OPTIMISATION OF MAGAT GEL DOSIMETER EMBEDDED WITH METHYLENE BLUE AND ZINC OXIDE NANOPARTICLES FOR RADIOTHERAPY APPLICATION

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by

AHMED MOHAMMED ABID ALASADY

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LIST OF SYMBOLS

ρ	Mass density
CTNs	Computed tomography number
μ	linear attenuation coefficient
μ/ρ	Mass attenuation coefficient
ρ_e	Electron density
Z_{eff}	Effective atomic number
$(S/\rho)_{total}$	Total stopping power
N_e	Number of electrons per unit mass of the material
μ_w	Linear attenuation coefficients of water
W_k	Weighted fractional proportions of atoms
Z_k	Atomic number
N_A	Avogadro's number
A_i	Atomic weight
λ_{max}	Maximum absorption wavelength
D	Absorbed dose
Abs	Absorbance
a.u	Arbitrary unit

LIST OF ABBREVIATIONS

0D	Zero Dimensional
1D	One Dimensional
2D	Two Dimensional
3D	Three Dimensional
3D-CRT	3D-Conformal Radiotherapy Treatment
9G	Polyethylene glycol 400 dimethacrylate
AAPM	American Association of Physicists in Medicine
AAPM-RTC	The American Association of Physics in Medicine, Radiation Therapy Committee
AgNPs	Silver nanoparticles
AscA	Ascorbic acid
AuNPs	Gold nanoparticles
BANANA	Bis, acrylamide, nitrous oxide and agarose dos
BANG	Bis, AAm, Nitrogen and Gelatin
BEV	Beam-eye-view
BIS	N,N'-methylene-bis-acrylamide
BNCT	Boron-neutron capture therapy
CBCT	Cone-Beam Computed Tomography
CT	Computerized Tomography
CTV	Clinical Target Volume
DEF	Dose enhancement factor
D_{max}	Maximum absorbed dose
d_{max}	Depth of maximum dose
DVH	Dose-Volume Histogram
FDA	Food and Drug Agency

G	Gelatin
GTV	Gross Tumour Volume
Gy	Gray
H&N	Head and Neck Cancer
H_2SO_4	Sulfuric acid
HEA	2-hydroxyethylacrylate
HEMA	2-hydroxyethyl methacrylate
HU	Hounsfield Units
IARC	International Agency for Research on Cancer
IC	Ionizations chamber
ICRP	International Commission on Radiological Protection
ICRU	International Commission on Radiation Units
IMRT	Intensity-Modulated Radiation Therapy
IORT	intra operative radiotherapy
IR	Ionizations radiation
ISO	International Organization for Standardization
keV	Kilo electron Voltage
LCV	Leuco crystal violet
LINAC	Linear accelerator
MAA	Methacrylic Acid
MAG	Methacrylic Acid based Gel
MAGAS	Methacrylic acid, ascorbic acid, gelatin
MAGAT	Methacrylic Acid, Gelatine and THPC
MAGIC	Methacrylic and ascorbic acid in gelatine initiated by copper
MB	Methylene Blue
MLC	Multi-Leaf Collimator
MOSFET	A metal-oxide semiconductor field-effect transistor

MRI	Magnetic Resonance Image
MU	Monitor unit
NCR	The National Cancer Registry
NIPAM	N-isopropylacrylamide
nMAG	Normoxic Methacrylic acid-based Gel
NMR	Nuclear Magnetic Resonance
nPAG	Normoxic Polyacrylamide Gel
NPC	Nasopharyngeal cancer
OARs	Organs at Risk
OCT	Optical computed tomography
PAG	Polymer acrylamide gel
PAGAS	Polyacrylamide Gel with Ascorbic acid
PAGAT	Polyacrylamide Gel And THPC
PDD	Percentage Depth Dose
PET	Positron Emission Tomography
PGD	Polymer Gel Dosimeter
PMMA	Polymethyl Methacrylate
PTV	Planning Target Volume
QA	Quality Assurance
QC	Quality Control
QM	Quality Management
ROS	Reactive Oxygen Species
RT	Radiotherapy
SDS	Sodium dodecyl sulfate
SRS	Stereotactic radiosurgery
SSD	Source-Surface Distance
TCAA	TriChloro Acetic Acid (CCl_3COOH)

TGMEMA	Triethylene glycol monoethyl ether monomethacrylate
THPC	Tetrakis (hydroxymethyl) phosphonium chloride
THPS	Tetrakis (hydroxymethyl) phosphonium sulfate
TLDs	Thermoluminescent Dosimeters
TPS	Treatment Planning Systems
VIPAR	N-vinylpyrrolidone argon
VMAT	Volumetric Modulated Arc Therapy
WHO	World Health Organization
ZnO NPs	Zinc Oxide Nanoparticles

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PENGOPTIMUMAN DOSIMETER GEL MAGAT DENGAN TAMBAHAN METHYLENE BLUE DAN NANOPARTIKEL ZINK OKSIDA UNTUK PENGGUNAAN RADIOTERAPI

ABSTRAK

Gel polimer ialah sejenis dosimetri kimia yang membolehkan pengukuran dos 3D dan dianggap sebagai alat yang berkesan untuk menganalisis dan memetakan rawatan radioterapi. Kajian ini bertujuan untuk membangunkan sistem pengesahan 3D yang berkesan menggunakan dosimeter gel MAGAT yang ditambah dengan metilena biru (MB) dan nanopartikel zink oksida (NPs) untuk meningkatkan ketepatan pengesahan dos dalam rawatan kanser nasofaring. Oleh itu, sifat radiologi gel MAGAT yang ditambah dengan NP metilena biru dan zink oksida dinilai, termasuk ketumpatan fizikal, ketumpatan elektron, nombor atom berkesan, nombor CT, pekali pengecilan linear dan jisim. Selepas itu, komposisi dosimeter gel MAGAT dioptimumkan untuk menentukan kepekatan terbaik MB dan ZnO NPs serta saiz NPs. Selain itu, suhu optimum semasa pengimbasan UV juga diukur. Manakala, sifat dosimetrik dosimeter gel polimer MAGAT yang ditambah dengan MB dan ZnO NPs ditentukan untuk ketepatan, kepekaan, kebolehulangan, peratusan dos kedalaman (PDD), dan pergantungan saiz medan untuk memastikan perancangan radioterapi yang tepat dan jitu. Dosimeter gel MAGAT yang dioptimumkan, ditambah dengan MB dan ZnO NP yang digabungkan ke dalam fantom kepala 3D, digunakan untuk terapi sinaran konformal tiga dimensi (3D-CRT) dalam perancangan rawatan kanser nasofaring. Keputusan menunjukkan bahawa sifat radiologi kesemua formulasi dosimeter gel MAGAT hampir sama dengan sifat tisu manusia. Manakala kepekatan optimum MB ialah 0.001%, kepekatan ideal untuk

ZnO NPs pula ialah 0.07% dengan saiz zarah 20 nm. Kepekatan khusus dan saiz zarah ini menunjukkan kepekaan dan ketepatan tertinggi untuk dosimeter gel polimer MAGAT. Formulasi MAGAT + MB + ZnO NPs mempunyai sensitiviti bersamaan 0.0311 yang lebih baik daripada sensitiviti bersamaan 0.0285 untuk formulasi MAGAT + MB dan 0.02403 untu MAGAT tunggal. Oleh itu, rumusan MAGAT + MB + ZnO NPs telah digunakan untuk menyiasat sifat dosimetrik. Perbandingan antara dos yang diserap yang diperoleh daripada kebuk pengionan dengan dosimeter MAGAT + MB + ZnO NPs, sisihan adalah minimum dengan sisihan piawai 0.3137%. Selain itu, formulasi MAGAT + MB + ZnO NPs mengurangkan ralat kurang daripada 3% dan menunjukkan ketepatan yang mencukupi, kebolehulangan, kestabilan, ukuran peratusan kedalaman (PDD) yang tepat dan jitu dan tidak bergantung pada saiz medan. Perbezaan peratusan untuk dosimeter MAGAT + MB + ZnO NPs dengan bacaan dari sistem perancangan rawatan (TPS) dan volum sasaran perancangan (PTV) ialah 2.49%. Manakala perbezaan antara bacaan TPS dan saraf tunjang (organ berisiko) ialah 1.085 %. Keputusan ini secara kolektif menunjukkan penggunaan berkesan formulasi dosimeter gel MAGAT dalam radioterapi kerana keserasian yang kuat dengan sifat – sifat dosimetrik dan pilihan terbaik untuk dosimeter yang digunakan dalam perancangan radioterapi.

OPTIMISATION OF MAGAT GEL DOSIMETER EMBEDDED WITH METHYLENE BLUE AND ZINC OXIDE NANOPARTICLES FOR RADIOTHERAPY APPLICATION

ABSTRACT

3D Polymer gel dosimeter is considered an effective tool for analyzing and mapping radiotherapy treatments. This study aims to develop an effective 3D verification system using MAGAT gel dosimeters embedded with methylene blue (MB) and zinc oxide nanoparticles (ZnO NPs) to enhance the reliability of dose verification in nasopharynx cancer treatment (NPC). Therefore, the radiological properties of MAGAT gel embedded with MB and ZnO NPs were assessed, including physical and electron density, effective atomic number, CT-number, linear and mass attenuation coefficients. Subsequently, the composition of MAGAT gel dosimeter were optimized to determine the best concentration of MB and ZnO NPs concentration and NPs size. Additionally, the optimum temperature during UV-scanning was also measured. Whereas, the dosimetric properties of MAGAT polymer gel dosimeter embedded with MB and ZnO NPs were determined for reliability, sensitivity, reproducibility, percentage depth dose (PDD), and field size dependence to ensure accurate radiotherapy planning. The optimized MAGAT gel dosimeters, embedded with MB and ZnO NPs incorporated into a 3D realism head phantom, were used for three-dimensional conformal radiation therapy (3D-CRT) in (NPC) treatment planning. The results indicate that the radiological properties of all MAGAT gel dosimeter formulations closely resemble those of human tissue. The results demonstrate that the optimal concentration of MB is 0.001%, and the ideal concentration for ZnO NPs is 0.07% with a particle size of 20 nm. These specific

concentrations and particle size demonstrated the highest sensitivity and reliability for the MAGAT gel dosimeter. The formulation of (MAGAT + MB + ZnO NPs) has a sensitivity equal to 0.0311 compared to formulations of (MAGAT + MB) and bare MAGAT which have sensitivity equal to 0.0285 and 0.02403, respectively. Therefore, the formulation of (MAGAT + MB + ZnO NPs) has been used to investigate the dosimetric properties. When compared to the absorbed dose obtained from an ionization chamber, the deviation is minimal, with a standard deviation of 0.3143% for (MAGAT + MB + ZnO NPs). Additionally, this formulation reduce errors to less than 3% and demonstrate sufficient reliability, reproducibility, and accurate measurements of PDD, and independence from field size. The percentage difference for (MAGAT + MB + ZnO NPs) between the treatment planning system (TPS) reading and the planning target volume (PTV) is 2.49%, while the difference between TPS reading and the spinal cord (organ at risk) is 1.085%. These results collectively demonstrate the effective use of formulation of (MAGAT + MB + ZnO NPs) in radiotherapy due to their strong alignment with dosimetric properties and an excellent choice for dosimeters used in radiotherapy planning.

CHAPTER 1

INTRODUCTION

1.1 Background

The National Cancer Registry of Malaysia (NCR) records a total number of 218,745 new cancer cases during the period of 2007 to 2016, with 98,299 (44.938%) were reported in males and 120,446 (55.062%) in females [1]. Nasopharyngeal cancer (NPC) is a common type of head and neck cancer in southeast asia with a prevalence rate of up to 5.1 cases per 100,000 people in 2017-2021, and it is the sixth-commonest cancer among males in 2017-2021 compared to 2012-2016 where it was the fifth commonest cancer among males [1]&[2], with the radiotherapy is used as the principal treatment modality [3]. In 2020 there were a total of 133,354 NPC incidence around world, where it was 65,866 new cases in eastern Asia, 62,444 new cases in china, 8366, 36,747 new cases in south-eastern Asia, and 2680 new cases in western Asia [4]. While in 2017-2021 incidence rate has been increased to 5.1 per 100,000 population in Malaysia compared to 5.2 in period of 2012-2016, the percentage diagnosed in Malaysia at late stages (Stage 3 & 4) is increased to 76.0% compared to 2007-2016 where it was 69.3% [2].

NPC is a complicated location to treat with intensity-modulated radiation therapy (IMRT),[5] with the benefit of the parotid glands preservation in comparison to the 3D-conformal radiation technique (3D-CRT) in terms of clinical results [6]. However, when compared to IMRT, 3D-CRT remains an effective therapeutic option in resource-limited communities since it provides comparable survival rates, locoregional control, and metastasis-free survival [7]. The effectiveness of 3D-CRT technique heavily depends on the expertise of the planner, and such plans need work in plan manipulation to obtain the best dose distribution. Furthermore, the complexity of 3D-CRT clinical treatment planning and TPS has resulted in the requirement for ongoing quality assurance (QA) [8] and pre-treatment verification of the given dose prior to patient treatment to make sure the linear accelerator has truly accomplished the dose distribution as planned [9].

TPS in radiotherapy Utilizes a 3D pattern of the beam to simulate the true radiation delivery and calculate the patient's radiation dose [10]. However, today only traditional 2D dosimeters are used to verify treatment dose [9,11]. Therefore, a 3D dosimeter is clearly required to verify the dose delivery technique, by the comparison between the TPS-calculated 3D dose distributions and the actual dose given to the patient or in a phantom. This point should be taken into consideration Where the accurate planning and dose evaluation are important to give optimal treatment results.

The American Association of Physics in Medicine, Radiation Therapy Committee (AAPM-RTC) strongly suggests using a phantom composed of a substance that resembles soft tissue. The phantom is utilized to precisely evaluate the patient contour while also verifying the 3D-CRT procedures during the commissioning and clinical stages. It should also represent the clinical location being treated in a realistic portrayal. These phantoms should ideally be anatomically accurate and exhibit radiologic characteristics that are equivalent to the examined tissues and make it possible to be used for a variety of measuring devices and for dose distribution verification in several crucial positions everywhere within the target and normal tissue volumes [12].

One of the promising developments in the radiotherapy verification system is the introduction of 3D radiation-sensitive gels (polymer gel dosimeter) [13-16] that are made of monomers, crosslinkers, gelatin, antioxidants, and water. Upon irradiation of polymer gel dosimeters, it will polymerize as a function of the absorbed dose. As the polymer gel dosimeters allow the integration of dose within the dosimeter, evaluation of a complete volume at once, equivalence of anatomical soft tissue, and enablement of true 3D dosimetry [17-19]. In addition, the utilization of gel system has been extended to the validation of spatial distributions and amplification dose in nanoparticle-enhanced radiotherapy.

Several studies have been published on the importance of nanoparticles and their impact on dose amplification during the application of polymer gel dosimeters [20-34]. However, considering the extensive investigations involving radiosensitizer using gold, bismuth and platinum, insufficient studies have been conducted to investigate the potential superiority of other high-Z nanoparticles especially on metal oxide nanoparticles for clinical treatment verification. A few decades ago, metal oxide nanoparticles have attracted noticeable attention particularly ZnO NPs, which are considered as one of the most significant metal oxide nanoparticles due to their extensive medical applications, biocompatibility, and biological functions [35]. The ZnO can be used as radiosensitizer in the polymer gel dosimeter due to the high atomic number of zinc and the release of reactive oxygen species (ROS). The advantage of a high atomic number of zincs will generate more photoelectrons [36] which allow more energy to be deposited into the polymer gel (higher attenuation properties). According to the attenuation and absorption data obtained from Hubbell physical data [37], the attenuation coefficient for Zn is noted to be higher than that of water. Whilst the reactive oxygen species (ROS) which released upon irradiation [38] will increase the rate of radical species generation in the polymer gel, this can increase the polymerization crosslinking or interaction and thus the gel’s sensitivity.

1.2 Problem statement

The treatment planning for head and neck cancer is one of the most difficult treatments plans due to the complex planning of PTVs and the surrounding important normal tissues. As a result, it's necessary to estimate doses precisely when treating the nasopharynx to prevent any overdose to the organ at risk such as spinal cord, parotid glands, optic nerves and chiasm, lacrimal glands and lenses.

NPC is a complicated location to treat with IMRT [3] with the benefit of the parotid glands preservation in comparison to 3D-CRT in terms of clinical results [5]. However, 3D-CRT is an effective therapeutic option in resource-limited communities since it provides comparable survival rates, locoregional control, and metastasis-free survival [6]. The effectiveness of 3D-CRT technique heavily depends on the expertise of the planner, and such plans need work in plan manipulation to obtain the best dose distribution. Furthermore, the complexity of 3D-CRT clinical treatment planning and TPS has resulted in the requirement for ongoing QA [7]. Indeed, even 5% of errors in dose delivery can be harmful to a patient's health, which could lead to differences in the range of 10%–20% in the probability of tumor control and 20% to 30% changes in the probability of normal tissue complications [21]. Therefore, the aim of this work is to employ the 3D polymer gel system as a 3D treatment verification tool by lowering the treatment error and improving the therapeutic ratio. Even though TPS in radiotherapy utilizes a 3D pattern of the beam and calculates the patient's radiation dose, but no 3D verification technique has been used in clinical routine and right now, the treatment is verified using 1D measurement with a small-volume ionization chamber and 2D verification with an array of detectors. The drawbacks of these techniques are the point dose measurement, cannot map rapidly the dose distributions around a target volume and cannot resolve high dose gradients [5,6]. Therefore, a 3D dosimeter is clearly required to verify the dose delivery technique, by the comparison between the TPS-calculated 3D dose distributions and the actual dose given to the patient or in a phantom.

Polymer gel dosimeter is a good developments in the radiotherapy verification system. After irradiation, the polymerization will take a place as a function of the absorbed dose [13,14]. And its utilization has been extended to the validation of spatial distributions and amplification dose in nanoparticle-enhanced radiotherapy.

Insufficient studies have been conducted to investigate the potential superiority of high-Z nanoparticles especially on metal oxide nanoparticles for clinical treatment verification. Thus, this work aims to determine the feasibility of using ZnO as radiosensitizer using MAGAT gel dosimeters embedded with MB and ZnO NPs to enhance the reliability of dose verification in nasopharynx cancer treatment.

ZnO was selected for its high atomic number, which enhances the photoelectric cross-section and thus increases dose absorption. Our hypothesis is that incorporating ZnO NPs and a specific chemical compound like MB into the original dosimeter composition will improve its dosimetric properties while maintaining an acceptable level of dose sensitivity. Where MB had been studied with polymer gel [39], which shows that the polymerization effect starts to initiate at 0.001% of the MB concentration. Other studies [40] have found that polymerization only begins at 0.01% of the MB concentration. There are contradictory results in a few studies [39, 40], and as far as we know, the problem has not been considered before. Therefore, there is a need for more studies to determine the optimum concentrations of MB that can produce the greatest interaction in the MAGAT gel dosimeter.

To evaluate the 3D data, this study aims to compare the 3D dose distributions calculated by the TPS with the actual dose delivered in a phantom.

1.3 Significance of the study

The significance of this study lies in its potential to advance the field of radiation therapy, specifically in nasopharynx cancer treatment. By developing a 3D verification system using MAGAT gel dosimeters with embedded ZnO NPs and MB, we aim to significantly enhance the reliability of dose verification. This improvement is essential for ensuring precise and effective radiotherapy, which can directly impact patient outcomes. Furthermore, the use of biocompatible and FDA-approved ZnO NPs adds an extra layer of safety and applicability to the study's findings. Overall, this research has the potential to contribute to the refinement of radiotherapy practices, offering more reliable treatment options for patients with nasopharynx cancer.

1.4 Objective

This work aims to develop an effective 3D verification system using MAGAT gel dosimeters embedded with MB and ZnO NPs to enhance the reliability of dose verification in nasopharynx cancer treatment. The specific objectives of the research work are summarized as follows:

1. To fabricate and assess the radiological properties of a polymer gel dosimeter.

2. To determine the allowable concentration of MB and ZnO NPs, along with the size of ZnO NPs and the temperature during the UV-visible scanning in order to achieve the optimum levels of reliability and sensitivity.

3. To assess the dosimetric properties of optimized MAGAT gel dosimeters embedded with MB and ZnO NPs.

To evaluate the verification of nasopharynx cancer treatment using the 3D-CRT technique by employing MAGAT polymer gel embedded with MB and ZnO NPs.

1.5 Scope of study

This thesis includes five individual chapters. **Chapter 1** provides a brief introduction about nasopharyngeal cancer (NPC) and development of gel dosimetry; followed by the problem statement, research significance and research objectives. **Chapter 2** presents the theoretical background followed by a comprehensive review of the study. It first clarifies the theoretical background of polymer gel dosimeter and nanoparticles, radiotherapy, and nasopharynx cancer in radiotherapy (NPC), and quality assurance (QA). Additionally, this chapter provides a comprehensive review of the literature and highlights the most essential background relevant to this thesis. **Chapter 3** presents in detail the research methodology involving the experimental procedures of MAGAT gel dosimetry in terms of materials and instrumentation used for fabrication, irradiation and reading out. It also outlines the method of evaluating radiological and dosimetric properties of MAGAT gel dosimeter of the optimal gel formulations. Furthermore, the method of evaluating dose verification for nasopharynx cancer (NPC) treatment planning. **Chapter 4** entails the results and discussion of all the experiments performed in this study; the radiological properties of MAGAT gel dosimeter, the optimization of all MAGAT gel dosimeter formulations, the dosimetric properties of MAGAT gel dosimeter of the optimal gel formulations, dose verification for nasopharynx cancer (NPC) treatment planning, **Chapter 5** presents the major findings of this thesis, and gives suggestions for future work with regard to this research.

CHAPTER 2

THEORETICAL BACKGROUND AND LITERATURE REVIEW

2.1 Polymer gel dosimeter

Polymer gel is one type of chemical dosimetry that enables the measurement of 3D dose and is known as a useful tool to analyze and map radiotherapy treatments. It is composed of radiation-sensitive chemicals that polymerize as a function of absorbed dose and form cross-linked polymer networks upon irradiation [41, 42]. The degree of polymerization is directly proportional to the amount of absorbed dose. Compared to other types of radiation dosimeters, polymer gels offer inherent advantages; for example, they are capable of measuring doses in 3D. The use of polymer gel for measuring radiation dose dates back to the early 1950s.

2.1.1 Ideal dosimetric properties

Many characteristics have been examined by various researchers [43-45], encompassing the composition of the polymer gel, variations of temperature during irradiation, type of radiation, energy of radiation, temperature and dose rate during MRI evaluation, strength of the magnetic field, and time between irradiation and MRI evaluation. Additionally, investigations into the dose response of polymer gels have been achieved utilizing X-ray CT by the utilization of linear attenuation data or CT numbers (HU), which directly correspond to changes in the physical density of the polymer gel dosimeters [46-48].

By relying on a paper by D Deene et al 2004 [49], it has been established that a trustworthy dosimeter must fulfil several conditions: "(1) a measurable dose response, significant and well-defined, (2) stable dose response with time, (3) dose distribution can be preserved over a time period, (4) independent from many environmental factors such as temperature changed during irradiation or scanning, pressure, light and atmospheric gasses, (5) tissue equivalent, (6) independent from variations of spectral range used during irradiation, and (7) can be operated in obtainable radiation unit".

2.1.2 Advantages of gel dosimetry

Gel dosimetry systems have several benefits in comparison with traditional dosimeters [50]. These advantages encompass independence of radiation direction, radiation quality and dose rate, integration of dose for a number of sequential treatment fields, evaluation of a complete volume at once, equivalence of anatomical soft tissue, and enablement of true 3D dosimetry.

Gel dosimeters have the potential to be formulated within an anthropomorphic phantom, acting as a valuable instrument for accurately measuring three-dimensional dose distributions. The utilization of three-dimensional (3D) image of dose distributions has significance in validating the efficacy of treatment plans.

Conventional dosimeters can be laborious and take a long time in their utilization, particularly when there is a need for a three-dimensional dose distribution. Additionally, they need several correction factors. The steep dose gradients measurements need that the dosimeter is as small as possible, avoiding disruption to the radiation field. No dosimeter available today can provide dosimetric information across an entire volume., therefore only a few points can be measured at once. Therefore, the development of a device capable of volumetric dosimetry becomes essential, particularly for the comprehensive evaluation and image of complicated conformal intensity-modulated, and stereotactic therapeutic treatments [51, 52].

In consideration of the utilization of gel dosimeters to validate intensity-modulated radiation therapy (IMRT), De Wagter (2001) [53] stated, "Gel dosimetry is the method of choice for dosimetric verification, as it is capable of detecting computational inaccuracies, inadequate beam data or malfunctions of the linear accelerator, error in the transfer of the treatment plan or the isocentric co-ordinates". Gel dosimetry encompasses a multitude of applications, covering various radiation dosimetry challenges, encompassing breast, prostate, head and neck, lung, intravascular brachytherapy, and also fulfilling quality assurance requirements. However, the methodology itself presents main challenges which require more improvement, particularly in terms of improving the accuracy of dose measurement [54].

2.1.3 History and development

In 1950, Day and Stein originally proposed the application of radiation-sensitive gels for radiation dosimetry by exploiting the ability of radiation to produce variable colors in gels containing dyes, such as methylene blue. Subsequently, Alexander et al. (1954) [55] advanced the field by introducing polymer gel dosimeters and study the effect of radiation on polymethylmethacrylate. Andrews et al. (1957) [56] then conducted a thorough exploration of depth doses by employing spectrophotometry and pH probe measurements of irradiated radiation-sensitive gels that contained chloral hydrate, which was thoroughly diffused in an agar gel. Subsequent investigations into radiation-induced polymerization in fluids by Hoecker et al. (1958) [57] have yielded significant insights in the field, while Boni (1961) [58] employed polyacrylamide as a gamma dosimeter. However, despite these advancements, precise dose mapping remained elusive until Gore and Kang (1984) [59] proposed the use of the ferrous sulfate chemical dosimeter (Fricke dosimeter), which could be explored by means of nuclear magnetic relaxometry and imaging using a magnetic resonance image (MRI) scanner. A Fricke gel dosimeter consists of ferrous ions with gelatin as the matrix. Ferrous ions undergo oxidation upon irradiation, leading to their transformation into ferric ions and the consequent alteration in the color of the gel matrix. However, as time elapses after irradiation, the diffusion of ferric ions causes color distortion or blurring, which represents a drawback of the Fricke gel dosimeter.

Gel dosimetry dates back to the 1980s; however, in the early 1990s, the creation of polymer gel formulations introduced a new era in this field. Since their initiation, polymer gel dosimeters have been extensively utilized in a multitude of preclinical radiotherapy applications. Audet and Schreiner (1991) [60] explored the alterations in NMR transverse relaxation quantities of irradiated polyethylene oxide, and Kennan et al. (1992) [61] carried out a study on the changes in NMR longitudinal relaxation of an irradiated aqueous solution of N,N-methylene-bis-acrylamide (Bis) and agarose, the results of the study revealed that the relaxation rates of the gel increased with the absorbed dose. Fong et al. (2001) [19] documented significant progress in the field of gel dosimetry, particularly through the innovation of MAGIC, a metallo-organic complex that bounds atmospheric oxygen. This novel approach constraint oxygen inhibition, enabling polymer gels fabrication in a laboratory setting. The proposed polymer gel dosimeters are summarized in Table 2.1.

2.1.4 Fundamental of polymer gel dosimeter

Polymer gel dosimetry is a technique used in radiation therapy to measure the dose of ionizing radiation. The fundamental principle behind polymer gel dosimetry is the radiation-induced polymerization or crosslinking of a radiation-sensitive polymer gel in response to ionizing radiation [41, 42]. Different techniques, such as (magnetic resonance imaging (MRI) [43], x-ray computed tomography [62], optical scanning [63], FT-Raman spectroscopy [64], and ultrasound [65]) can record the change in dose distribution in three dimensions.

Polymer gel dosimetry offers several advantages over other dosimetry techniques such as ion chambers, TLDs and films, including high spatial resolution, and also can integrate radiation doses from multiple directions, tissue-equivalent properties, and the ability to measure both the dose and spatial distribution of radiation. Because of its advantage of radiologically soft-tissue equivalent, it has an ability to be modified depending on the application. Therefore, it has become an important tool in radiotherapy research and quality assurance.

2.1.5 Type of polymer gel dosimeter

Polymer gel dosimeters contain monomer dissolved in a matrix of gelling agents. Free radicals in water are created during irradiation, and these radicals cause the monomers to polymerize, such that monomers are converted to polymers. The rate of polymerization is proportional to the amount of radiation absorbed. As previously stated, the oxygen amount during polymer fabrication should be kept as low as possible. The amount of oxygen in the polymer gel dosimeters has to be lowered to less than 0.01 mg l0-1, the temperature during fabrication and storage may also have an impact on the quality of the gel. The perfect polymeric gel should be characterized by these features [18] such us stability in space and time, tissue equivalency, dose rate and energy independent with the effect of temperature and pressure on the gel negligible.

By the monomers utilized in gel formation, polymer gels are divided into two general categories. Furthermore, polymeric gels are called as normoxic gels if they are created under normal atmospheric conditions. Methacrylic-based gels are known as MAGAT/nMAG, while acrylamide-based gels are known as PAGAT/nPAG [13]. According to the many chemical agents utilised in gel production, there may be subtypes of each gel here. The summarized list of polymer gel dosimeters is shown in Table 2.1 [13].

The number of different monomers is used in the polymer gel formation: acrylamide, acrylic acid, methacrylic acid, 1-vinyl-2-pyrrolidinone, 2-hydroxyethyl methacrylate and 2-hydroxyethyl acrylate. N,N-methylenebis- acrylamide was used as a co-monomer in each polymer gel dosimeter [66]. The structural formulas of main monomers are presented in Figure 2.1 [66].

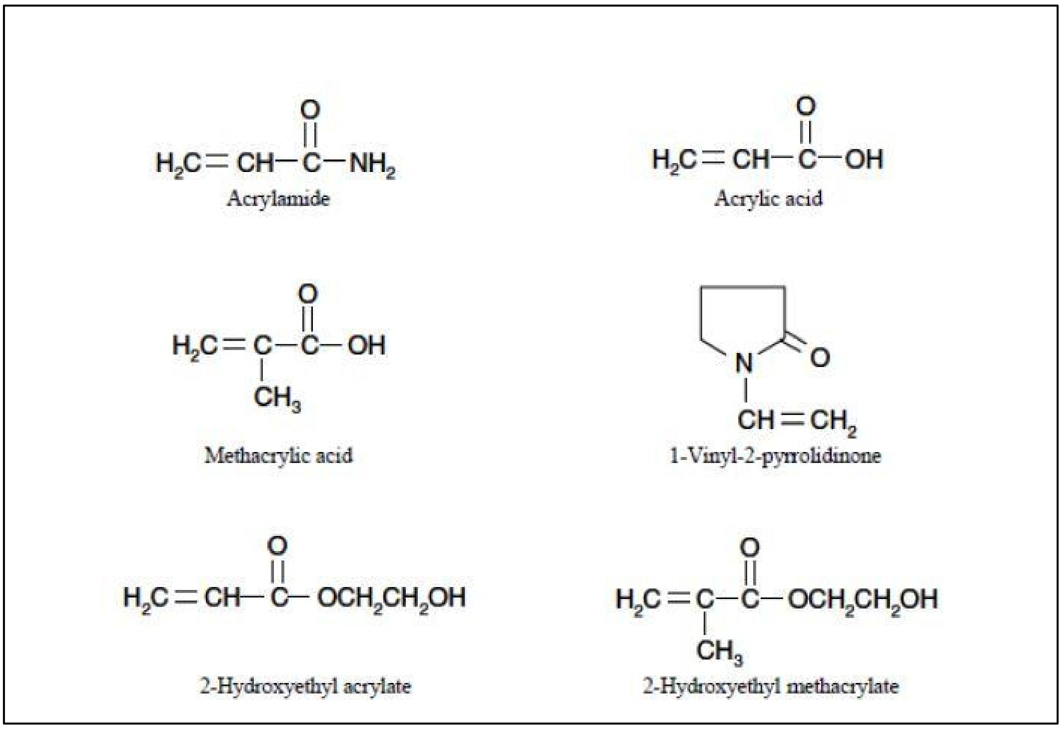

Figure 2.1 Chemical structures of different monomers used in polymer gel formation [66]

Table 2.1 Summary of polymer gel dosimeters [13]

Dosimeter name	Type	Gelling agent	Monomer	Crosslinker	Catalyzer/ stabilizer	Scavenger/ antioxidant
BANANA	PAG	Agarose	Acrylamide	BIS		Nitrous oxide
BANG	PAG	Gelatin	Acrylamide	BIS	Ammoniumpersulphate, TEMED	
BANG-2	MAG	Gelatin	Methacrylic acid	BIS	Sodium Hydroxide	AscA
BANG-3	MAG	Gelatin	Methacrylic acid		$CuSO_4 \cdot 5H_2O$	AscA
MAGIC	MAG	Gelatin	Methacrylic acid		$CuSO_4 \cdot 5H_2O$ Hydroquinone	
MAGAT	MAG	Gelatin	Methacrylic acid			THPC
nPAG	PAG	Gelatin	Acrylamide	BIS		THPS
nMAG	MAG	Gelatin	Methacrylic acid			THPS
nMAG	MAG	Gelatin	Methacrylic acid			THP
MAGIC-f	MAG	Gelatin	Methacrylic acid	Formaldehyde	$CuSO_4 \cdot 5H_2O$	AscA
HEA		Gelatin	HEA	BIS		
VIPAR		Gelatin	VIPAR	BIS		
NIPAM		Gelatin	NIPAM	BIS		
Genipin gel	MAG	Gelatin	MAA, genipin			Sulfuric acid
LCV micelle radiochromic gel		Gelatin	LCV, surfactant- Triton, TCAA	Formaldehyde		
PAG	PAG	Gelatin	Acrylamide	BIS	NaI	THPC
nMAG	nMAG	Gelatin, Agarose	Methacrylic acid			THPC
nMAG	nMAG	Gelatin	HEMA, TGMEMA, 9G			THPC
Radiochromic gel		Gelatin	SDS, Chloroform, TCAA		LMG dye	

BIS: N,N'-methylene-bis-acrylamide; MAA: Methacrylic acid; AA: Ascorbic acid; THPC: Tetrakis (hydroxymethyl) phosphonium chloride; THPS:Tetrakis (hydroxymethyl) phosphonium sulfate; NIPAM: N-isopropylacrylamide; LCV: Leuco crystal violet; TCAA: TriChloro Acetic Acid (CCl_3COOH);VIPAR: N-vinylpyrrolidone argon; HEA: 2-hydroxyethylacrylate; HEMA: 2-hydroxyethyl methacrylate; TGMEMA: Triethylene glycol monoethyl ether monomethacrylate; 9G: Polyethylene glycol 400 dimethacrylate; SDS: Sodium dodecyl sulfate

2.1.5(a) BANG gels

In 1992, Maryanski et al introduced a novel formulation for gel dosimetry, based on the polymerization of acrylamide (AA) and Bis monomers spread within an aqueous agarose matrix, and this formulation was named as BANANA because of its chemical composition (Bis, AAm, Nitrous oxide and Agarose) [67]. The BANANA polymer gel dosimeter [43] effectively addressed the diffusion challenges that were observed in Fricke gels, thus demonstrating improved stability. Subsequently, in 1994, Maryanski et al substituted agarose with gelatin in their formulation, naming it as BANG (Bis, AAm, Nitrogen and Gelatin) [68]. Notably, the BANG gel dosimeter demonstrated a reduced R2 value in its unirradiated state, while the irradiated area displayed heightened transparency and optical visibility [69]. Expanding on these advancements, Maryanski et al. introduced another formulation of the BANG gel in 1996, designated as "BANG-2." This formulation integrated bis, acrylic acid, sodium hydroxide, water, and gelatine, with acrylic acid replacing acrylamide [69]. Remarkably, this product also became commercially available through MGS Research Inc., being aptly branded as "Bandana". In subsequent developments, both BANG-3 and BANG-4 were created and also commercially available under MGS Research Inc. Bandana.

2.1.5(b) PAG

During the early 1990s, Maryanski et al introduced a dosimeter based on a polyacrylamide gel (PAG). This dosimeter consisted of the acrylamide monomer, along with co-monomers N, N'-methylene-bis-acrylamide, and gelatin [70]. The PAG dosimeter quickly gained favor among numerous research groups due to its multiple benefits customized for three-dimensional polymer dosimetry, such as stability, reliability, and reproducibility [68, 71-77]. Using magnetic resonance imaging (MRI) to visualize the PAG dosimeter led to a three-dimensional (3D) dose distribution for complex radiation treatments [78]. In 1996, Maryanski et al [70] expanded their imaging repertoire beyond MRI, using optical computed tomography (optical-CT) as a second method for imaging technique, a technique that was subsequently explored in depth by Oldham et al. [79, 80]. By the year 2000, Hilts et al. [62] used X-ray CT to accurately determine dose distributions for stereotactic procedures. Then, in 2002, Mather et al. [65] employed ultrasound technique to measure the dose distribution of polymer gel dosimeters. Rintoul et al. 2003 [81] employed Raman imaging to evaluate PAG dosimeters for electron depth dose measurement.

2.1.5(c) Normoxic

While gel dosimetry offers a multitude of benefits for verifying 3D doses, it has not yet achieved the status of a standard clinical device. Nevertheless, polymer gel dosimetry systems encounter a notable challenge: the presence of oxygen during manufacturing interferes with the polymerization process within the gel. Oxygen is scavenging OH and H radicals that initiate the generation of free radicals resulting from water radiolysis [43, 57, 71]. In the initial production of polymer gel dosimeters, attempts were made to eliminate oxygen by exposing the gel solution to inert gases like nitrogen and argon for some hours [43, 68, 69, 78]. Furthermore, the gel vials must exhibit characteristics of low oxygen permeability in addition to solubility.

A significant development occurred in a later batch of polymer gel dosimeters, where the harmful effects of oxygen were notably decreased by incorporating an antioxidant into the gel solution. This antioxidant binds with the oxygen molecules, effectively stops the scavenging of free radicals and thus helps the polymerization process [19]. Consequently, polymer gel systems can now be created under standard atmospheric conditions, and thus named as ‘normoxic’. In 2001, Fong et al.

introduced a novel gel formulation called MAGIC (methacrylic and ascorbic acid in gelatine initiated by copper). These gels exhibited good sensitivity to absorbed doses when synthesized under normoxic conditions [19]. Significantly, the normoxic gel demonstrated tissue-equivalent characteristics, showing enhanced dose sensitivity and an expanded dynamic range compared to other polymer gel formulations, as evaluated by MRI technique [82]. Furthermore, these gels formulations provided convenience in handling and storage. A subsequent innovation in normoxic gel formulation, named MAGAT, was introduced by substituting ascorbic acid and copper sulfate with THPC in the original MAGIC formulation, where MAGAT consists of methacrylic acid, gelatine and THPC [83].

2.1.5(d) MAG

The standard MAG dosimeter is comprised of methacrylic acid, gelatin, water, and small quantities of other agents (Table 6). During the process of radiation-induced water radiolysis, resultant radicals consume metacrylic acid as a monomer, then initiating polymerization. These formed polymers then precipitate and are anchored in place by the gelatin matrix [42].

Unlike other dosimeters, polymethacrylic acid precipitates without the need for a cross-linking agent like bisacrylamide. Therefore, cross-linking agents are unnecessary for dosimeters based on methacrylic. Importantly, it's worth noting that MAG dosimeters have lower levels of toxicity compared to PAG, making them more convenient and appropriate for clinical applications.

However, a study conducted by Y. De Deene et al. in 2006 aimed to compare the suitability of PAG and MAG for dosimetry purposes (it should be well-known that this investigation exclusively examined normoxic gel properties for nMAG and nPAG) [84]. The results revealed that the nMAG gel demonstrated improved dose sensitivity and long-term stability, while nPAG performed better in other aspects. As previously mentioned, a crucial characteristic of dosimeters is their ability to mimic human tissue. In this aspect, MAG dosimeters exhibit better tissue equivalency compared to other types of dosimeters, as indicated in Table 2.2 [19, 49, 85].

Table 2.2 Mass density, electron density, for MAG, PAG, MAGIC gels, water, human muscle tissue, bone, lung and fat [19, 49, 85]

Material	Mass density (g/cm^3)	Electron density relative to water
MAG	1.046-1.05	1.044
PAG	1.035- 1.042	1.031
MAGIC	1.027-1.060	1.05
Water	1	1.0
Muscle	1.04	1.0328
Fat	0.916	0.9132
Bone	1.40	1.3492
Lung	0.296	0.293

2.1.5(e) Presage polymer gel dosimetry

In recent times, a modern form of polymer dosimeter has been created identified as PRESAGETM (Heuris Pharma, Skillman, NJ). PRESAGE represents an innovative type of solid dosimeter founded on clear polyurethane. It is composed of radiochromic components (leuco-dye) as well as halogen-based free radical initiators. Which undergoes a process of polymerization, resulting in a polyurethane structure that is optically clear after being exposed to ionizing radiation [86]. The leuco dyes reach their maximum absorption at a wavelength of 633 nm, and perfectly compatible with an optical scanning system that relies on a He-Ne laser [86, 87]. PRESAGE has many advantages when compared to both conventional polymers and Fricke gels. One notable feature is that PRESAGE eliminates the need for a container due to its robust solid nature, thus simplifying the process of optical matching. Within the PRESAGE system, the region that undergoes irradiation exhibits exceptional stability, a slight diffusion of the colored medium. The preliminary investigations conducted on PRESAGE have yielded highly promising outcomes as stated by a few researchers [86-89].

2.1.6 MAGAT gel Dosimeter

The first attempt to manufacture A ‘normoxic’ polymer dosimeter (MAG) was carried by Peter M Fong et al. 2001 [19], which aimed to create a dosimeter under standard oxygen conditions, with the intention of enhancing the polymer gel's responsiveness and practical utility for radiation dosimetry. Inspired by Fong's concept [19] of developing a normoxic polymer gel, De Deene et al. conducted a detailed chemical analysis of the MAGIC gel in 2002 [17]. They introduced innovative formulations for normoxic gels that have a less complicated chemical composition than the MAGIC gel. Notably, their research emphasized the antioxidative potential of THPC and its capacity to amplify the gel's sensitivity to radiation doses. Consequently, the presence of THPC and methacrylic acid (MAA) is shown as fundamental factors in generating free radicals and enhancing the gel's sensitivity, thereby influencing the polymerization process [17].

In 2004, Brindha et al. [90] started a study focusing on the attenuation properties of normoxic polymer gel dosimeters, specifically PAGAT and MAGAT. Their investigation involved calculating computerized tomography (CT) numbers or Hounsfield units (H) based on linear attenuation coefficients and compared with values obtained using a CT scanner. A notable characteristic appeared in the calculated variations of linear attenuation coefficients with absorbed dose for PAGAT and MAGAT polymer gels. Importantly, the CT number exhibited a direct correlation with absorbed dose, and the measured CT number increased linearly with the linear attenuation coefficient. The study established a linear CT-dose response up to 15 Gy for PAGAT and 10 Gy for MAGAT polymer gels, conforming CT's potential as a measurement tool for normoxic polymer gel dosimeters.

In 2005, A. J. Venning et al. [82] searched the radiological water equivalence of normoxic polymer gel dosimeters, namely MAGIC, MAGAS, and MAGAT, revealed that the MAGAT gel formulation represented the best of radiological water equivalence among the other examined normoxic polymer gel dosimeters. This excellence was attributed to its noticeably reduced mass density measurement when compared to the MAGAS and MAGIC gels. This variation was determined according to the examination of the depth dose profile compared to water.

Whereas Hurley et al. 2005 [83] revealed that the formulation with concentrations of 10mM THPC, 0.05 mM HQ, 6–9% MAA, and 4–6% gelatin, MAGAT polymer gel dosimeters provided substantial evidence supporting the efficiency and potential for use in the radiation therapy dosimetry field.

P. Sellakumar et al. (2007) [91] conducted an extensive investigation into the water equivalence and radiation transport characteristics presented by a different 14 forms of polymer gel dosimeters over a range of photon and electron energies. The study focused on several critical parameters, including the effective atomic number (Z_{eff}), electron density (ρ_e), photon mass attenuation coefficient ($\frac{\mu}{\rho}$), photon mass energy absorption coefficient ($\frac{\mu_{en}}{\rho}$), and total stopping power $(S/\rho)_{total}$ of electrons. Among the 14 noticeable polymer gel types subjected to analysis, the results revealed that PAGAT and NIPAM demonstrated 3% differences and MAGAT has 2% differences compared to water which were considered acceptable for energy levels higher than 80 keV.

In 2009, Min-Hsing Lin et al. [92] employed the MAGAT formulation devised by Venning et al. (2005b) to investigate the effects of employing different matrix sizes of the smoothing filter for post-processing of images, along with different slice thicknesses during MRI. Their focus was on evaluating the dose estimation in Ir-192 HDR brachytherapy. The research contained a comprehensive comparative evaluation between measured and planned dose distributions. This evaluation aimed to determine the most suitable matrix size for the smoothing filter and to assess the influence of slice thickness. To achieve this, the researchers utilized multiple radioactive sources to validate the accuracy of the MAGAT gel dosimeter's capability in precisely estimating complex dose distributions.

In 2009, Mahbod Sedaghat et al. [93] embarked on an extensive and systematic experimental investigation. They searched into the level to which temperature increases occur within polymer gel dosimeters because of exothermic polymerization reactions during the process of irradiation. This investigation was conducted within two normoxic polymer gels, namely MAGAT and PAGAT for a range of doses, dose rates and gel volumes. Furthermore, the research also investigates the possible effect on the gels dose response. The outcomes of the study clearly demonstrate a relationship between the degree of temperature increases and the volume of the irradiated gel, and notably, the results reveal that the temperature increases for MAGAT gel dosimeter is approximately twice that observed in the PAGAT dosimeter.

In 2009, A research conducted by M. Yoshioka et al. [94] revealed a different gelling agent composition by replacing gelatin with agarose as gelatin had been unstable due to temperature dependence of gelatin’s viscosity. This investigation presents an innovative MAGAT formulation, highlighting its enhanced stability compared to the previous MAGAT version. This progression offers significant advantages, especially when the gel remains exposed to ambient temperatures for over 24 hours after irradiation.

Da-Chuan Cheng et al. (2012) [95] investigated the utilization of MAGAT polymer gel for the measurement of three-dimensional dose distribution given by the RapidArcTM technique. They employed cone-beam CT (CBCT) as the instrument for dose evaluation. resulting in the achievement of a notably superior level of precision in the three-dimensional dose measurement.

In 2012, Shin-ichiro Hayashi et al. [96] started a study into the influence of inorganic salt on the dose sensitivity of MAGAT polymer gel dosimeter, and the results show that inorganic salt increase the polymerization rate and subsequently increases the dose sensitivity.

Govi N. et al. conducted a study in 2013 [97] that explored the response of MAGAT normoxic polymer gel for breast brachytherapy applications. This study involved the use of two different balloon applicators (MammoSite® and Contoura®) and validate the dose distribution. The findings from this research demonstrated that the MAGAT polymer gel has the potential to be utilized as a reliable tool for three-dimensional dose verification of balloon brachytherapy techniques.

In 2013, Siti Aishah Abdul Aziz et al. [98] optimize MAGAT by utilizing a formaldehyde gel for the purpose of dose evaluation. The dosimetric characterization of this innovative formulation exhibited promising results, demonstrating the feasibility of this novel dosimeter for the precise measurement of three-dimensional dose distributions.

In 2014, Nik Noor Ashikin Nik Ab Razak et al. [99] initiated an investigation into the dose response and dose sensitivity of a MAG gel dosimeter system, which incorporated two different antioxidants, namely ascorbic acid (AscA) and tetrakis-hydroxy-methyl-phosphonium chloride (THPC). The objective was to differentiate the optimal antioxidant that produces the greatest influence on the dose response. The results revealed that MAGAT exhibited the highest change of R2 and showed sensitivity better than MAGAS by 10 times.

Shin-ichiro Hayashi et al. 2015 [100] investigated the utilization of the nuclear magnetic resonance (NMR) response of MAGAT gel containing boron. This study aimed to measure the depth dose responses when exposed to neutron beams produced by various energy spectra generated by a nuclear reactor, and suggested that MAGAT system could be an essential tool in dosimetry of Boron-neutron capture therapy (BNCT).

In 2015, Nik Noor Ashikin Nik Ab Razak et al. studied two crucial dosimetric properties of the MAGAT gel dosimeter: accuracy and precision [101]. The findings relating to these properties indicate that the MAGAT gel dosimeter exhibits a notable dose response. Moreover, the investigation proposes the feasibility of utilizing the MAGAT gel dosimeter as a three-dimensional dosimeter for radiotherapy purposes. And later on, 2015, Nik Noor Ashikin Nik Ab Razak et al. [102] evaluated the dose response of the polymer gel dosimeter by utilizing both MRI and x-ray CT techniques. The purpose was to determine the optimal imaging technique for polymer gel dosimetry. The results demonstrate that MRI is a more favourable evaluation technique in comparison to x-ray CT-imaging.

In the study conducted by Farideh Pak et al. in 2016 [103], a comprehensive exploration was started to show the fundamental characteristics of the low-density MAGAT polymer gel. This investigation included a detailed examination of the influence of radiation beam energy, dose rate, linearity, and the reproducibility of dose