance of 5 mm from the centre of SE_0 . To decrease the time of calculation, one could rather choose only the closest neighboring seeds of SE_0 to evaluate the interseed effect. In the case of a primitive cubic lattice, only six neighboring seeds of SE_0 would then be chosen but the precision of the evaluation of the interseed effect would decrease. On the contrary, one could choose more than twenty-six neighboring seeds when the lattice 10 is a primitive cubic lattice. This would result in a larger time of calculation and an increase of precision.

[0044] Figure 8 shows another example of a periodic lattice 10 that is a prism with a regular hexagonal base when the distance between each node is equal to 5 mm. Actually, only two planes of such a lattice are shown in figure 8. Each node of this lattice is assumed to be occupied by one cylindrical seed with an axis parallel to $\bar{z}$ but for clarity reasons, the seeds are not shown in figure 8. One possible choice of the X neighboring seeds of SE_0 used to evaluate the interseed effect in this case is to choose twenty seeds, six in the same plan as SE_0 , six in the upper plane and that do not lie along the same $\bar{z}$ axis as SE_0 , six in the lower plane and that do not lie along the same $\bar{z}$ axis as SE_0 , and two along the same $\bar{z}$ axis as SE_0 but such that the distance between their center and the center of SE_0 is equal to two times the distance between two closest nodes of the lattice (see figure 7).

[0045] To determine the attenuation created by the chosen X neighboring seeds of SE_0 on its radiation dose distribution, it is not necessary to know the individual attenuations

created by each of them. By using the symmetry properties of the lattice 10, one only has to know the individual attenuations created by some of them. From these results, one can deduce the individual attenuations created by the other chosen neighboring seeds by applying to these results mathematical operations that take into account the symmetry of the lattice 10. In steps S04, SE_k seeds are chosen among the X neighboring seeds with $k = 1 \dots P$ and $P \leq X$. To decrease the time of calculation, the minimum value of the P parameter could be chosen. This minimum value of P is obtained by choosing among the X neighboring seeds those that produce the same attenuation on the radiation dose distribution created by SE_0 . We now detail how to determine the minimum value of P when the lattice 10 is a primitive cubic lattice or a prism with a regular hexagonal base. In both cases, we assume that seeds have a cylindrical shape with their axis parallel to $\vec{z}$. In the first geometry, we further assume that twenty-six neighboring seeds of SE_0 have been chosen in step S03, these neighboring seeds being shown in figures 5, 6 and 7. In the second case, we assume that twenty neighboring seeds have been chosen in step S03: six in the same plane as SE_0 , six in the upper plane of SE_0 , six in the lower plane of SE_0 , and where the distance between these neighboring seeds and SE_0 is equal to the distance between two closest nodes of the lattice 10; and finally two seeds along the same $\vec{z}$ axis as SE_0 but such that the distance between their center and the center of SE_0 is equal to two times the distance between two closest nodes of the hexagonal lattice of figure 8.

[0046] For cylindrical seeds having their axis parallel to $\vec{z}$, a primitive cubic lattice as the one shown in figure 5 presents an invariance under rotations of 90° around the $\vec{z}$ axis. As a consequence, if one knows the attenuation created by one of the seeds 90 of figure 5, one can deduce the individual attenuations created by the other seeds 90. The same property holds for the individual attenuations created by the seeds 100 on the radiation dose distribution created by the seed SE_0 . For the same reasons, if one knows the attenuation created by one of the seeds 110 of figure 6 on the radiation dose distribution created by the seed SE_0 , one can deduce the individual attenuations created by the other seeds 110. The same property holds for the individual attenuations created by the seeds 120 of figure 6 on the radiation dose distribution created by the seed SE_0 . For the two neighboring seeds of SE_0 lying along the same $\vec{z}$ axis (seeds 125 in figure 7), one only has to know the attenuation carried out by one of them. So, one only has to consider one seed among each set of the seeds 90, 100, 110 and 120, and 125, which leads to five seeds. We deduce that for this case, the minimum value of P is equal to five. Step S06 that is detailed below allows one to get the attenuations created by all the chosen neighboring seeds of step S03 from the attenuations created by the SE_k seeds.

[0047] We now turn to the hexagonal geometry (figure 8). To obtain the individual attenuations carried out by the twenty chosen neighboring seeds of step S03 on the radiation dose distribution created by SE_0 , it is only necessary to consider three SE_k seeds among them. Indeed, with respect to the seed SE_0 , the seeds 130, respectively 140, of figure 8 are equivalent for symmetry reasons. Please note that only half of the seeds 140 is shown in figure 8 for clarity reasons. For the two neighboring seeds of SE_0 lying along the same $\vec{z}$ axis (seeds 125 in figure 7), one only has to keep one of them. If we consider one seed among each set, 125, 130 and 140, one obtains three seeds.

[0048] Step S05 aims at determining the individual attenuations carried out by the SE_k seeds on the dose distribution created by the seed SE_0 . These individual attenuations are

named basic individual attenuations $BIE_k(x, y, z)$ (or Basic Interseed Effects), $k = 1 \dots P$. To obtain the BIE_k attenuations, one has to subtract from the unit radiation dose distribution, $D_{Single}(x, y, z)$, the dose distribution created by the same seed SE_0 in the presence of one of the SE_k seeds that is assumed to be non-active. As in step S02, the dose distribution created by the seed SE_0 in the presence of one of the SE_k seeds can be determined experimentally or from a calculation. In the first case, one has to measure at different points of the space the radiation dose created by one active seed in the presence of another one that is inactive, the two seeds being placed at the nodes of a periodic lattice. As $D_{Single}(x, y, z)$, the attenuations $BIE_k(x, y, z)$ can be continuous functions or matrices.

[0049] Step S06 aims at determining the individual attenuations created by the neighboring seeds of SE_0 , chosen in step S03 and that are not considered in step S05. These individual attenuations are named $OIE_m(x', y', z')$ (or Other Interseed Effects), $m = 1 \dots X - P$. Such a step is only necessary when $P < X$. As the seeds are assumed to be positioned at the nodes of a three-dimensional periodic lattice 10, one can obtain these $OIE_m(x', y', z')$ individual attenuations from the basic individual attenuations $BIE_k(x, y, z)$ determined in step S05 and by applying to them mathematical operations which take into account the symmetry of the lattice 10. Seeds typically have the form of a cylinder or of a sphere. In the first case, the axis of the cylinder is typically parallel to the $\vec{z}$ axis. This leads to two main symmetry properties. Considering a seed SE_0 placed in (x_0, y_0, z_0) , the first property of symmetry is an invariance of the lattice if it undergoes a rotation of an angle θ around an axis parallel to the $\vec{z}$ axis and placed in (x_0, y_0) . The value of the θ angle depends on the type of the periodic lattice 10. For some types of lattices, different θ angles can be identified. For a primitive cubic lattice, $\theta = 90^\circ$, whereas $\theta = 60^\circ$ for a prism with a regular hexagonal base. The second property of symmetry is an invariance of the lattice if it undergoes a reflection with respect to a plane perpendicular to the $\vec{z}$ axis and located at $z = z_0$. This type of symmetry is sometimes called mirror symmetry. As a consequence of these symmetry properties, the individual attenuations $OIE_m(x', y', z')$ can be expressed from the basic individual attenuations $BIE_k(x, y, z)$ by using the following equations:

$$OIE_m(x', y', z') = BIE_k(x, y, z), \text{ (Eq 1)}$$

with

$$\begin{pmatrix} x' \\ y' \\ z' \end{pmatrix} = \begin{pmatrix} \cos \theta & -\sin \theta & 0 \\ \sin \theta & \cos \theta & 0 \\ 0 & 0 & 1 \end{pmatrix} \begin{pmatrix} x - x_0 \\ y - y_0 \\ z - z_0 \end{pmatrix} + \begin{pmatrix} x_0 \\ y_0 \\ z_0 \end{pmatrix}, \text{ (Eq 2)}$$

or

$$(x', y', z') = (x, y, 2z_0 - z), \text{ (Eq 3)}$$

or (x', y', z') being determined from a combination of (Eq 2) and (Eq 3). The only condition is that the attenuations OIE_m and BIE_k of equation (Eq 1) correspond to seeds that induce the

same attenuation on the radiation dose distribution of SE_0 . Equation (Eq 2) illustrates the invariance of the lattice if it undergoes a rotation of an angle θ around an axis parallel to the $\vec{z}$ axis and placed in (x_0, y_0) whereas equation (Eq 3) is representative of the invariance of the lattice if it undergoes a reflection with respect to a plane perpendicular to the $\vec{z}$ axis and located at $z = z_0$. In a standard right-handed coordinate system, the angle θ is positive if the rotation is counterclockwise. When the dose distributions are computed in a discretized space, BIE_k and OIE_m are matrices. Some computational systems allow one to perform operations of rotation with matrices. As an example, the software Matlab proposes the function `rot90` that allows one to rotate a matrix of 90° around an axis. In the case of a primitive cubic lattice with cylindrical seeds, some OIE_m matrices can then be obtained by applying to the corresponding BIE_k matrices this function `rot90`, eventually several times. Rather than applying a combination of operations of rotation and mirror symmetry, one can apply in an equivalent manner operations of reflection with respect to the node occupied by SE_0 , (x_0, y_0, z_0) , to obtain some attenuations $OIE_m(x', y', z')$ from the basic individual attenuations $BIE_k(x, y, z)$. Then one has to use equation (Eq 1) in combination with the following equation:

$$(x', y', z') = (2x_0 - x, 2y_0 - y, 2z_0 - z) \quad (\text{Eq 4})$$

[0050] To illustrate the operations of step S06, we consider again the case of a primitive cubic lattice such as the one illustrated in figures 5 and 6, with cylindrical seeds. As before, we assume that twenty-six neighboring seeds of SE_0 have been chosen in step S03, these twenty-six neighboring seeds being represented in figures 5, 6 and 7. We also assume that among these twenty-six neighboring seeds, five of them have been chosen in step S04 ($P = 5$). An example for the choice of these five seeds SE_k , $k = 1 \dots 5$, is referred in figures 5, 6 and 7 as seeds 91, 101, 111, 121, and 126. If one knows the attenuation due to the seed 91 on the dose distribution created by the seed SE_0 , one can obtain the individual attenuations carried out by the other seeds referred as 90 in figure 5 by using equation (Eq 1) and successively equation (Eq 2) with $\theta = 90^\circ, 180^\circ, 270^\circ$. The same operations can be applied to the attenuation carried out by the seed 101 to obtain the individual attenuations created by all the seeds 100. We now consider the seeds 111 and 121 of figure 6. If one knows the individual attenuations of such two seeds on the dose distribution created by SE_0 , one can obtain the individual attenuations carried out by the other seeds 110 and 120 that lie in the same plane by applying the same procedure as the one used when considering the seeds 90 and 100. To obtain the individual attenuations carried out by the seeds 110 and 120 that do not lie in the same plane as 111 and 121, one has to use (Eq 1) and (Eq 3) or (Eq 1) and a combination of (Eq 2) and (Eq 3). In an equivalent manner, one can obtain one individual attenuation carried out by one seed 90 (respectively 100, 110 or 120) by applying to the attenuation due to the seed 91 (respectively 101, 111 or 121) an operation of reflection with respect to the point (x_0, y_0, z_0) by using (Eq 1) in combination with equation (Eq 4). Finally, if one knows the attenuation carried out by the seed 126 of figure 7 on the radiation dose distribution of SE_0 , one can obtain the attenuation carried out by the other seed 125 by using equation (Eq 1) in combination with equation (Eq 3) or (Eq 4).

[0051] Steps S01 to S06 constitute the first stage T01 of the method of the invention. These steps have been discussed by assuming that all the nodes 15 of the lattice 10 are occupied by a seed 20. Depending on the radiation dose that is wanted in the volume 30, some

of the nodes 15 of the lattice 10 are occupied by a seed and other ones are empty, leading to different seeds configurations. For a chosen type of lattice and seed, the steps of the stage T01 have to be performed only once if their results are saved, even if all the nodes of the lattice are actually not occupied by a seed. The steps of stage T01 are therefore called preliminary steps.

[0052] For a large number of seeds, the method of the invention is preferably performed with a computational system running on a computer. An example of such a system is the software Matlab. If the preliminary steps of stage T01 have been performed prior to the time when the radiation dose distribution is wanted and if the results of the preliminary steps have been saved, one has first to load in the used computational system the unit radiation dose distribution, $D_{Single}(x, y, z)$, and the X individual attenuations determined in steps S05 and S06:

$BIE_k(x, y, z)$ and $OIE_m(x, y, z)$ that we rename $IE_c(x, y, z)$, $c = 1 \cdots X$, where X is the number of neighboring seeds chosen in step S03. Steps S07 and S08 of stage T02 relate to these optional loading phases. These steps have to be performed each time that the used computational system is started. However, once the computational system is running, one does not need to repeat the steps S07 and S08 to obtain the radiation dose distribution created by different seeds configurations if the seeds are positioned at some nodes of a periodic lattice 10 that is always of the same type as the one used to determine the X attenuations of steps S05 and S06. The terms ‘load’ or ‘loading’ are commonly used by the one skilled in the art and mean e.g. an action of transferring data from a mass storage to an active memory. These terms could be replaced by ‘provide’ and ‘providing’.

[0053] Steps of the stage T03 have to be performed each time that a radiation dose distribution created by a set of seeds is wanted. First (step S09), the actual positions (x_n, y_n, z_n) of the seeds that are or that will be inserted in the volume 30, are loaded in the computational system. The seeds are named S_n , $n = 1 \cdots N_s$ and their actual positions can be obtained from a treatment planning and verified by using ultrasound-based imaging techniques as an example.

[0054] In step S10, the total radiation dose distribution created by the N_s seeds S_n and without taking into account the interseed effect is calculated. This distribution is called $D_{noIE}(x, y, z)$ and is obtained by adding the individual radiation dose distributions created by each seed. The seeds 20 that are placed in the volume 30 are often of the same type. If this type is the same as the one of the seed that is used in step S02 to determine $D_{Single}(x, y, z)$, the individual radiation dose distributions created by each seed are simply equal to this unit radiation dose distribution $D_{Single}(x, y, z)$. If the inserted seeds are of different types, it is necessary to determine in step S02 different unit radiation dose distributions corresponding to each type of seeds. In step S02, $D_{Single}(x, y, z)$ is determined by assuming that the seed creating this dose is located at (x_0, y_0, z_0) . To obtain $D_{noIE}(x, y, z)$, it is necessary to take into account the actual positions (x_n, y_n, z_n) of the N_s seeds S_n when performing the summation of the individual contributions. This is illustrated in the following equation:

$$D_{noIE}(x, y, z) = \sum_{n=1}^{N_s} D_{Single}(x + x_0 - x_n, y + y_0 - y_n, z + z_0 - z_n)$$

which summarizes the step S10.

[0055] The importance of the attenuation carried out by a neighboring seed on the radiation dose distribution created by another one decreases as the distance between such two

seeds increases. For I25.S06 seeds commercialized by IBt Bebig, the inventors have quantified the distance above which the attenuation due to a seed can be neglected in the calculation of the interseed effect. For neighboring seeds that do not lie along the same $\bar{z}$ axis of a seed (the $\bar{z}$ axis being parallel to the direction of insertion of seeds and to seed axes), the inventors have found that the interseed effect mainly results from those whose centers are strictly closer than 10 mm from the center of this seed. For neighboring seeds that lie along the same $\bar{z}$ axis of a seed, the interseed effect mainly results from seeds whose centers are strictly closer than 20 mm from the center of this seed. If another type of seeds were used, this distance criterion could change. In step S11, for each seed S_n , the total attenuation created by its neighboring seeds, $IE_n(x, y, z)$, is determined by adding the individual attenuations $IE_c(x, y, z)$ corresponding to neighboring seeds that are located at a distance that is strictly smaller than one or two predetermined criterion's from said each seed S_n . The attenuations $IE_c(x, y, z)$ are determined in steps S05, and S06 by assuming that the seed surrounded by neighboring seeds is located at (x_0, y_0, z_0) . To obtain $IE_n(x, y, z)$, it is necessary to take into account the actual positions (x_n, y_n, z_n) of the N_s seeds S_n when performing the summation of the individual attenuations. This is illustrated in the following equation:

$$IE_n(x, y, z) = \sum_{c=1} IE_c(x + x_0 - x_n, y + y_0 - y_n, z + z_0 - z_n)$$

[0056] To obtain the global interseed effect, $IE(x, y, z)$, one has to add the N_s attenuations determined in step S11. This is the aim of step S12 which is summarized in the following equation:

$$IE(x, y, z) = \sum_{c=1}^{N_s} IE_n(x, y, z)$$

[0057] Finally, in step S13, the radiation dose distribution created by the N_s seeds taking into account the interseed effect is obtained by subtracting the global attenuation determined in step S12 from the dose distribution obtained in step S10:

$$D(x, y, z) = D_{noIE}(x, y, z) - IE(x, y, z).$$

[0058] According to one aspect of the invention, the inventors use an apparatus to carry out the method described above. As an example, figure 9 is a block diagram of a computer 200 for performing the present invention. The computer 200 contains three main software modules that implement the various steps of the method of the invention: preliminary calculation module 201, optional loading module 202, and dose distribution calculation module 203. The computer 200 can be an ordinary, single processor personal computer that includes an internal memory for storing computer program instructions which control how a processing unit within the computer accepts, transforms, and outputs data. The internal memory includes both a volatile and a non-volatile portion. Those skilled in the art will recognize that the internal memory can be supplemented with computer memory media, such as a compact disk, flash memory cards, a magnetic disc drive or a dynamic random access memory.

[0059] Before the computer 200 can calculate the radiation dose distribution, means M01 (a software component of the module 201) virtually position seeds at the nodes of a

three-dimensional periodic lattice 10. Eventually, a user can specify the type of three-dimensional periodic lattice 10 whose nodes are assumed to be occupied by seeds 20, and the type of such seeds 20. Reading means within the preliminary calculation module then accept these input parameters 211 specified by the user. Otherwise, the type of lattice 10 and of seeds 20 is fixed. Four examples of periodic lattice 10 are cubic lattices, tetragonal lattices, orthorhombic lattices, and a prism with a regular hexagonal base. Means M02 (another software component of the module 201) determines the unit radiation dose distribution $D_{Single}(x, y, z)$ created by one seed SE_0 when said seed SE_0 is alone in the volume (30) and when its centre is positioned at (x_0, y_0, z_0) . This unit radiation dose distribution $D_{Single}(x, y, z)$ can be obtained from a calculation unit that uses the method of Monte Carlo. Means M03 of the module 201 chose in the lattice 10 X neighboring seeds of SE_0 . When the lattice 10 is a primitive cubic lattice, these X neighboring seeds can be the six closest neighboring seeds of SE_0 in said lattice 10. Another choice for such a lattice is to choose twenty-four neighboring seeds as shown in figures 5, 6 and 7. When the lattice 10 is a prism with a regular hexagonal base, twenty neighboring seeds of SE_0 can be chosen as shown in figures 7 and 8. Means M04 of the module 201 then chose among these X neighboring seeds of SE_0 SE_k seeds with $k = 1 \dots P$, $P \leq X$ and means M05 determine the basic individual attenuations $BIE_k(x, y, z)$, $k = 1 \dots P$ created by these SE_k seeds. Such a determination is carried out by subtracting from $D_{Single}(x, y, z)$ the radiation dose distribution created by the seed SE_0 in the presence of one of the seeds SE_k that is assumed to be non active. Typically this operation can be performed by using the method of Monte Carlo. When $P < X$, means M06 (a last software component of the module 201) determine the individual attenuations $OIE_m(x, y, z)$, $m = 1 \dots X - P$, created by the neighboring seeds of SE_0 chosen by means M03 and that are not taken into account with means M05, from the basic individual attenuations $BIE_k(x, y, z)$ and by applying to them one or more mathematical operations selected from the list of rotation, reflection with respect to a plane or a point. Software components referred as means M01 to M06 constitute the preliminary calculation module 201. Eventually, an additional means allows one to save the results of this preliminary calculation module 201.

[0060] After, the optional loading module 202 comprising the software components referred as means M07 and M08 allows one to load the unit radiation dose distribution $D_{Single}(x, y, z)$ and the X individual attenuations determined by means M05 and M06 when these results have been saved.

[0061] The dose distribution calculation module 203 that includes components referred as means M09 to M13 actually determines the radiation dose distribution created by a set of radioactive seeds 20 in a volume 30. First, means M09 allows one to input the actual positions (x_n, y_n, z_n) of the S_n seeds that are placed in the volume (30), $n = 1 \dots N_s$. Then, means M10 determine the total radiation dose distribution without the interseed effect by adding all the unit radiation dose distributions created by each seed S_n , said unit radiation dose distributions being obtained from $D_{Single}(x, y, z)$ and to which spatial translations are applied. For each seed, means M11 determine the attenuation $IE_n(x, y, z)$ that represents the total attenuation created by the neighboring seeds of each said seed S_n , by adding for each said seed S_n , the individual attenuations created by its neighboring seeds that are closer from said each seed S_n than one or two predetermined distances, the individual attenuations being

obtained from means M08 and to which spatial translations are applied. When I25.S06 seeds commercialized by IBt Bebig are used, the inventors have quantified the distance above which the attenuation due to a seed can be neglected in the calculation of the interseed effect. For neighboring seeds that do not lie along the same $\bar{z}$ axis of a seed, the inventors have found that the interseed effect mainly results from those whose centers are strictly closer than 10 mm from the center of this seed. For neighboring seeds that lie along the same $\bar{z}$ axis of a seed, the interseed effect mainly results from seeds whose centers are strictly closer than 20 mm from the center of this seed. Means M12 add all the attenuations $IE_n(x, y, z)$ and finally, M13 subtract the result obtained by means M12 from the result obtained by means M10.

[0062] The inventors have used a personal computer having the following characteristics, Intel Core Duo 2.83 GHz, and the three modules described above, 201, 202 and 203 to determine the radiation dose distribution created by a set of seeds 20 placed in a volume.

[0063] Figures 10 (a) and 10 (b) show two cross-sections of a prostate 60 with iso-dose curves calculated by different methods and corresponding to a given distribution of I25.S06 seeds commercialized by IBt-Bebig. As stated above, a full Monte Carlo calculation for determining the radiation dose distribution created by a set of seeds is long (several hours). Such a method which takes into account the interseed effect can nevertheless be used for benchmarking purposes. Figure 10 (a) shows the iso-dose curves calculated by a TG-43 based method and by the full Monte Carlo method. The iso-dose curves determined by the first method are located at the exterior of those determined by the full Monte Carlo method. A clear difference is observed at the level of the 116 Gy iso-dose curve that is more curved inside the prostate when the interseed effect is taken into account. As a consequence, a TG-43 based method overestimates the dose distribution in the prostate 60. Figure 10 (b) shows the iso-dose curves calculated by the method of the invention and by the full Monte Carlo method. In this figure, the iso-dose curves of both methods are close to each other, indicating the efficiency of the method of the invention to take into account the interseed effect. Actually, a complete comparison between the full Monte Carlo method and the method of the invention for this seeds distribution leads to differences that are at most equal to 3 %, whereas differences up to 10 % are observed between results obtained with the full Monte Carlo technique and the TG-43 based method for the seeds distribution corresponding to figures 10 (a) and 10 (b).

[0064] Figure 11 (a) shows in a plane iso-value curves for the absolute value of the difference in percent between the dose distribution calculated by a method that does not take into account the interseed effect and by a full Monte Carlo technique. The used method that does not take into account the interseed effect consists in adding the unit radiation dose distributions corresponding to the different seeds 20, one unit radiation dose distribution being obtained by a Monte Carlo calculation (superposition principle). Figure 11 (b) shows in a plane iso-value curves for the absolute value of the difference in percent between the dose distribution calculated by the method of the invention and by a full Monte Carlo technique. Both figures 11 (a) and 11 (b) correspond to the insertion of forty-five I25.S06 seeds 20. The black dots of figures 11 (a) and 11 (b) represent the seeds 20 that are positioned in the planes of these figures (the scales are in millimeters). By comparing figures 11 (a) and 11 (b), we clearly observe that the method of the invention corresponds to an increase of precision with respect to a simple superposition technique: for the latter, the difference with respect to the dose distribution calculated by the full Monte-Carlo technique reaches around 12 %. With the

method of the invention, the maximum difference is around 5 % in figure 11(b).

[0065] Contrary to a full Monte-Carlo calculation method, the method of the invention is fast. For sixty seeds, the steps of the stage T03 (steps S09 to S13) require about 1 second. Due to this fast response, it is possible, using the method and apparatus of the invention to perform a verification of the dose distribution when inserting each of the successive seeds of a set. The method of the invention is also simple: it does not require new complex mathematical steps as it is the case in the MCPI technique.

[0066] The terms and descriptions used herein are set forth by way of illustration only and are not meant as limitations. Those skilled in the art will recognize that many variations are possible within the spirit and scope of the invention as defined in the following claims, and their equivalents, in which all terms are to be understood in their broadest possible sense unless otherwise indicated. As a consequence, all modifications and alterations will occur to others upon reading and understanding the previous description of the invention. In particular, dimensions and other parameters, given in the above description may vary depending on the needs of the application.

[0067] Summarized, the invention may also be described as follows. A system and method are disclosed for determining the radiation dose distribution created by a set of radioactive seeds (20) placed in a volume (30). The method includes three stages. Stage T01 comprises preliminary steps that allow one to obtain the unit radiation dose distribution created by one seed and the individual attenuations created by its neighboring seeds when said neighboring seeds are assumed to be positioned at the nodes of a three-dimensional periodic lattice. Steps of stage T02 are optional and load some results of the preliminary steps, said results being used by steps of stage T03 that actually determine the dose distribution created by a set of seeds (20). The invention also relates to an apparatus, a program and a computer readable medium adapted for the execution of this method.

Claims

1. A method for determining the radiation dose distribution created by a set of radioactive seeds (20) placed in a volume (30), including:

a first stage (T01) comprising the steps of:

assuming (S01) that seeds are positioned at nodes of a three-dimensional periodic lattice (10);

determining (S02) the unit radiation dose distribution, $D_{Single}(x, y, z)$, created by one seed SE_0 when said seed SE_0 is alone in the volume (30) and when its centre is positioned at (x_0, y_0, z_0) ;

choosing (S03) in the lattice (10) X neighboring seeds of SE_0 ;

choosing (S04) among these X neighboring seeds of SE_0 , SE_k seeds, $k = 1 \cdots P$, $P \leq X$;

determining (S05) the basic individual attenuations $BIE_k(x, y, z)$, $k = 1 \cdots P$, by subtracting from $D_{Single}(x, y, z)$ the radiation dose distribution created by the same seed SE_0 in the presence of one of the SE_k seeds that is assumed to be non active;

when $P < X$, determining (S06) the individual attenuations $OIE_m(x, y, z)$, $m = 1 \cdots X - P$, created by the neighboring seeds of SE_0 of step S03 and that are not considered in step S05, from the basic individual attenuations $BIE_k(x, y, z)$ and by applying to them one or more mathematical operations selected from the list of rotation, reflection with respect to a plane or a point;

an optional second stage (T02) comprising the steps of:

loading the unit radiation dose distribution $D_{Single}(x, y, z)$ (S07) and the X individual attenuations (S08) determined in steps S05 and S06;

a third stage (T03) comprising the steps of:

inputting (S09) the actual positions (x_n, y_n, z_n) of the S_n seeds that are placed in the volume (30), $n = 1 \cdots N_s$;

determining (S10) the total radiation dose distribution without the interseed effect by adding all the unit radiation dose distributions created by each seed S_n , said unit radiation dose distributions being obtained from $D_{Single}(x, y, z)$ and to which spatial translations are applied;

determining (S11) for each seed the attenuation $IE_n(x, y, z)$ that represents the total attenuation created by the neighboring seeds of each said seed S_n , by adding for each said seed S_n , the individual attenuations created by its neighboring seeds that are closer from said each seed S_n than one or two predetermined distances, the individual attenuations being obtained from $BIE_k(x, y, z)$ and $OIE_m(x, y, z)$ and to which spatial translations are applied;

adding (S12) all the attenuations $IE_n(x, y, z)$;

determining (S13) said radiation dose distribution by subtracting the result of

step S12 from the result of step S10.

2. Method according to claim 1 further comprising between first (T01) and third (T03) stage an optional second stage (T02) comprising the steps of:
loading the unit radiation dose distribution $D_{Single}(x, y, z)$ (S07) and the X individual attenuations (S08) determined in steps S05 and S06.
3. Method according to claim 1 or 2, wherein the three-dimensional periodic lattice (10) of step S01 is a primitive cubic lattice and wherein six neighboring seeds of SE_0 are chosen in step S03, these six neighboring seeds being located at the closest neighboring nodes of SE_0 .
4. Method according to claim 1 or 2, wherein the three-dimensional periodic lattice (10) of step S01 is a primitive cubic or tetragonal lattice, wherein twenty-six neighboring seeds of SE_0 are chosen in step S03 and where five seeds are chosen in step S04 among these twenty-six seeds.
5. Method according to claim 1 or 2, wherein the three-dimensional periodic lattice (10) of step S01 is a prism with a regular hexagonal base, wherein twenty neighboring seeds are chosen in step S03 and where three seeds are chosen among these twenty seeds in step S04.
6. Method according to any of the previous claims, wherein the unit radiation dose distribution $D_{Single}(x, y, z)$ is obtained from a calculation using the method of Monte Carlo.
7. Method according to any of the previous claims, wherein the predetermined distance of step S11 is equal to 10 mm for neighboring seeds that do not lie along the same $\bar{z}$ axis as each said seed S_n , and equal to 20 mm for neighboring seeds that lie along the same $\bar{z}$ axis as each said seed S_n , the $\bar{z}$ axis being parallel to the direction of insertion of the seeds.
8. An apparatus adapted for calculating the radiation dose distribution created by a set of radioactive seeds (20) placed in a volume (30), comprising:

means (M01) for virtually positioning the seeds at nodes of a three-dimensional periodic lattice (10);

means (M02) for determining the unit radiation dose distribution, $D_{Single}(x, y, z)$, created by one seed SE_0 when said seed SE_0 is alone in the volume (30) and when its centre is positioned at (x_0, y_0, z_0) ;

means (M03) for choosing in the lattice (10) X neighboring seeds of SE_0 ;

means (M04) for choosing among these X neighboring seeds of SE_0 , SE_k seeds,

$k = 1 \dots P$, $P \leq X$;

- means (M05) for determining the basic individual attenuations $BIE_k(x, y, z)$, $k = 1 \cdots P$, by subtracting from $D_{Single}(x, y, z)$ the radiation dose distribution created by the same seed SE_0 in the presence of one of the SE_k seeds that is assumed to be non active;
- means (M06) for determining when $P < X$ the individual attenuations $OIE_m(x, y, z)$, $m = 1 \cdots X - P$, created by the neighboring seeds of SE_0 chosen by means M03 and that are not considered with means M05 from the basic individual attenuations $BIE_k(x, y, z)$ and by applying to them one or more mathematical operations selected from the list of rotation, reflection with respect to a plane or a point;
- means (M09) for inputting the actual positions (x_n, y_n, z_n) of the S_n seeds that are placed in the volume (30), $n = 1 \cdots N_s$;
- means (M10) for determining the total radiation dose distribution without the interseed effect by adding all the unit radiation dose distributions created by each seed S_n , said unit radiation dose distributions being obtained from $D_{Single}(x, y, z)$ and to which spatial translations are applied;
- means (M11) for determining (S11) for each seed the attenuation $IE_n(x, y, z)$ that represents the total attenuation created by the neighboring seeds of each said seed S_n , by adding for each said seed S_n , the individual attenuations created by its neighboring seeds that are closer from said each seed S_n than one or two predetermined distances, the individual attenuations being obtained from $BIE_k(x, y, z)$ and $OIE_m(x, y, z)$ and to which spatial translations are applied;
- means (M12) for adding all the attenuations $IE_n(x, y, z)$;
- means (M13) for determining said radiation dose distribution by subtracting the result obtained by means M12 from the result obtained by means M10.
9. Apparatus according to claim 7 wherein the three-dimensional periodic lattice (10) is a primitive cubic lattice and where six neighboring seeds of SE_0 are chosen by means M03, these six neighboring seeds being located at the closest neighboring nodes of SE_0 .
 10. Apparatus according to claim 7 wherein the three-dimensional periodic lattice (10) is a primitive cubic or tetragonal lattice, where twenty-six neighboring seeds of SE_0 are chosen by means M03, and where five seeds are chosen by means M04 among these twenty-six seeds.
 11. Apparatus according to claim 7 wherein the three-dimensional periodic lattice (10) is a prism with a regular hexagonal base, where twenty neighboring seeds are chosen by means M03 and where three seeds are chosen among these twenty seeds by means M04.
 12. Apparatus according to any of claims 7 to 10 wherein the unit radiation dose distribution $D_{Single}(x, y, z)$ is determined by a calculation unit that uses the method of Monte Carlo.
 13. Apparatus according to any of claims 7 to 11, wherein the predetermined distance used with means M11 is equal to 10 mm for neighboring seeds that do not lie along the same $\vec{z}$ axis as each said seed S_n , and equal to 20 mm for neighboring seeds that lie along the same $\vec{z}$ axis as each said seed S_n , the $\vec{z}$ axis being parallel to the direction of insertion

of the seeds.

14. A computer program comprising software code adapted to cause the apparatus according to claims 8-13 to perform steps of the method according to claims 1-7.
15. A computer readable medium comprising a computer program comprising software code adapted to cause the apparatus according to claims 8-13 to perform steps of the method according to claims 1-7.

Abstract

A system and method are disclosed for determining the radiation dose distribution created by a set of radioactive seeds (20) placed in a volume (30). The method includes three stages. Stage T01 comprises preliminary steps that allow one to obtain the unit radiation dose distribution created by one seed and the individual attenuations created by its neighboring seeds when said neighboring seeds are assumed to be positioned at the nodes of a three-dimensional periodic lattice. Steps of stage T02 are optional and load some results of the preliminary steps, said results being used by steps of stage T03 that actually determine the dose distribution created by a set of seeds (20). The invention also relates to an apparatus, a program and a computer readable medium adapted for the execution of this method.

Fig. 9

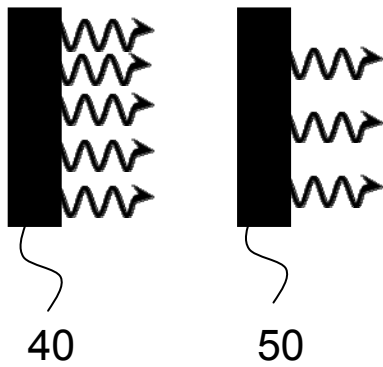


Fig. 1

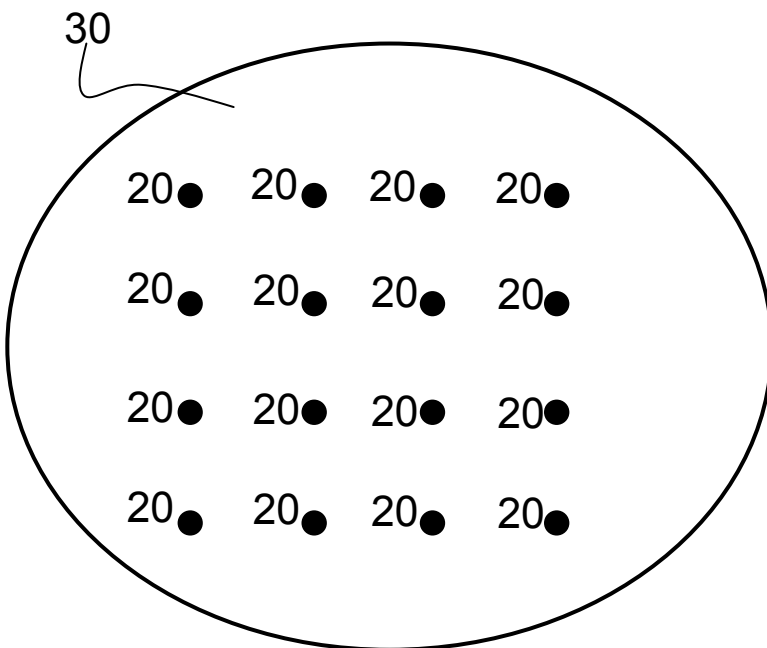


Fig. 2

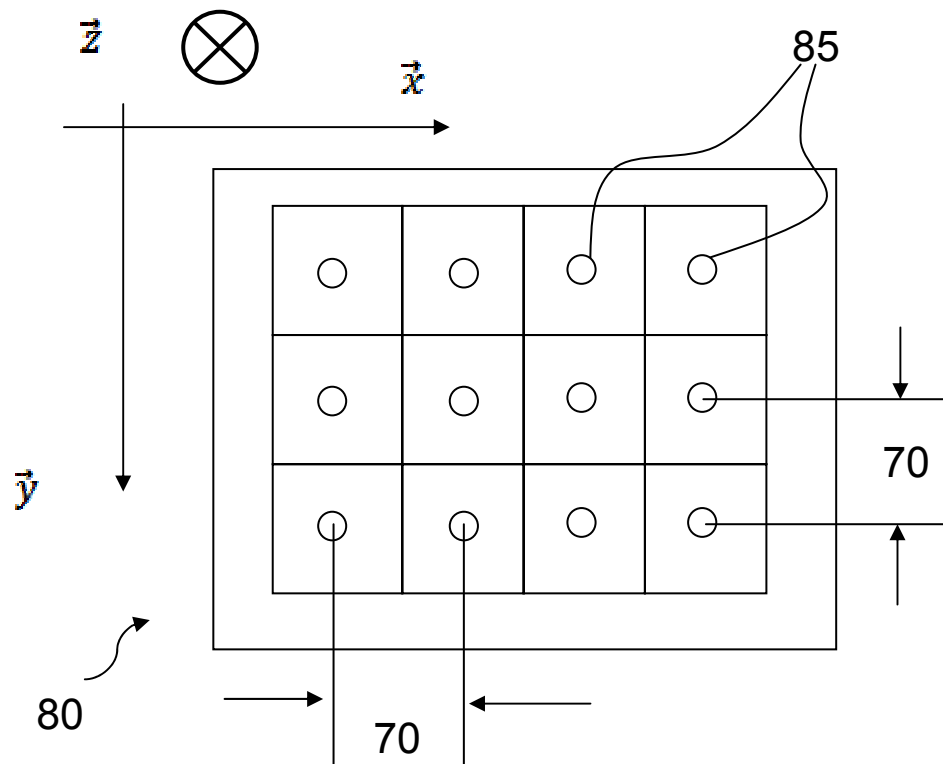


Fig. 3

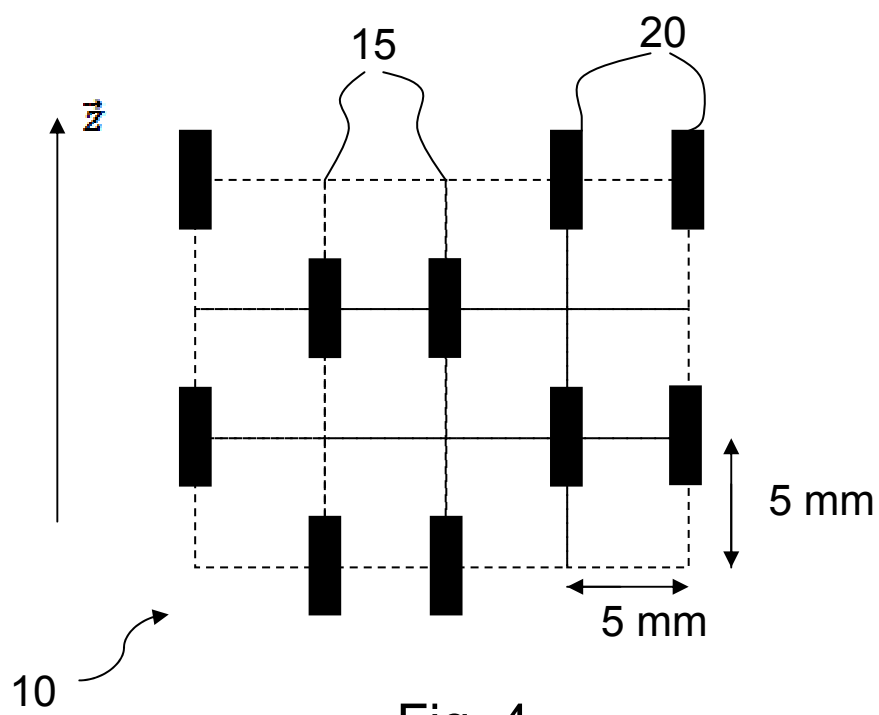


Fig. 4

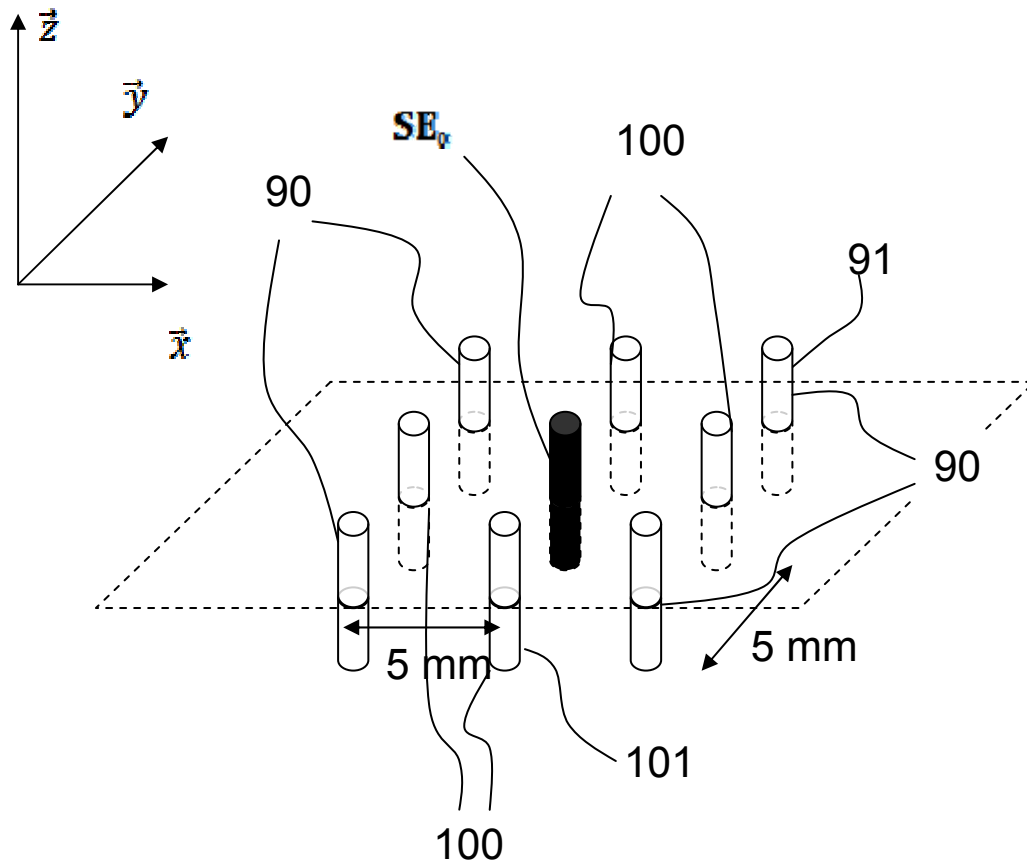


Fig. 5

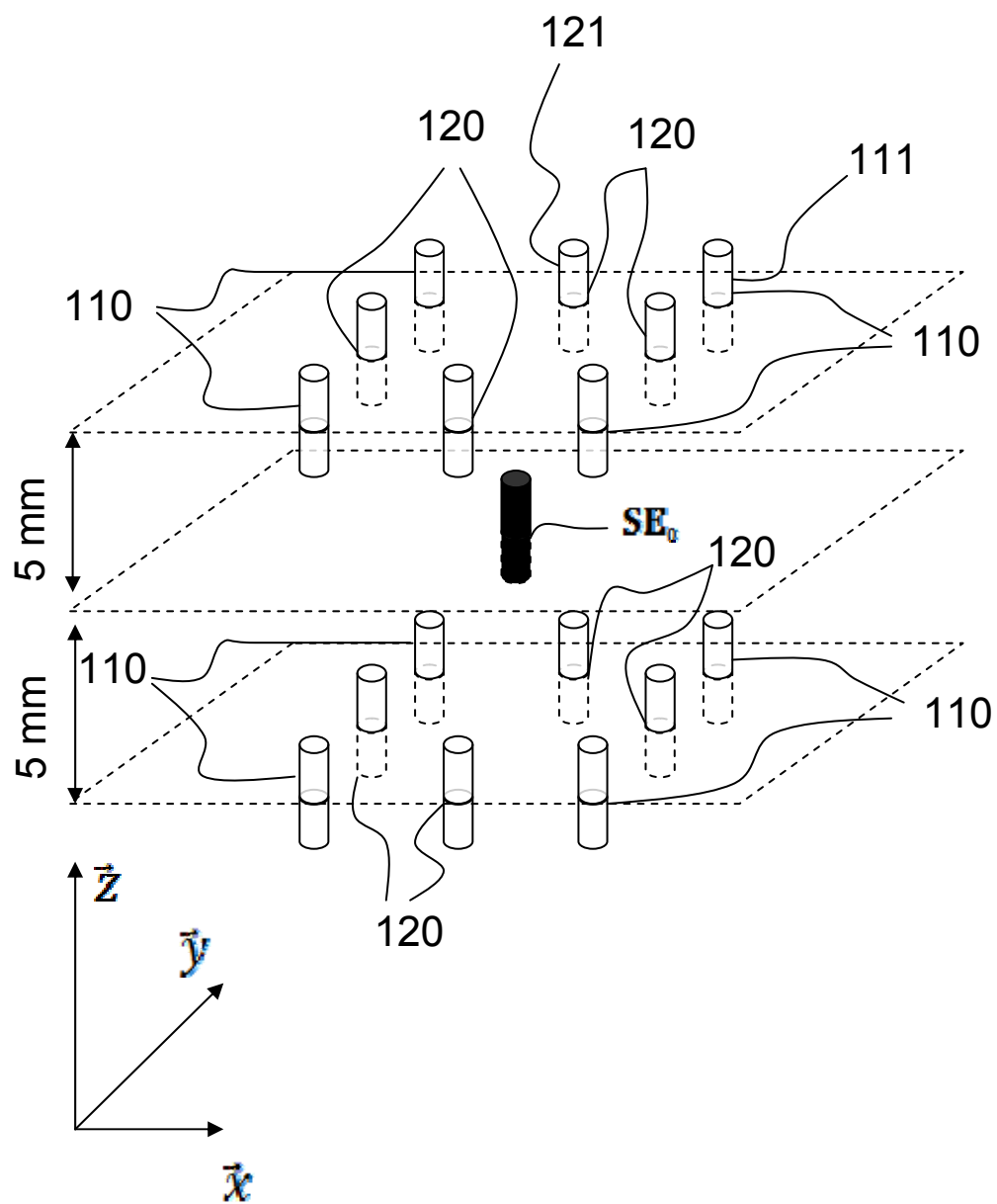


Fig. 6

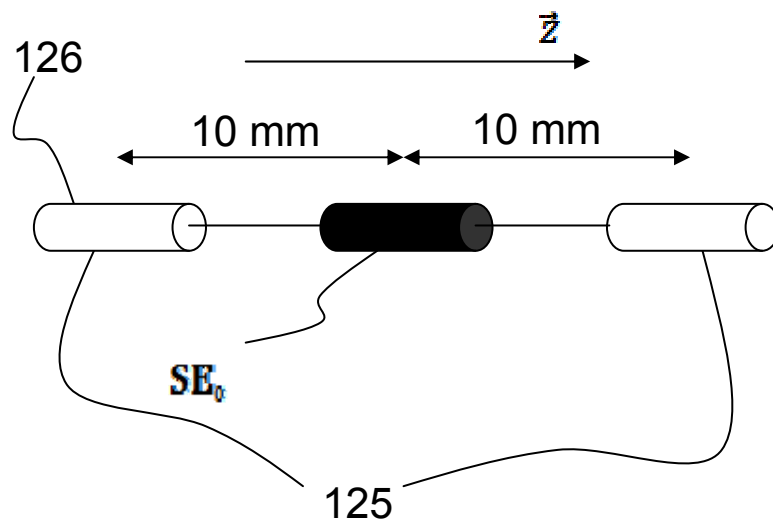


Fig. 7

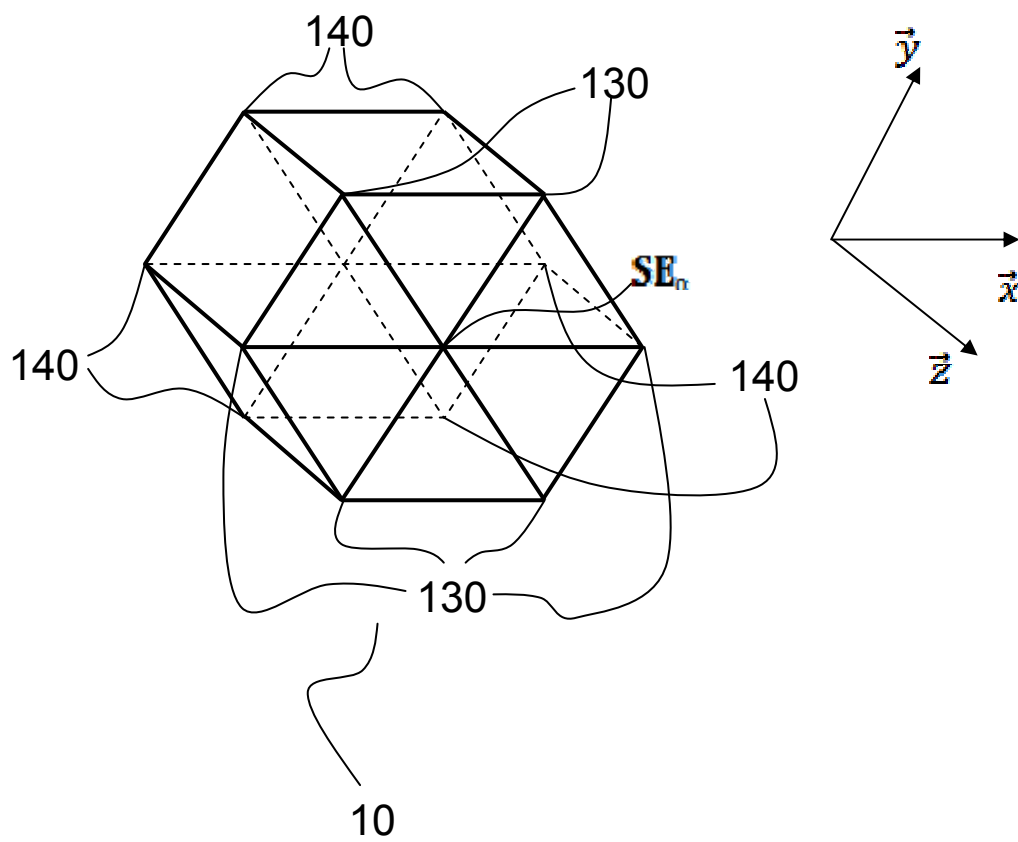


Fig. 8

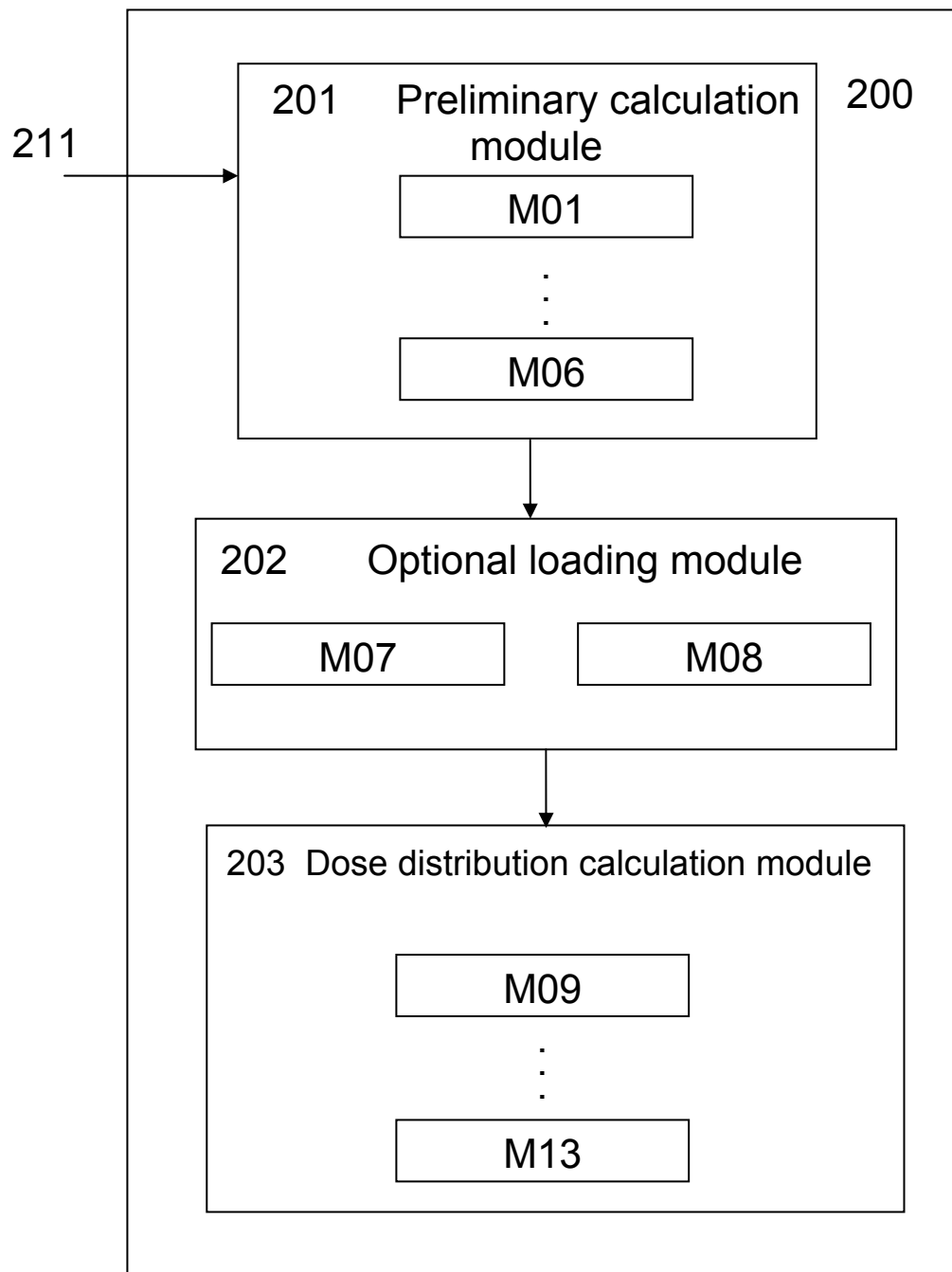


Fig. 9

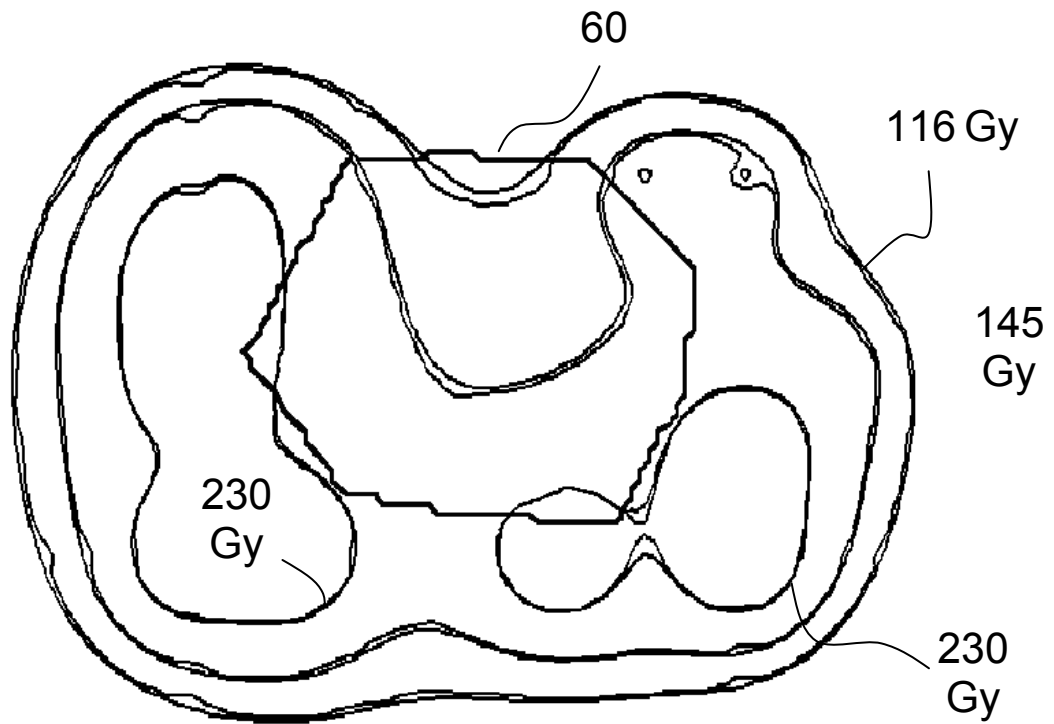


Fig. 10(a)

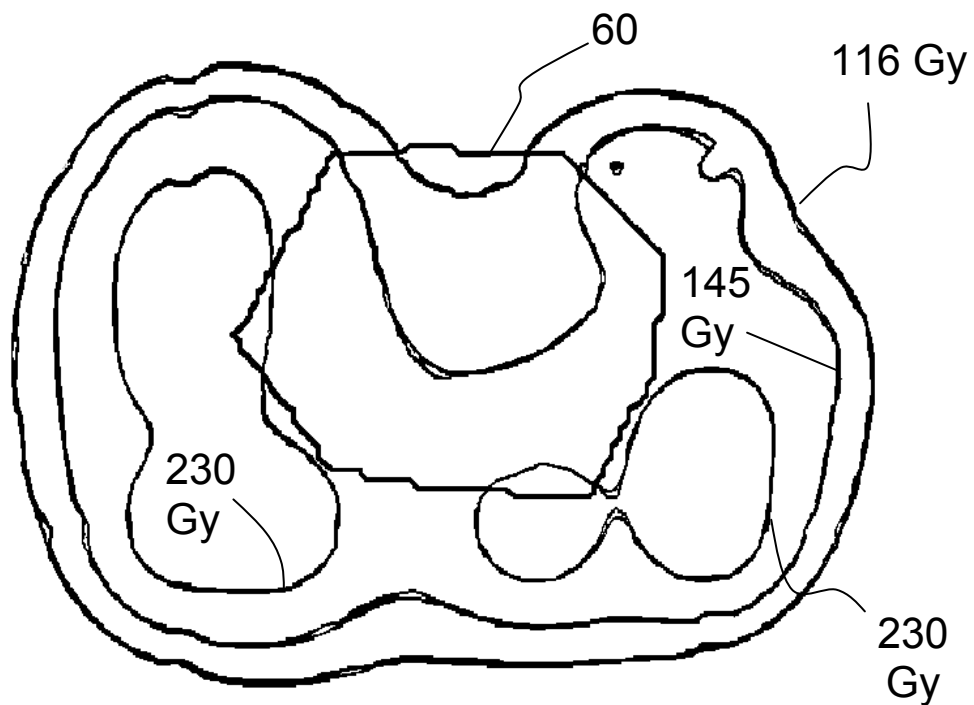


Fig. 10(b)

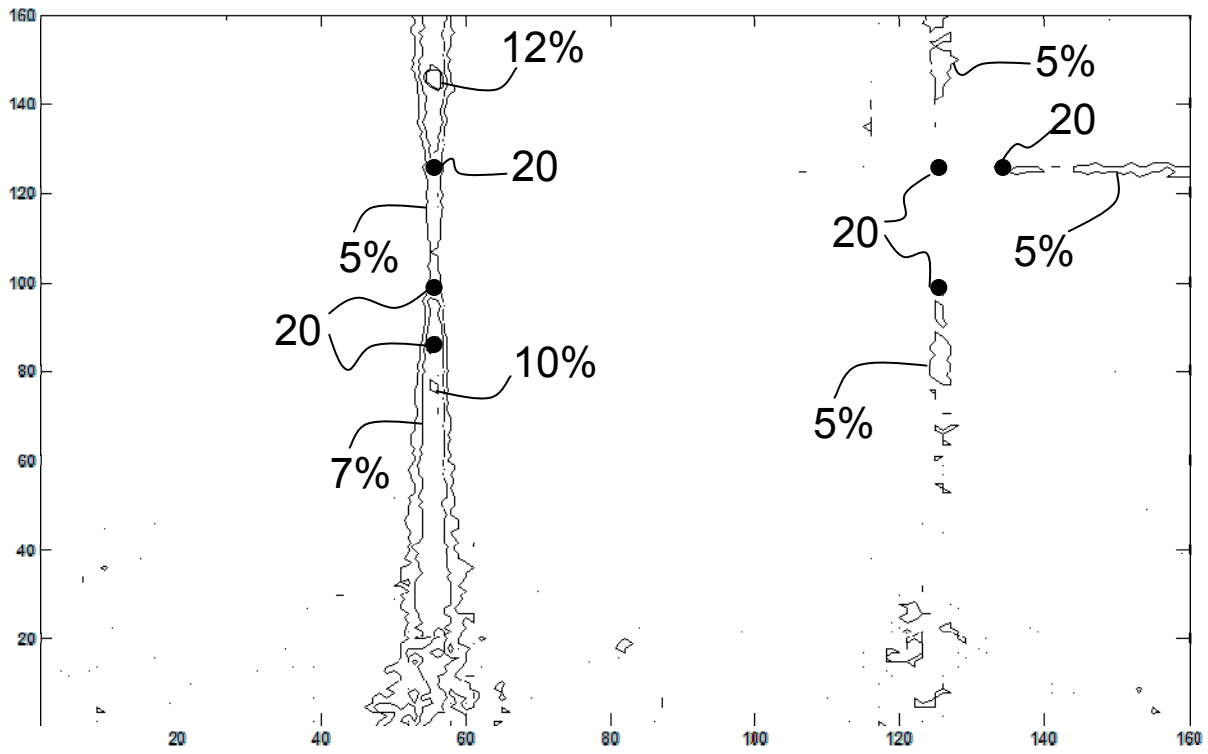


Fig. 11(a)

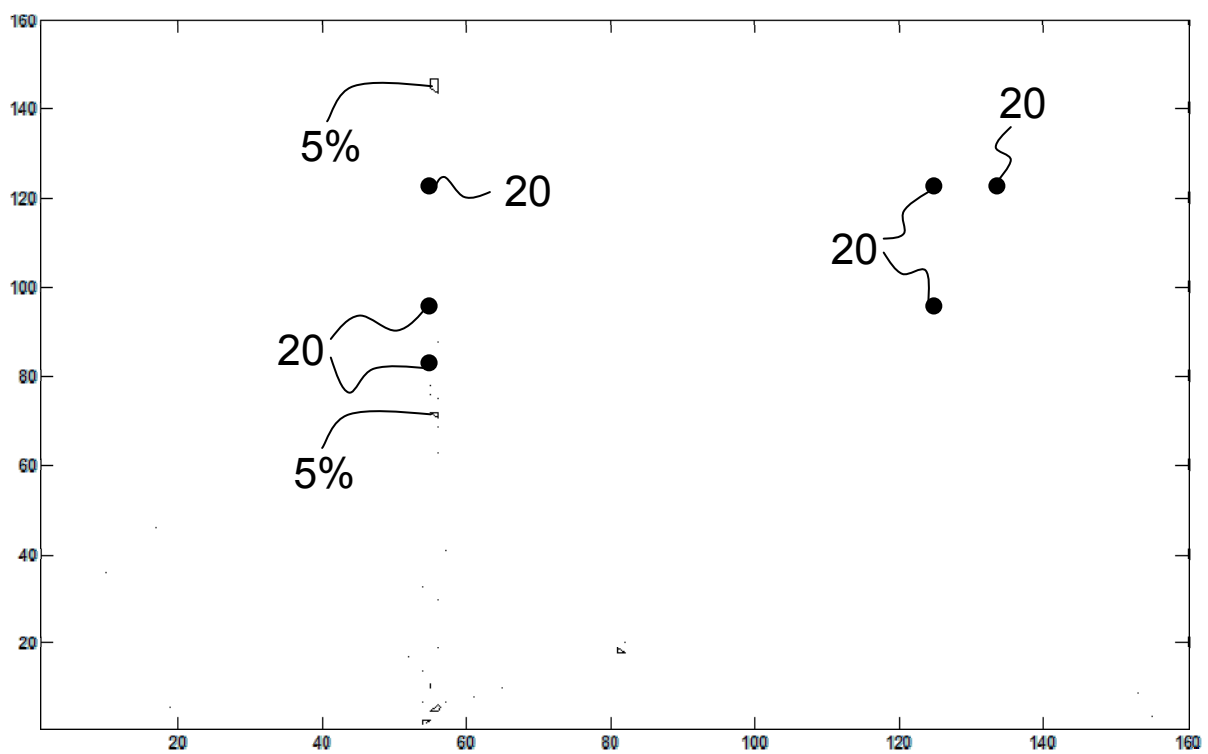


Fig. 11(b)