World Journal of Radiology

Submit a Manuscript: http://www.wjgnet.com/esps/ *World J Radiol* 2017 March 28; 9(3): 112-125

DOI: 10.4329/wjr.v9.i3.112 ISSN 1949-8470 (online)

REVIEW

Three-dimensional radiation dosimetry using polymer gel and solid radiochromic polymer: From basics to clinical applications

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Author contributions: Watanabe Y wrote the article; Warmington L provided the data and reviewed the manuscript; Gopishankar N reviewed the manuscript and made suggestions for improvement.

Conflict-of-interest statement: Authors declare no conflict of interests for this article.

Manuscript source: Invited manuscript

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Received: October 10, 2016
Peer-review started: October 13, 2016
First decision: November 30, 2016
Revised: December 31, 2016
Accepted: January 16, 2017
Article in press: January 18, 2017
Published online: March 28, 2017

Abstract

Accurate dose measurement tools are needed to evaluate the radiation dose delivered to patients by using modern and sophisticated radiation therapy techniques. However, the adequate tools which enable us to directly measure the dose distributions in three-dimensional (3D) space are not commonly available. One such 3D dose measurement device is the polymer-based dosimeter, which changes the material property in response to radiation. These are available in the gel form as polymer gel dosimeter (PGD) and ferrous gel dosimeter (FGD) and in the solid form as solid plastic dosimeter (SPD). Those are made of a continuous uniform medium which polymerizes upon irradiation. Hence, the intrinsic spatial resolution of those dosimeters is very high, and it is only limited by the method by which one converts the dose information recorded by the medium to the absorbed dose. The current standard methods of the dose quantification are magnetic resonance imaging, optical computed tomography, and X-ray computed tomography. In particular, magnetic resonance imaging is well established as a method for obtaining clinically relevant dosimetric data by PGD and FGD. Despite the likely possibility of doing 3D dosimetry by PGD, FGD or SPD, the tools are still lacking wider usages for clinical applications. In this review article, we summarize the current status of PGD, FGD, and SPD and discuss the issue faced by these for wider acceptance in radiation oncology clinic and propose some directions for future development.

Key words: Optical computed tomography; Three-dimensional dose measurement; Solid radiochromic polymer; Magnetic resonance imaging; Polymer gel

Core tip: Polymer gel and solid radiochromic polymer dosimeters are promising tools for measuring the radiation dose distributions in three-dimensional space. The techniques have been studied for last 20 years, but are not used for routine clinical applications to improve the radiation delivery quality. In this review, we summarize the current status and discuss the necessary development to make these tools more accessible for wider usages.

Watanabe Y, Warmington L, Gopishankar N. Three-dimensional radiation dosimetry using polymer gel and solid radiochromic polymer: From basics to clinical applications. *World J Radiol* 2017; 9(3): 112-125 Available from: URL: http://www.wjgnet.com/1949-8470/full/v9/i3/112.htm DOI: http://dx.doi.org/10.4329/wjr.v9.i3.112

INTRODUCTION

The accurate quantification of radiation dose absorbed by the medium is the fundamental requirement in radiation physics. Particularly, when the radiation is used for medical purpose, the high accuracy of dose determination delivered to a patient is mandatory. In radiation therapy, the amount of the radiation dose absorbed by the tissue strongly correlates to the killing probability of both cancer cells and healthy cells[1]. Hence, the radiation must be delivered precisely to the planned location. The absolute dose can be very accurately measured by ion-chambers[2]; hence, it serves as a starting point for evaluating the overall accuracy of dose delivery methods. With the introduction of sophisticated technologies, for example, the intensity modulated radiation therapy (IMRT), the volumetrically modulated arc therapy (VMAT), and the stereotactic ablative radiation therapy, we can deliver the radiation dose distributed in an ideal three-dimensional (3D) shape with the maximum dose delivered to the cancer cells and the minimum dose to the healthy cells[3]. Many factors make the delivered dose very different from the ideal dose distributions. Therefore, the validation of the dose delivered to the patient in comparison to the planned dose is the most important task which one needs to perform before the actual application of the new technologies to patients.

A modern treatment planning requires sophisticated software, which can reproduce the actual radiation delivery and compute the radiation dose to the patient. The treatment planning system (TPS) uses the 3D model of the beam for the dose calculations. The beam data necessary for this process must be supplied by the users, who collect the data by using a 3D water scanning system consisting of a water phantom and an appropriate dosimeter. Hence, the main application of 3D dosimeters is the validation of the dose delivery technique through the comparison of the 3D dose distributions calculated by the TPS with the actual dose delivered to the patient or in a phantom that mimics the patient as a surrogate of the patient.

There are many measurement tools available for characterizing the dose distribution in multi-dimensional space. One can move a point detector, such as an ionization chamber and a silicon diode in a 3D space to cover a volume of interest. An extension of this line of thought is to place many point detectors such as ionization chambers, silicon diodes, thermoluminescent detectors (TLD), in a line, or in the one dimension, and on a flat plane or curved surface in the two dimensions (2D). One of the limitations of this approach is the achievable spatial resolution. Note that the moving point detector method may be able to remedy this problem to some extent with longer measurement time.

The spatial resolution problem can be solved by using a real multi-dimensional detector such as radiographic and radiochromic films. The films can record the dose on a microscopic scale, but it requires specialized equipment to decipher the recorded dose information. The concept of these 2D dose measurement tools can be easily extended into the 3D space. Some materials change its material characteristics when they are irradiated. Hence, if we can build an appropriate instrument to convert the changes to the absorbed dose, we can measure the dose in 3D.

The Fricke ferrous sulfate dosimeter, a type of chemical dosimeters, was developed in early 20th century and was capable of recording the dose in a 3D space[4]. Besides the lack of adequate dose quantification method, the dosimeter suffered a major drawback because the recorded dose distribution quickly fades out due to the diffusion of the ferrous ions. The problem was finally solved by the invention of a non-ferrous solution such as the acrylamide-based polymer gel in the mid-1990s. The first of such material was the BANANA gel manufactured and sold by the MGS Research (now 3D Dosimetry Inc., Madison, CT, United States). Later the dosimeter went through a few cycles of improvement, and it is now available commercially as BANG from the same company. A major drawback of the first polymer gel dosimeter (PGD) was its high sensitivity to the oxygen contamination, which necessitated a hypoxic environment for the manufacturing, for example, in a glove box, and often lead to an incorrect radiation response in the area where the oxygen interacted with the gel. A solution to this problem was the introduction of polymer gels with much-reduced sensitivity to oxygen. The first of these was called MAGIC (Methacrylic and Ascorbic acid in Gelatin Initiated by Copper)[5]. Subsequently, many other groups developed variations of MAGIC. In the same time period, a 3D dosimeter in the solid form, the solid plastic dosimeter (SPD), was commercialized as PRESAGE (Heuris Inc., Skillman, NJ, United States)[6]. For the last 20 years, there have been very active research and development in the field of 3D dosimetry. In this review article, we summarize the current status of the 3D dosimeters and discuss the issue faced by these for wider acceptance in radiation oncology clinic and propose some directions for future development.

Table 1 Summary of polymer gel dosimeter

Dosimeter name	Type	Base	Monomer	Crosslinker	Catalyzer/ stabilizer	Scavenger/ antioxidant	Key investigator	Country	Ref.
BANANA	PAG	Agarose	Acrylamide	BIS		Nitrous oxide	Maryanski	United States	[58]
BANG	PAG	Gelatin	Acrylamide	BIS		Ammonium-persulphate, TEMED	Maryanski	United States	[59,60]
BANG-2	PAG	Gelatin	MAA	BIS	Sodium Hydroxide	AA	Maryanski	United States	[42]
BANG-3	MAG	Gelatin	MAA		$CuSO_4$-$5H_2O$	AA	Maryanski	United States	[61]
MAGIC	MAG	Gelatin	MAA		$CuSO_4$-$5H_2O$, Hydroquinone	AA	Gore	United States	[5]
MAGAT	MAG	Gelatin	MAA			THPC	Baldock	Australia	[62]
nPAG	PAG	Gelatin	Acrylamide	BIS		THPS	De Deene	Belgium	[63]
nMAG	MAG	Gelatin	MAA			THPS	De Deene	Belgium	[63]
nMAG	MAG	Gelatin	MAA			THP	Ceberg	Sweden	[64]
MAGIC-f	MAG	Gelatin	MAA	Formaldehyde	$CuSO_4$-$5H_2O$	AA	Baffa	Brazil	[65]
HEA		Gelatin	HEA	BIS			Baldock	Australia	[66]
VIPAR		Gelatin	VIPAR	BIS			Pappas	Greece	[67]
NIPAM		Gelatin	NIPAM	BIS		THPC	Schreiner	Canada	[68]
Genipin gel	MAG	Gelatin	MAA, genipin			Sulfuric acid	Jordan	Canada	[69]
LCV micelle radiochromic gel		Gelatin	LCV, surfactant-Triton, TCAA	Formaldehyde			Jordan	Canada	[70]
PAG	PAG	Gelatin	Acrylamide	BIS	NaI	THPC	Elleaume	France	[71]
nMAG	nMAG	Agarose, Gelatin	MAA			THPC	Yoshioka	Japan	[72]
nMAG	nMAG	Gelatin	HEMA, TGMEMA, 9G			THPC	Hiroki	Japan	[73]
Radiochromic gel	RGD	Gelatin	SDS, Chloroform, TCAA		LMG dye		De Deene	Australia	[10]

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 (CCl3COOH); 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.

3D DOSIMETER

Here we define 3D dosimeter as a dose measurement device, which can record the 3D dose distribution in a continuous medium. Consequently, the spatial resolution of this dosimeter is mostly determined by the read-out technique used with this dosimeter. In contrast, a dosimeter which is made of many point-like detectors at discrete points and a non-negligible distance among those can be called as pseudo 3D dosimeter. In this review, we will minimize the discussion on the pseudo 3D dosimeter. The following 3D dosimeters are currently available commercially or in research laboratories: The PGD; the Fricke gel dosimeter (FGD); the SPD.

Furthermore, we cannot ignore two other 3D dosimeters, scintillators, and Cherenkov-radiation detectors. The former is a rather old technology, but it has not gained much attention as a 3D dosimetry tool mostly because the material has mass density and effective atomic number very different from those of the water[7]. The Cherenkov detector has been studied by one group for last few years and has a potential to be an excellent 3D dosimeter[8], but it needs further extensive studies by many different investigators before clinical applications. Therefore, we focus on PGD, FGD and SPD in the rest of this article.

PGD

PGD is composed of five chemical components: water, gelatin, monomer, catalyzer, and oxygen scavenger[9]. Note that the oxygen scavenger is added to make PGD more resistant to oxygen contamination. Such a PGD is called normoxic PGD or nPGD. Usually, we can group PGD/nPGD into two groups. Those with methacrylic as a monomer are called MAGAT/nMAG and those with acrylamide are called PAGAT/nPAG. There are many variations of those depending on the chemical agents. We summarized the MAGAT/nMAG and PAGAT/nPAG in Table 1. Notably, Vandecasteele *et al*[10] recently developed the radiochromic gel dosimeter (RGD), which is composed of 92% weight of water, gelatin, sodium dodecyl sulfate, trichloroacetic acid (CCl3COOH) and leuco-malachite green (LMG). The RGD was mainly developed to be used with an optical computed tomography (OCT) scanner as a read-out method[10]. The list is certainly incomplete, but can show a significant contribution from many investigators in many countries and demonstrate the international nature of this field. The photo in Figure 1 shows the PAGAT dosimeter. The white cloud in the center of the clear PAGAT gel contained in a cylindrical plastic container indicates the high radiation dose volume generated by a 6MV photon beam.

Table 2 Summary of ferrous gel dosimeter

Dosimeter	Type	Base	Monomer	Key investigator	Country	Ref.
Fricke	Fluid	None	Ammonium ferrous sulfate	Gore	United States	[11]
FeMRI	FGD	Agarose	Seaplaque, seagel	Olsson	Sweden	[74]
PVA-FX	FGD	Hydrogel	PVA, FBX	Chu	Canada	[75]
FAX	FGD	Agarose	XO, ferrous	Leong	Malaysia	[76]
FX	FGD	Gelatin	Ferrous ammonium sulfate, XO, sulfuric acid	Jordan	Canada	[70]
PVA cryogel	FGD	Hydrogel	FBX, PVA, dimethyl sulfoxide	Eyadeh	Canada	[77]
XO-PVA	FGD	Hydrogel	PVA, XO, ferrous sulfate, sulfuric acid	Trapp	Australia	[78]
NC-FG	FGD	Gelatin	Nano-clay, ammonium iron (Ⅱ) sulfate, Perchloric acid	Maeyama	Japan	[41]

PVA: Polyvinyl alcohol; XO: Xylenol orange; FBX: Ferrous benzoic xylenol orange (= ferrous ammonium sulfate, XO, H2SOF4); FGD: Ferrous gel dosimeter; MRI: Magnetic resonance imaging; NC-FG: Nano-composite Fricke gel.

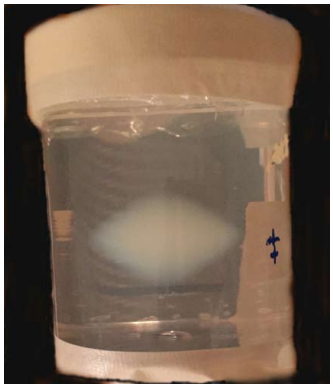

Figure 1 The photo of PAGAT polymer gel dosimeter.

Figure 2 The photo of solid plastic dosimeter.

FGD

Fricke ferrous sulfate dosimeter is a type of chemical dosimeter. The radiation induces a chemical change as Fe^{2+} ions convert to Fe^{3+} ions[11]. The concentration of the ferric ions can be measured by absorption photospectrometry. Since the ferric ion concentration strongly affects its magnetic property, magnetic resonance imaging (MRI) is an ideal tool to determine the ferric ion distribution. Later, to prevent the diffusive motion of the ferric ions, which blurs the dose distribution, hydrogels were introduced as the background material[12,13]. Babic *et al*[13] used radiochromic ferrous xylenol orange with the Fricke gel so that it changes the color upon irradiation, allowing the utilization of an optical technique for 3D dose quantification. FGD is summarized in Table 2.

SPD

The SPD, often called a solid radiochromic dosimeter, is a new type of 3D dosimeters. Some plastic material such as polydiacetylene polymerizes when it interacts with photons. The characteristic of the photopolymerization can be amplified by adding coloring dye to produce a radiation responding medium. Radiochromic or gafchromic films were developed from this material. Those are commercially available as EBT series products (Ashland Inc., Covington, KY, United States). The same chemical principle can be realized in a 3D material. Adamovics *et al*[6] produced the first 3D radiochromic dosimeter based on polyurethane with LMG. The radiation sensitivity was enhanced by adding chemical catalyzer such as chloroform[6]. This dosimeter is available commercially as PRESAGE and may contain proprietary ingredients. As shown in Table 3, there are only a few investigators who currently produce SPD in-house. Fortunately, the production of SPD is rather straightforward since there is a commercial product which was developed for artwork. A mixture of Clear Poly A and B (Smooth-On Inc., Easton, PA) can cast in any shape. By adding LMG, this material can be quickly turned into SPD[14]. Figure 2 shows the SPD manufactured in-house. The green bar vertically running in the middle of the cylindrical phantom indicates the beam path of 18 MV photons with 1 cm × 1 cm field size.

Water equivalency

One of the requirements for a dosimeter is its ability to measure the dose absorbed by water in water[4]. The detectors, therefore, must be placed in a water equivalent medium, which includes the actual water, such as the 3D water scanning system, and a solid phantom that is equivalent to water such as the white water and solid water[15]. The equivalency, however, needs a special consideration when the atomic composition of the material is different from that of water. The actual equivalency of radiological characteristics means that the photon and electron scattering cross sections are the same as those of water for all energy of photons and electrons. This definition of water equivalency also applies to heavier charged particles such as protons and heavy ions. It is

Table 3 Summary of solid plastic dosimeter

Dosimeter	Type	A	B	Initiator	Dye	Key investigator	Country	Ref.
SPD	SPD	Diacetylene	Ethyl trichloroacetate, heptachloropropane, *etc.*	Radiochromic (fuschin cyanide, *etc.*)	Leuco crystal violet, or LMG	Patel	United States	[79]
PRESAGE	SPD	Polyol_A, diasocyanate	Polyol_B	Carbon tetrachloride, methylene chloride, tetra-chloroethane, Chloroform	LMG	Adamovics	United States	[6]
PRESAGE	SPD	Crystal clear A	Crystal clear B	Carbon tetrachloride	LMG	Hashemi	Iran	[80]
PRESAGE	SPD	Crystal clear A	Crystal clear B	Chloroform, bromoform, or iodoform	LMG	Geso	Australia	[81]
PRESAGE	SPD	Crystal clear A	Crystal clear B	Bromoform	LMG	Watanabe	United States	[14]

LMG: Leuco-malachite green; SPD: Solid plastic dosimeter.

Table 4 Water equivalency of three-dimensional dosimeters

Dosimeter	Type	Relative effective atomic number	Relative mass density	Relative electron density
PAGAT	PGD	1.013[1]	1.026[4]	0.928[4]
MAGAT	PGD	1.014[1], 0.984[3]	1.032[3]	0.993[3]
nMAG	PGD	1.018[1]		
MAGIC	PGD	1.018[1], 0.987[3]	1.037[3]	0.990[3]
Genipin gel	PGD	1.014[2]	1.001[2]	0.9982[2]
PRESAGE-A	SPD	1.037[2]	1.054[2]	0.977[2]
Water		1.00 (Zeff = 7.42)	1.000	1.0 (3.343 x 10^{23} Electrons/g)

The numbers in parentheses indicate the references. [1]Ref. [82] (for 18MeV photon energy); [2]Ref. [83]; [3]Ref. [84]; [4]Ref. [85]. PGD: Polymer gel dosimeter; SPD: Solid plastic dosimeter.

important to remember that the radiological quantity often depends on the radiation energy.

To simplify the discussion, we focus on the photons and electrons in this section. Then, the cross sections can be replaced by the photon attenuation coefficients and electron stopping power. To quantify the radiological quantity of the materials, we can use the effective atomic number, mass density, and electron density. We use the photon energy above the energy of gamma rays produced by Cobalt-60, or. 1.25 MeV, and below 20 MeV, which is the maximum photon and electron energy currently clinically in use. For this range of energy, we might assume three quantities mentioned above can be evaluated for one energy, say, at 6 MeV. In Table 4 we summarized those for some of the standard 3D dosimeters. Note that the genipin PGD has the radiological quantities the closest to those of water.

DOSE QUANTIFICATION TECHNIQUES

All 3D dosimeters under review are not absolute dosimeters in the sense of calorimeter or ionization chambers since those do not quantify either energy absorbed by a medium or the number of ion-electron pairs produced in a medium. Those rather rely on a monotonic relationship between the expected absorbed dose and the amount of the quantitative changes of the characteristic of the dosimeter material. PGD material polymerizes when the radiation interacts with the material. The polymerization occurs among the monomers which are suspended in the gelatin matrix. This process, in turn, causes a change in the molecular structure and the mass density. Consequently, these changes lead to an alteration of the mechanical, optical, and magnetic properties. FGD relies on a mechanism different from PGD. In FGD, new ferrous ions are produced by radiation. The change in the concentration of ferrous ions is closely related to the absorbed dose. In SPD, the radiation causes copolymerization of the monomers and the change of color at the same time. It is noteworthy that we always need to obtain a calibration relationship between the dose absorbed by the 3D dosimeter and the amount of quantitative changes measured by the dose quantification tool for the dose measurement.

Here, we discuss three dose quantification techniques; MRI, OCT, and X-ray computed tomography (XCT). There are other techniques such as the ultrasound device, but those will not be considered in this review because they are not readily available in clinics or their unproven measurement accuracy. Each system has its advantages and disadvantages. In Table 5, we summarized the cons and pros of those systems. Note that since the technology keeps changing and improving, some of the disadvantages may disappear in the future.

MRI

The most common method of the dose quantification of PGD and FGD is MRI. MRI can measure the changes of the transverse (or spin-lattice) relaxation time (T1), the lateral (or spin-spin) relaxation time (T2), the magnetization transfer, the susceptibility, and radio-frequency spectra. Because of the solid nature, MRI cannot be used with SPD.

Table 5 Comparison of dose quantification techniques

Method	Pros	Cons
MRI	Commonly available at a hospital	Low SNR
	Easily accessible scan protocol	Image artifacts
	Known accuracy and precision	Limited spatial resolution
	Linear dose response	Long scan time
OCT	High spatial resolution	Optical artifacts
	Small physical size or compact	Needs refractive index
	Easy and free access if owned	matching
XCT	Easy access at hospital	Low image contrast
	High SNR	
	Very fast scan	

SNR: Signal-to-noise ratio; MRI: Magnetic resonance imaging; OCT: Optical computer tomography; XCT: X-ray computed tomography.

The T2 change is most noticeable in PGD; hence, it is the most important parameter. The 3D distribution of T2 or the inverse of T2, the spin-spin relaxation rate (R2), can be measured by using a multiple spin echo pulse sequence such as Car-Purcell-Meiboom-Gill[16]. The T1 change is quantified for FGD since the ions strongly influence the spin-lattice relaxation[17].

OCT

The change in the mass density in PGD and the color change of SPD naturally lead to an optical method for the dose quantification. By borrowing the ideas from both the optical densitometer used for radiographic and radiochromic films and the X-ray CT, the 3D distribution of the change in the optical properties can be measured by OCT. There are three types of OCT systems. The first generation OCT uses the line of laser light with a pair of a light source and a point photon detector. The entire 3D volume can be covered by moving the laser light and the sensor together both in the transverse and longitudinal directions while the sample is rotated. The standard image reconstruction algorithm can be used to obtain full 3D dose distribution data. The second generation scanner uses a mirror to sweep the light ray along the transverse direction to speed up the scanning time. For an even quicker scan, the third generation OCT uses a broad cone beam of laser light, either parallel beam or a divergent beam in the object, and a charge coupled detector camera as the sensor. Some researchers proposed a fan-beam type scanning system by generating a horizontal fan beam[14,18]. OCT measures the attenuation of photons, and this is represented by the optical density (OD). Hence, the dose must be estimated by using an appropriate calibration relationship between OD and the dose.

XCT

XCT relies on the photon attenuation by the object. Since the radiation changes the density of PGD, the dose pattern can be visualized by using XCT. This approach might be the most attractive method for routine applications of the 3D dosimetry because of the wide-spread use of the XCT in the radiation therapy clinic. However, the practicality of XCT as the readout tool yet needs to be proven.

Comparison of dose quantification methods

Important factors which determine the quality of the dose quantification methods are the accuracy, the precision, the spatial resolution, the speed, and the cost. The accuracy depends on the quality of the calibration data which are used to convert the measured physical parameters to dose to the dosimeter (or often to the water). Hence, a parameter more important than the accuracy is the uncertainty or the precision of the measurement. We compare these parameters of MRI, OCT and XCT, based on the published results. The scanning speed and the precision are strongly correlated for MRI, to some extent, for both OCT and XCT. For example, the repeated acquisition of MR images decreases the image noise, though the noise only decreases with the square root of the number of image acquisition, resulting in a significant increase in the scanning time or slower scanning speed. Note that among these, only OCT is not used in radiation oncology clinics as a standard imaging tool for routine clinical work and needs to be purchased specifically for the 3D dosimetry purpose.

For dosimetric applications, the precision must be high, and it should be smaller than 5%. In Table 6, we summarize the precision quoted in literature. It is, however, worth mentioning that those values are a combination of the precision stemming from the dosimeter itself and the dose quantification tool. Furthermore, many items in Table 6 are not known, and systematic studies are needed to quantify those uncertainty values.

Long scanning time is acceptable if the scanning system is used solely for the 3D dosimetry such as a dedicated OCT system. Otherwise, the system should be capable of acquiring 3D dose data in a reasonable time frame, *i.e.*, shorter than one hour and at most 2 h.

The cost of the dose data quantification is user fees for MRI and XCT. Usually, the fee is about $500 per hour at the most institutions in the United States if any payment is needed. Note that in this review the cost is estimated at the United States dollars. The cost of OCT, if purchased, could range from $10000 to $50000. Hence, for repeated uses, OCT could be the most economical system unless the MRI and XCT are available for free.

ACCURACY AND PRECISION

Accuracy of absolute dose measurement

The primary purpose of 3D dose measurements is not the absolute quantification of the absorbed dose, but rather it is often a measurement of the relative 3D distribution of the dose produced by a radiation delivery technique. Hence, the capability of the absolute dose measurement is not the most important requirement for the 3D dosimeters. However, the 3D dosimeters can be used as an absolute dosimeter if the radiation response is adequately characterized.

Table 6 Precision (or uncertainty) of three-dimensional dosimetry[22]

Uncertainty type	Source	Factor	PGD	FGD	SPD
A	Physicochemical	Chemical composition	< 2%		< 2%
		Temperature variation			
		Temporal and spatial integrity			
	Irradiation	Dose rate			
		Energy			
		Temperature			2%
		Phantom position setup		1 mm	
	MRI	Image noise	< 0.4% (3 mm^3)		
	OCT	Image noise			
	XCT	The standard deviation of CT number		2% to 8%	
B	MRI	B0 non-uniformity	< 3%		
		B1 non-uniformity			
		Gradient non-uniformity			
		Temperature during scanning			
	Medium	Non-uniform refractive index			
	OCT	Refractive index matching			
		Unstable light source			
		Ambient stray light			
		Desynchronization between galvanic mirror and detector			
		Misalignment of light, subject, and detector			
	XCT	Image processing		5%	
		Calibration equation			

MRI: Magnetic resonance imaging; OCT: Optical computer tomography; XCT: X-ray computed tomography; FGD: Ferrous gel dosimeter; PGD: Polymer gel dosimeter; SPD: Solid plastic dosimeter.

The accuracy of the dose measured by a detector depends on the accuracy of the original signal recorded inside the 3D dosimeter medium and the precision of the dose-response data or the calibration equation, which is used to convert the raw signal data to the absorbed dose[16,19]. To study this more quantitatively, let us assume the calibration equation represented by a second order polynomial, which is the most common response characteristics of the 3D dosimeters. For the raw data X recorded by the 3D dosimeter, the absolute dose D can be now expressed by

$$D = aX^2 + bX + c \quad (1)$$

It is well known that the uncertainty of D can be given as the function of the uncertainties of the raw data X, and the three coefficients, a, b and c, in Eq.(1):

$$\delta D = \{(X^2\delta a)^2 + (X\delta b)^2 + (\delta c)^2 + [(2aX + b)\delta X]^2\}^{1/2} \quad (2)$$

If the calibration equation (1) is exact, *i.e.*, $\delta a = \delta b = \delta c = 0$, Eq.(2) can be modified as

$$\delta D/D = (X/D) \times (dD/dX)\,(\delta X/X) = \{[(2aX + b)X]/D\} \times (\delta X/X) \quad (3)$$

Eq.(3) implies that the relative uncertainty of D is proportional to the relative uncertainty of X; in other words, the smaller the uncertainty of X the smaller the uncertainty of the dose. In reality, however, the uncertainty of the coefficients, a, b and c, is not negligible; hence, the uncertainty of D can be much larger than the uncertainty given by Eq.(3). Another point which is often forgotten is that the uncertainty of dose also depends on the dose itself because the proportional constant in Eq.(3) is a function of X and D.

Precision

The precision or the uncertainty of the measured dose is a summation of the uncertainty due to the random errors (or Type A) and systematic errors (Type B). The Type A uncertainty can be estimated by Eq.(2) or a similar equation derived for a particular calibration equation. It is not simple, however, to characterize the Type B errors.

MacDougall *et al*[20] attempted to estimate the measurement uncertainty of PGD and FGD in 2002. They gave a rather pessimistic estimate of the accuracy obtainable, *i.e.*, 10% for PGD and 5% for FGD, and the estimated uncertainty was 1.5% for FGD only. Since that time, the dose read-out technique and the quality of 3D dosimeter have improved. The issues of the measurement uncertainty with the 3D dosimeters were, again, reviewed by De Deene and Andrew[21] in 2015. The nominal uncertainty values from this article are summarized in Table 6. The data are still sparse mainly because the uncertainty is unique to every measurement and dosimeter quality and there is a significant variation in the quality of both measurements and the dosimeters. It is important to note that there are many boxes which are not filled in Table 6. Those are not easily measurable and not well characterized yet. However, eventually, all those uncertainty factors must be estimated to provide a reliable 3D dosimetry tool to the medical community.

PRECLINICAL APPLICATIONS

Besides the highly 3D nature of the dose distribution delivered by modern radiation therapy devices, three

factors affect the dose, consequently the treatment effectiveness. The human body is mostly made of water, or about 50%-65% with the rest composed of higher density tissue, such as bone and lower density material such as lung or air cavity. Furthermore, some patients receive implants often made of high-density material for medical reasons. The dose distribution drastically changes in the vicinity of or near the interface between media with different mass density. The heterogeneity of the medium generates the highly complex dosage patterns and often the current dose calculation algorithms used by the TPS system cannot handle this circumstance accurately. Hence, the effect of tissue heterogeneity must be studied through experimental measurements. Another factor significantly impacting the dose to the tissue is that the temporal change of the human body, consequently the changes in the shape and the material density distribution during a radiation therapy. Such a temporal change is more important when more fractions are used. Note that radiotherapy for the treatment may last for even longer than two months. The effect on the 3D dose distributions can be studied by taking many CT scans. However, what is not known is that the motion of specific points in 3D space and the accumulated dose at that point. We cannot figure out where a tissue volume at a point A on day 1 is on day 2 when the body is deformed. Perhaps, this problem could be solved by creating a mechanical model of the inside of the human body. Alternatively, we can measure the exact accumulated 3D dose distribution to the volume at the end of the treatment with an appropriate dosimetric tool. The third factor is the size of the volume in which the dose must be measured. If the volume is less than 1 cm^3 and we need to obtain the 3D dose distribution in this volume, there is a lack of adequate dosimetry tools, currently.

Heterogeneity effects

The interface dosimetry in which one addresses the dose distribution near the tissue and non-tissue interface is well studied at least in a simple geometry such as in the vicinity of a planar heterogeneous material. When we move to heterogeneous materials with more complex 3D shape, the standard dose measurement tools such as ionization chambers, TLD, silicon diodes, radiographic and radiochromic films, are not useful because those cannot provide a real 3D dose distribution with high spatial resolution and add extra heterogeneity due to the measurement tool itself. For this type of measurements, the 3D dosimeters, PGD, FGD and SPD, are ideal dosimeters. There are only a few studies addressing the 3D interface dosimetry by the 3D dosimeters. Since the current deterministic dose calculation methods may not be accurate for this problem, one need to use Monte Carlo simulation methods to create a reference data, to which the measured data are compared to the evaluation of the measurements[22,23].

Deformable object

There is commercially available software such as Velocity (Varian Medical Systems, Palo Alto, CA, United States) and MIM Maestro (MIM Software Inc., Cleveland, OH, United States), which can deform the shape of the body image and provide the sum of the doses delivered to many differently deformed objects. Experimental measurements should validate the algorithms of this software. The shape of soft material can be easily deformed. Hence, by implanting many small detectors, *i.e*., silicon diodes or MOSFET, in the material, we can track the dose to points. At the end of such a study, we can obtain the accumulated dose. The more attractive approach is to use a deformable material which can measure 3D dose distributions. PGD and FGD are ideal for this study because of their flexible nature of the material and the ability to record the dose in 3D space. Applications of PGD in this area of research are not advanced at all, and only a few researchers are currently working on this topic, including the De Deene's group[24].

Small field

When the size of the radiation beam is small, *e.g*., less than 1 cm, the only currently available measurement tool is either radiographic/radiochromic films or the 3D dosimeters. There are a few publications on applications of PGD/FGD/SPD[25-30], and more studies on this topic are needed.

CLINICAL APPLICATIONS

3D dosimeters can be used in clinical practice in radiation oncology. Currently, it is used for evaluation of new tools and radiation delivery techniques. It is also being used as an external QA auditing tool to monitor the quality of dose delivery[31]. In Figure 3, we present a standard measurement and analysis procedure when we use the 3D dosimeter for evaluation of the delivered dose in comparison to the dose predicted by the TPS.

3D dosimetry products

BANG series dosimeter (nMAG-type PGD) is manufactured and sold by 3D Dosimetry Inc. The same company recently introduced the RGD as CrystalBall™[32]. PRESAGE SPD is available from Heuris Inc., owned by Dr. Adamovic. The most common imaging device for the dose quantification of PGD/FGD is the MRI system, and it is readily available at most medical facilities. There are only two companies which supply OCT systems for PGD/FGD/SPD. The 3D Dosimetry, Inc. sells its OCTOPUS series system. Modus Medical, Inc. (London, ON, Canada) manufactures two types of cone-beam-based OCT systems, named as Vista.

Analysis software

The analysis software should be able to process the raw image data acquired by the imaging device and convert the raw data to the 3D dose. Also, it is desirable for the software to be able to perform the evaluation of the measured dose in comparison to the reference data from

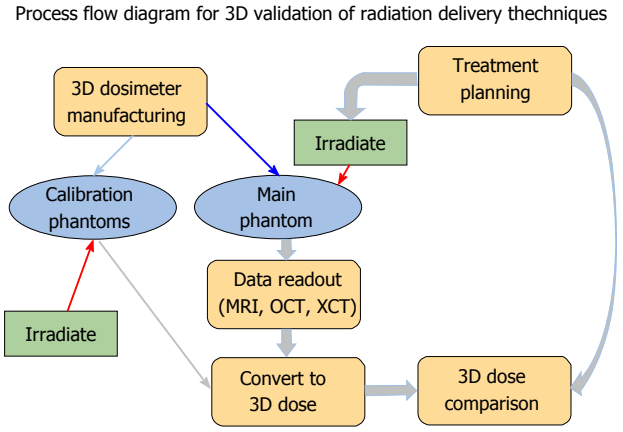

Figure 3 The process flow for dose evaluation using the three-dimensional dosimeters. MRI: Magnetic resonance imaging; OCT: Optical computer tomography; XCT: X-ray computed tomography; 3D: Three-dimensional.

TPS, Monte Carlo code, or other 3D dose measurement tools. The gamma index analysis capability in addition to volumetric analysis, such as generation of dose volume histograms (DVH) using the contour data from TPS is the desired function.

The commercial OCT systems, OCTOPUS and Vista, come with the analysis software. The OCTOPUS system from the 3D Dosimetry Inc. comes with built-in VOLQA™ software. A commercial software PolyGeVero is available from the GeVero Co (Lotz, Poland). Additionally, RTSafe, P.C. (Athens, Greece) and 3D Dosimetry Inc. provide the dosimetry analysis service.

Most research groups in this field developed own data analysis software. Those cannot be used for the work directly related to routine patient treatments, but are excellent tools for research related to new equipment and delivery techniques. These can be easily available for free from the developers[33].

Routine quality assurance

The regular quality assurance (QA) involves the measurements of beam output and the evaluation of mechanical and dosimetric accuracy[34]. Other regular QA includes the dosimetric validation of the treatment plans for every IMRT/VMAT treatment[34]. Thorough dosimetric measurements performed at the acquisition of the new accelerator, or the annual QA can be included in this category. The 3D dosimeters are not used for this purpose currently.

Testing new dosimetry equipment

Pseudo 3D dosimetry tools are being introduced into clinics for routine applications. The device must be tested, and its accuracy must be evaluated before actual applications for patients. PGD/FGD/SPD are ideal tools for such evaluation studies. One example in this area is the assessment of the ArcCHECK device (SUN NUCLEAR, Melbourne, FL, United States). This device contains 1383 small silicon detectors arranged helically on the cylindrical surface. The device measures the radiation dose deposited by both incident and exiting beams. The device is specifically designed for QA of VMAT. Furthermore, special software 3DVH can be used to reconstruct the radiation dose distribution inside the cylinder where there is no detector or in the patient by using the dose data measured by ArcCHECK. The 3D dose data can be mathematically reconstructed from the available fluence data. Hence, this device can provide the users a 3D dose distribution data in a phantom or a patient. Since the device is based on a new idea and its design is very innovative, the evaluation of its performance is essential. Watanabe and Nakaguchi, hence, undertook an assessment study by using BANG3[33]. They measured the 3D dose distribution generated by VMAT and compared the results with those obtained by ArcCHECK. Their results demonstrated a satisfactory agreement between those two measurement techniques, hence, confirming the measurement accuracy of the new device as a pseudo-3D dosimeter. This application of PGD is a critical step to demonstrate its value and suggests that the PGD should be invaluable. PGD may become the standard tool for evaluation of psedo-3D dosimeters which will be developed in the future.

End-to-end QA

A task group of AAPM, TG-142, recommends the end-to-end test of a new dose delivery system such as SRS and IMRT/VMAT[34]. Such a test can be accomplished the most adequately by using the 3D dosimeter because the shape of a patient can be simulated easily by using these tools. The earliest application of PGD was made to the end-to-end QA of Gamma Knife stereotactic radiosurgery (GKSRS). One of the studies could, in fact, point out a non-negligible geometric error associated with the imaging, which was not considered or quantified before[35]. As a matter of fact, all the MRI-based PGD of GKSRS is considered as an end-to-end test of the dose delivered when the dose delivery is planned on the MR image which was taken before planning and radiation delivery.

SRS

The application of 3D dosimeters for GKSRS is well established as discussed before. Applications of 3D dosimeters to other types of SRS technique have not been performed as often as GKSRS for an unknown reason. Björeland *et al*[36] used nMAG for the dosimetric evaluation of a linac-based hypofractionated SRS system. PAGAT was used for QA of SRS by multi-leaf collimator (MLC), m3 (BrainLab)[37].

IMRT/VMAT/tomotherapy

The dose delivery technique of IMRT and VMAT (including tomotherapy) requires very sophisticated mechanical maneuver of the MLC, jaws, and the angles of gantry and collimator. The radiation delivery is, in essence, four-dimensional because the positions of all these components move during a single delivery of treatment. Hence, the precision of delivering dose is affected by the composite of many factors. An individual test of this element is not sufficient. Hence, the actual 3D dose evaluation of these technologies should be performed at least once before the introduction to clinical usages.

Table 7 IMRT/VMAT/tomotherapy three-dimensional dosimetry

Ref.	Dosimeter	Read-out method	Treatment site	Delivery type	Photon energy/ number of fields	Comparison on the plane or in volume	Gamma index criteria % dose difference (global/ local)/DTA (mm)/ threshold (%)	Gamma index passing rate
[86]	MAGIC	MRI/T2	Model	IMRT/GKSRS	6MV/Co-60	Volume	3/3/	50.3%
[87]	FX gel	OCT/Vista	Head and Neck	IMRT	6MV	Volume	3/3/none	84.1%
[88]	BANG3	MRI/T2	Prostate	Tomotherapy	6MV/Arc	Volume	3/3	53%
[89]	PRESAGE	DLOS	Brain	IMRT	6MV	Volume	3/3	95%
[90]	MAGIC-f	MRI/T2	Prostate	Tomotherapy	6MV/Arc	Plane	3/3	88.4%
[91]	nPAG	OCTOPUS-IQ	Prostate	IMRT	/7fields	Volume		95.3%
[10]	PAGAT	MRI/T2	Pituitary	IMRT	6MV/7fields	Volume	2/2	99.4%
[33]	BANG3	MRI/T2	Prostate	VMAT (Elekta)	6MV/Arc	Volume	3 (global)/3/25	95.7%
[92]	BANG3	MRI/T2	Prostate	VMAT (Varian)	6MV/Arc	Volume	3 (global)/3/50	90.0%
[93]	PRESAGE	DMOS	Brain	IMRT	6MV/5fields	Volume	3 (global)/3/10	99.4%
[94]	NIPAM	MRI/T2	Eye	IMRT	6MV/5fields	Plane	3/3/	98.5%

MRI: Magnetic resonance imaging; DTA: Distance to agreement; DMOS: Duke Mid-Sized Optical-CT Scanner; DLOS: Duke Large field-of-view Optical-CT Scanner.

The 3D dosimetry tools can be used effectively for this purpose.

The major goal of the 3D dosimetry, hence, is the validation of the 3D dose distribution predicted by TPS by comparing with the measured dose which reflects the performance of the radiation delivery system. There are many studies on this topic. In Table 7, we summarize the published studies, which provide the gamma index passing rates. There are many other studies, most of which are earlier publications without the gamma analysis.

Proton/heavy ions

Because of its unique depth dose generated by ion beams such as protons and heavy ions, *i.e.*, carbon-12, a tremendous interest in those technologies exists. In fact, the use of protons for radiation therapy is rapidly expanding. The desirable depth-dose characteristics, mainly due to the existence of the Bragg peak at a particular range, however, suffers from a significant uncertainty of the actual location of the sharp peak in the dose. This issue is sometimes called as range uncertainty. The measurement of the depth dose of particle beams, hence, is an important task, which every new facility should perform. The 3D dosimeter can be a good candidate for this type of applications if those materials are tailored to adequately simulate the linear energy transfer (LET) of particles in water or tissue.

Gustavsson *et al*[38] used BANG3 for the measurement of the central axis depth dose curve of a 68MeV proton beam. They found that the dose at the Bragg peak was underestimated by a factor of two by BANG3 because of the "quenching". The quenching or under-response of the BANG3 occurred because the proton energy changes as those travel into deeper locations. LET depends on the proton energy. Thus, calibration data obtained by a specific energy at a shallow depth cannot be applied to the depth dose measurement. We can solve this problem by using the estimated proton energy as the function of depth theoretically, for example, by Monte Carlo simulation[38]. The introduction of BANG3-Pro eventually solved the issue of PGD due to the LET dependence of its radiation response. The new PGD had gelatin matrix with higher viscosity than the original BANG3[39]. PGD was also tested with heavy ion beams[40]. Recently, Maeyama et al. used the nano-composite Fricke gel (NC-FG), a type of FGD, with carbon and argon ion beams, whose LET ranged from 10 to 3000 eV/μm[41]. NC-FG showed a consistent dose response for the range of LET tested in their study.

Brachytherapy

Brachytherapy uses the small size of the radioactive material as radiation sources for radiation therapy. It is easy to expect, hence, that the dose distributions generated by single brachytherapy source or multiple sources are highly three-dimensional. Because of the large dose gradient, the 3D dosimeters are potentially an ideal dose measurement device. Therefore, 3D dosimeters were widely used with radioactive sources. The primary application is in the 3D dose distribution measurement of the single radioactive source. The results can be compared with the standard data of TG53 which are clinically in use. The measurements were done with various types of radioactive sources: Iridium-192 high dose rate (HDR) source[42-48], low dose rate (LDR) Iodine-125 seed[49,50], and LDR Cesium-137 source[51]. Additionally, the 3D dosimeters were used for the dosimetry of beta-emitting radioactive sources such as Ruthenium-103[52], Renium-188[53], and Ytirium-90[54]. The SPD was also used with a radioactive source[55,56].

For many brachytherapy procedures using LDR and HDR sources, the high dose is delivered to a large volume by placing many sources or moving a single HDR source over the volume. There is a lack of 3D dosimetry study in this more clinically useful source configuration.

DISCUSSION AND SUMMARY

Current technical issues

An ultimate goal of the 3D dosimeter study is to produce a tool for 3D dosimetry, which can be routinely used in all radiation therapy clinics all over the world. This goal

is yet to be reached. It seems that even institutions with sufficient expertise in this field are not using the tool routinely except occasional applications, mostly, for research purpose or evaluation of new devices or software. There are two major factors for this somewhat depressing situation after over 20 years of extensive research. The first factor is the precision of the measurements in comparison to the existing tools. As discussed in the precision section, the state-of-art methods in PGD, FGD, and SPD can achieve ± 5% uncertainty with 95% confidence if the measurements and instruments are well prepared and managed. This accuracy is still less than that of other more standard tools such as a 3D water scanning system with an ionization chamber, which can provide a 3D dose distribution, but with coarser measurement grids than PGD and SPD. Note that the 3D water scanning is faster than PGD and SPD when the measurement time includes the preparation and the data analysis. Hence, the current 3D dosimeters cannot replace the 3D water scanning system, which is always used for commissioning and annual QA of the accelerator.

Therefore, the improvement of the measurement precision should be the primary goal of the 3D dosimetry community. The uncertainty is composed of the random errors (Type A), which are caused by the random nature of the signal acquired by the measurement device, and the uncertainty of the calibration data, which is again strongly affected by the random errors during the calibration. However, a larger uncertainty stems from other factors (Table 6): (1) the non-uniformity of the detector medium; (2) the reproducibility of dosimetric properties; and (3) the uncertainty associated with the dose quantification device.

The issues (1) and (2) can be overcome by improving the manufacturing process and the distribution (or delivery of the product to the customer) system. The issue (3) can be solved by using an imaging device specifically designed for the 3D dosimetry. MRI cannot be easily made just for the 3D dosimetry. Since MRI is a diagnostic tool, it is not suited for the quantitative measurement. However, the situation will improve because the community is now more interested in the "quantitative" imaging. On the other hand, OCTs are designed for the 3D dosimetry to provide the most accurate result, although the current system still requires further improvement.

The cost of the 3D dosimetry is another obstacle preventing its widespread acceptance as a routine measurement tool. Let us examine this issue further by using an example. Suppose we would like to use PGD for the regular patient specific IMRT/VMAT QA. Assume that the current standard is the use of ArcCHECK and the price of the ArcCHECK system is $50000. Now, then we purchase a commercial PGD, whose price is $500 for an 18-cm diameter 20-cm long cylindrical phantom containing PGD. The cost of the dose quantification device is zero if MRI is used or $30000 if a commercial OCT system is purchased. Assume we use an OCT system. Then, the difference of the device costs between the ArcCHECK and PGD approach is $20000 by excluding the cost of PGD. This difference can cover 40 PGD phantoms, which are the number needed for one year of patient specific QA at a typical radiation oncology department. If we assume that we use these systems for five years, the total cost of the ArcCHECK approach is still $50000. However, the total cost of PGD is $130000. Hence, there is a tremendous disadvantage of the PGD over the ArcCHECK regarding the cost. However, this cost analysis does not diminish the value of the 3D dosimeter approach as we discuss next. It is evident from this analysis, furthermore, that the development of reusable 3D dosimeters could lead to significant cost saving[57].

Now, let us consider the information obtained by these tools. The information is quantified by the number of pixels and voxels, which record the dose data, for PGD, and the number of diode detectors in ArcCHECK, which is 1386. The voxel size of typical OCT scan is 1 mm × 1 mm × 1 mm or 1 mm^3 (= 0.001 cm^3). The volume of dose measurement is a 20-cm diameter and 20-cm long; hence, this volume is 833 cm^3 and contains 833000 voxels. Assume we use the system for 40 × 5 = 200 times in five years. The dollar per the data point or information is 18 cents for the ArcCHECK method; whereas it is 0.08 cents for PGD. Therefore, PGD is much more cost effective if all the acquired data can be utilized to improve the treatment quality.

CONCLUSION

The 3D dosimeters have been under development for many years and were studied by researchers all over the world. It seems that the lack of the acceptance for wider radiation oncology applications stems from the inherent or unknown uncertainty of the tools and the cost needed for everyday usages. These issues should be addressed in the future. More focused studies are needed to resolve these problems.

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P- Reviewer: Arisan V, Tomizawa M, Tsalafoutas IA **S- Editor**: Ji FF
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