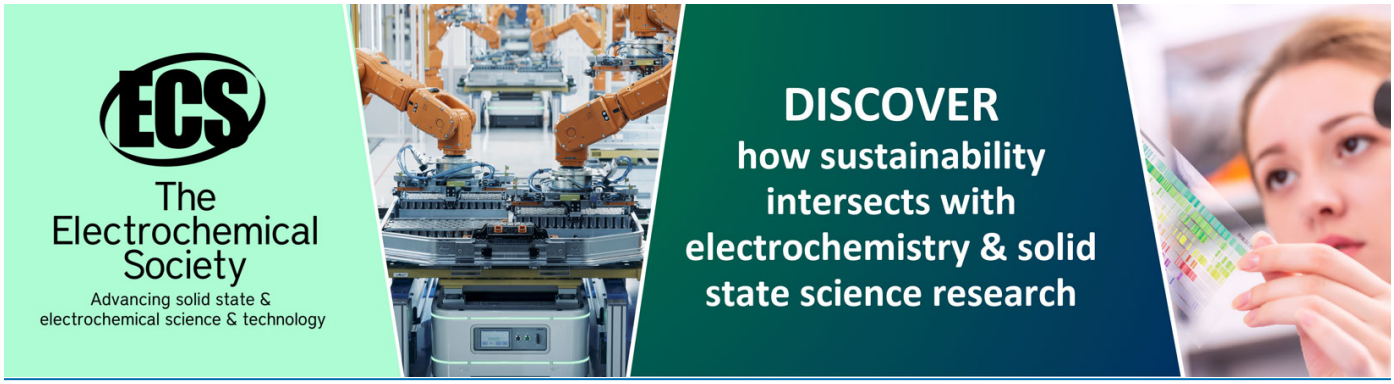
True 3D chemical dosimetry (gels, plastics): Development and clinical role



True 3D chemical dosimetry (gels, plastics): Development and clinical role

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Abstract. Since the introduction of volumetric chemical dosimetry with Fricke gel dosimeters in the 1980s, three-dimensional (3D) dosimetry has been a promising technique for the clinic, since it provides a unique methodology for 3D dose measurement of the complex conformal dose distributions achieved by modern techniques such as Intensity Modulated and Volumetric Arc Radiation Therapy. In the last decade, the potential for improved clinical applicability has been advanced by the development of improved 3D dosimeters such as normoxic polymer gel systems, radiochromic plastics (such as PRESAGE) and, recently, newer radiochromic gel dosimeters. Some of these new 3D dosimetry systems were enabled by the availability of optical computed tomography imaging systems for fast dose readout. However, despite its promise, true 3D dosimetry is still not widely practiced in the community. Its use has been confined primarily to select centres of expertise and to specialised quality assurance or commissioning roles where other dosimetry techniques are difficult to implement. In this paper I review some of the current 3D chemical dosimeters available, discuss the requirements for their use and briefly review the roles that these systems can provide to complement the other dose delivery validation approaches available in the clinic. I conclude by describing two roles that may be uniquely served by 3D chemical dosimetry in end-to-end process testing and validation in the complex environment coming into play with the development of Image Guided Adaptive Radiation Therapy.

1. Introduction

Radiotherapy is a localized treatment used in the treatment of approximately 50% of all patients undergoing cancer care in North America. Treatment is personalized to the individual patient so that a sufficient (usually uniform) dose is delivered to the target to achieve tumour control, while the dose to adjacent normal tissue and organs at risk is limited in order to minimize unwanted complication (see figure 1). Over the years, radiation therapy has progressed considerably [1] by the development of three dimensional (3D) external beam conformal radiation therapy delivery such as provided by Intensity Modulated Radiation Therapy (IMRT), Volumetric Modulated Arc Therapy (VMAT), Stereotactic Ablative Radiation Therapy (SABR), etc. and through improved procedures for high-dose rate brachytherapy. The advances in treatment were made possible by enhanced three dimensional imaging for planning, by the superior treatment planning systems which more faithfully calculate radiation doses in the heterogeneous patient and better plan the treatment unit's delivery trajectory through inverse planning approaches, and by the sophisticated networking and control systems that enable the data to flow from the planning systems to the treatment unit [1]. The radiation delivery associated by these modern conformal techniques is complex and results in 3D shaped dose distributions structures that must be correctly registered to the patient's anatomy (see figure 2) to achieve the treatment intent. To this end treatment units have been enhanced with imaging to enable Image Guided Radiation Therapy (IGRT) for validation of the patient position immediately prior to

treatment. Conventional IGRT systems use kV x-ray imaging with cone beam computed tomographic capabilities and novel

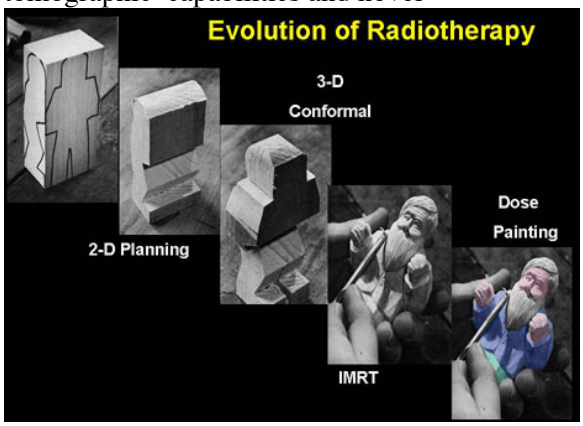


Figure 1. A simple analogy (from woodcarving) for modern radiation therapy [5]. The target treated by radiation often has a complex shape. The goal of the proposed research is to advance gel dosimetry to provide a 3D approach to delivery validation. The colours in the last panel suggest dose painting in which the dose to the target is intentionally not be uniform throughout (Rock Mackie, IC3D, 2010).

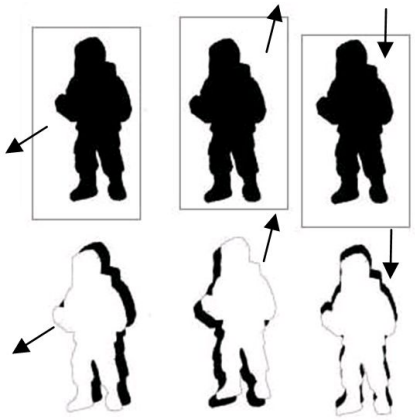


Figure 2. Dosimetric validation of modern radiation delivery is vital, since the radiation delivery has been made more precise. A miss that may have been acceptable in the past may in modern conformal delivery underdose target and overdose organs at risk. To account for displacement the target volumes are increased by some margin to allow for expected displacement over the course of treatment. (From [5])

units are under development incorporating magnetic resonance imaging systems [2-4]. The usual implementation of IGRT is to correct the observed displacements shown in figure 2 prior to the each treatment (see figure 3). The impact of such correction via IGRT has been a reduction of the margins used around targets during treatment, since these margins can now be patient specific rather than population based, again increasing the need for treatment validation. By using IGRT over the multiple fractions of the patient's treatment, there is a further potential to check for changes of anatomy in the region of the tumour and its surroundings [6]. Such changes, which may be seen over the weeks of treatment, have led to proposals for of off-line approaches in which the treatment plan is re-designed (daily or weekly) to maintain target coverage and healthy normal tissue sparing as the volume changes. Such Image Guided Adaptive Radiation Therapy (IGART) may incorporate the daily use of the on-line imaging (kV, MV or perhaps MRI) not only to ensure patient positioning or to monitor anatomy changes but also, perhaps, to flag re-planning (perhaps requiring new CT simulation, or maybe using the IGRT imaging itself [7]. In very simple terms, such *adaptive* radiation therapy approaches (ART) have defined a new class of radiation therapy in which the patient's treatment is modified during the course of care based on new information gained during the treatment [8, 9]. More sophisticated approaches for inter-fraction ART [10] are not limited to corrections for tissue geometry. The potential for on-line dosimetry (perhaps via exit beam dosimetry with electronic portal imaging devices, EPIDs, or tomotherapy CT detectors) during each treatment raises the feasibility of dose delivery monitoring. That is, with on-line dosimetry ART processes might be used to correct the under and overdosing in figure 2 in subsequent fractions of the treatment course by modifications of the future deliveries [11].

In all implementations, IGART processes consist of multiple steps for imaging, measurement, assessment, optimization, re-imaging, dose verification, etc. that may not be independent and further validation, perhaps with independent measurements, is necessary to establish the robustness of the adaptive treatment process. The challenge for delivery validation has been further increased [5] through the development of four dimensional treatment approaches in which the dose delivery is modified (through motion suppression techniques, increased margins, or beam gating) to account for the target motion inherent in the treatment of particular cancers.

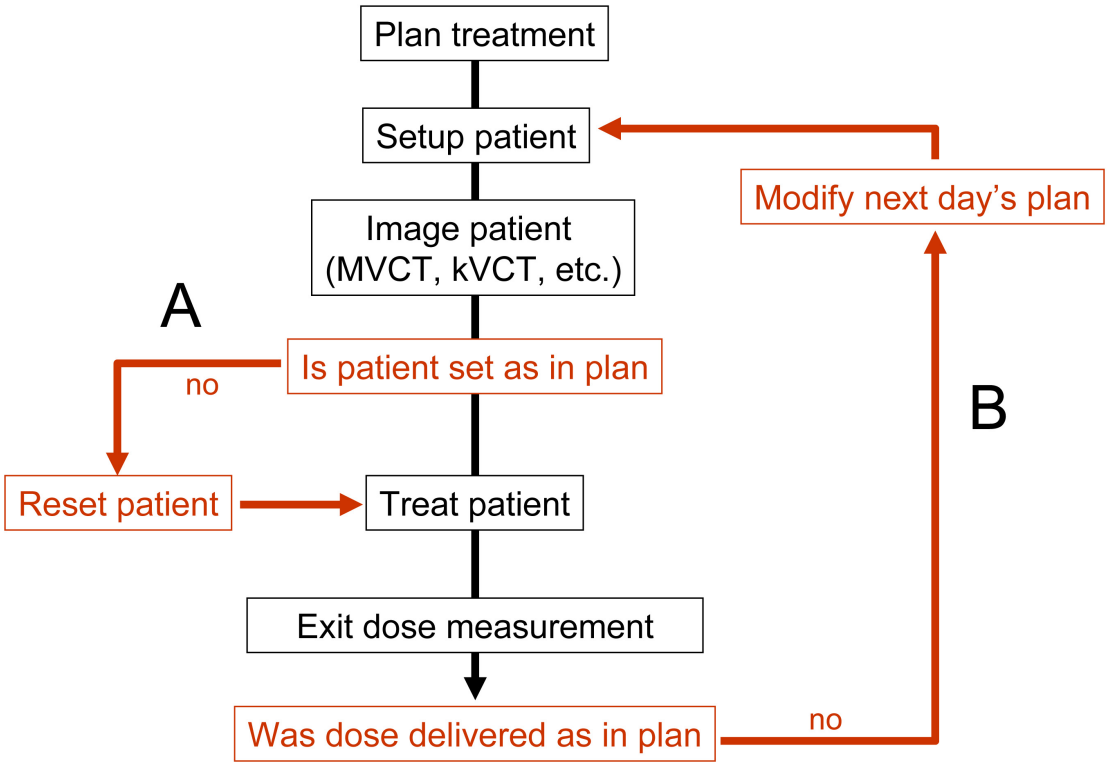


Figure 3. An example of two simple IGART processes: A) patient set-up verification at time of treatment (e.g., using kV CBCT image registration with a simulation CT reference image from the initial treatment planning) is already standard in the clinic. If a discrepancy is noted by the treating therapist the patient is moved to the correct position prior to irradiation. B) In a more sophisticated schema exit dose measurements could be used to determine the dose delivered in a given fraction. If the dose delivery was not as intended, one then could modify the next fraction to correct and bring the cumulative dose to the intended delivery over the multiple fractions. [from ref. 12].

All this is to say, modern radiation therapy has become very complex and as new approaches have advanced from 3DCT, through IMRT, VMAT, IGRT, ART to IGART - Image Guided ART, the quality assurance for technical components, the treatment unit and patient specific dose delivery validation, and the process assurance requirements have increased.

Numerous approaches have been established in the clinic to validate various points or steps in modern dose delivery [5, 13, 14]. In particular, there has been considerable development using 2D and 3D arrays of detectors to verify complex patient specific dose delivery [15-20]. And electronic portal imaging based assessment [21, 22] has been shown to provide convenient and sensitive patient specific delivery validation. These approaches have their place and are clinically very useful. But they typically provide sparse 3D data and only surrogate validation of 3D dose delivery. They do not fully fulfil the Resolution-Time-Accuracy-Precision (RTAP) performance criteria that were proposed by Mark Oldham *et al* [23, 24] as a useful benchmark for clinically useful true 3D dosimetry (see below). And there can be problems associated with their use if care is not taken; for example problems have been identified with the use of 2D data measurements of individual beams to validate patient specific IMRT delivery [25].

A novel class of scintillation and Cherenkov based radiation dosimeters has also been in development the last decades with recent advances to 3D measurement [26-28]. These detectors rely on the detection of immediate light emission from the irradiated media. Some of the systems under

study do provide high resolution isotropic data; however, these systems are not dose integrating, and will also not be discussed further here.

This paper is a review of three dimensional chemical dosimeter systems that can provide, through some post irradiation imaging, continuous integrated dose measurement through an irradiated volume (see figure 4). The main dosimetry systems will be briefly described and the applicability of the dosimeters to the issues raised above addressed. This discussion is not new and many of the points addressed have been discussed previously [5, 12, 29]. My desire is to show that some of the considerations for the use of 3D dosimeters date back to the initial work motivating their development in the 1980's, while some are new. The description of these systems will be cursory; very comprehensive reviews of the systems, and of the requirements for good readout of the dose information, have been presented in past DosGel and IC3D proceedings articles freely available in the *Journal of Physics Conference Series*, and in the comprehensive review of polymer gel dosimeters by Baldock *et al* [30]. Additional fundamental descriptions of the systems are given in two comprehensive educational reviews by Oldham [24] and Schreiner and Olding [31].

This paper is intended to set the stage for remainder of the conference with the many contributions reviewing the fundamental science and technical challenges of 3D dosimetry and reporting the current status of 3D dosimetry in the clinic [14, 19, 20, 27, 28, 33, 40, 54, 56-59, 62, 64].

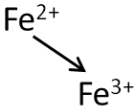
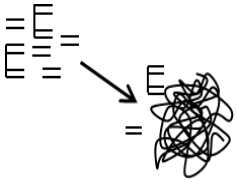
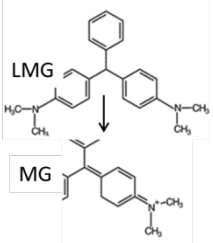
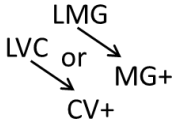
Figure 4. Illustration of the 3D dose information captured in three different gel dosimeters. (left) The Fricke-xylenol-orange-gelatin dosimeter shows a colour change in the volume irradiated with a12 MeV electron beams. (centre) The polyacrylamide polymer gel dosimeter shows increased scatter in the high dose areas radiated using a Cobalt-60 tomotherapy IMRT delivery. (right) A VMAT prostate irradiation of a Leuco-crystal-violet micelle gel dosimeter.

2. Chemical dosimeters for three dimensional measurement

As noted above, elements of the RTAP criteria [23, 24] are used in this work to set the definition of 'true' 3D dosimeters (with one additional feature). Under RTAP an ideal true 3D dosimetry system (dosimeter and associated readout) should be able to deliver dose measurements in a 3D volume with 1 mm isotropic spatial resolution in less than one hour with an accuracy of 3% and a precision of 1%. While the resolution, accuracy and precision criteria may be relaxed in various clinic practice, depending on the validation being performed; the criteria for high resolution isotropic measurement has limited true 3D radiation dosimeters (to date) to chemical radiation dosimetry based on quantifying the effects of radiation-induced chemical changes occurring within some volume of material [24, 29-31]. For clinical utility, the response of the true 3D dosimeter must also be reproducible, and stable [31-33]. The degree of the chemical change must be related to the absorbed dose and the changes must be able to be spatially localized in the irradiated volume by some imaging.

Historically the choice of appropriate chemical constituents for a 3D dosimeter has been determined a number of factors. The species that change under irradiation must be quantifiable by some approach. The species that changes under irradiation must be dispersible in a substrate that fixes

Table 1. A review of the main classes of 3D chemical dosimeters showing the basic mechanism for interaction, and conventional readout mechanism (with typical dose sensitivity). The dose sensitivities listed are rough ranges only as the sensitivity for a given dosimeter is highly dependent on the system preparation and readout details. More complete summaries detailing these characteristics are available in instructive reviews [24, 30, 31]. The acronyms for the polymer gel dosimeters follow common convention [31].

Class	Dosimeter		Readout		
	Basic mechanism	Usual Stabilizing substrate	MRI ($s^{-1}Gy^{-1}$)	Optical CT ($cm^{-1}Gy^{-1}$)	X-ray CT ($HUGy^{-1}$)
Fricke Gels			Δ relaxivity	Δ absorbance	N/A
Fricke		Gelatin or agarose	~0.04 (R1)	~0.01	
Fricke Xylenol			~0.009 (R2)	~0.1	---
Polymer Gels			Δ dynamics and structure	Δ scatter	Δ density
PAG, PAGAT, MAGIC, NIPAM, VIPAR, BANG etc.		Gelatin or agarose	~0.1 – 1.0	~0.1	~0.25 – 0.85
Novel Radiochromic systems			N/A	Δ absorbance	N/A
Plastic		polyurethane	---	~0.01-0.05	---
Silicone		Poly-dimethyl-silocane	---	~0.01	---
Micelle gel		Gelatin +micelles	---	~0.003-.007	---

radiation induced changes locally until they can be imaged [24, 29-31]. The initial 3D dosimeters primarily used gelatin or agarose as the localizing matrix, while some new dosimeters dissolve the radiation reporting leucodyes within a solid (when set) polyurethane matrix or in micelles dispersed through the aqueaous gel. There are distinct advantages to each system. Some of the properties of the various dosimeters with their appropriate readout systems are summarized in Table 1 above.

3. Readout methods for three dimensional measurement

The initial 3D dosimeter was the Fricke gel read out using magnetic resonance imaging MRI [34] although optical readout was soon proposed for polymer gels [35] and modified Fricke Xylenol dosimeters [36]. The motivation for optical readout was driven greatly by the desire to make 3D imaging readout more readily available since MRI access was often limited in the clinical setting of a radiation therapy centre. The desire for more accessible readout also initiated the development of x-ray computed tomography (CT) based 3D dosimetry with polymer gels [37, 38]. MRI, optical CT (optCT) and x-ray (CT) remain the main imaging modalities for 3D dose readout [24, 29-31].

The dose quantification using MRI results from the dose dependent change in the nuclear magnetic relaxation (NMR) properties of the dosimeter under irradiation. In Fricke gels the NMR spin-lattice relaxation rates (the usually measured parameter) depend directly on the concentration of the ferric (Fe^{2+}) and ferrous (Fe^{3+}) ion species since they have different relaxivity [31]. In polymer dosimeters the distinct monomer, polymer, gelatin and water protons environments of the protons providing the NMR signal change with dose. For the most part the relaxation of water protons in bulk and hydrating monomers remains unaffected as radiation induced polymerization progresses, however, the relaxation of the water molecules hydrating the growing polymer changes [30, 31]. The fraction of water hydrating these macromolecules increases with dose and the NMR spin-spin relaxation of this water is modified since it is mediated by chemical and physical interactions with the polymer (through mechanisms such as chemical exchange and magnetization transfer [39]).

While optical computed tomography readout was first proposed for polymer gels [35], the optCT technique has flourished mainly when coupled to radiochromic dosimeter (Fricke xylenol and the various leucodye) systems. In these dosimeters the radiation induced changes in colour or transparency at visual wavelengths enable optCT imaging based dose quantification [40]. In Fricke gels prepared with xylenol orange (a metal ion indicator) the change in Fe^{3+} concentration leads to the dose dependent optical changes [36, 40]. The radiation induced optical-contrast of leucodye radiochromic dosimeters is generated through the oxidation of a leucodye dispersed in stabilizing matrix that has been doped with a halogenated hydrocarbon free radical initiator. In the plastic PRESAGE dosimeter the dye is leuco-malachite-green (LMG), the dye which was also studied in early aqueous micelle gel dosimeters [40-42]. Newer radiochromic dye systems use leuco-crystal-violet (LCV) [43, 44]. These radiochromic dosimeters have the advantage that the optical response is primarily the result of light attenuation through absorption with minimal scattered light perturbation. This provides a major advantage over the optical readout of polymer gel dosimeters in which the primary mechanism for attenuation changes results from light scattering from particles which are formed as radiation induced polymer precipitates in the gel. This mechanism for change in polymer gels presents challenges to optical quantification which must be carefully considered for good dosimetry [24, 31, 45].

The relationship between the X-ray CT and material properties of irradiated polymer gels arises from x-ray CT quantifying and mapping linear attenuation coefficients [31, 37, 38]. For materials with dominant x-ray interactions similar to water, the CT number in Hounsfield units (HU) (a unit which normalizes a local attenuation coefficient to that of water) scales directly to a physical density [31, 46]. Thus, in X-ray CT based dosimetry, it is the change in density of the irradiated polymer gel that determines the change in CT number and enables dose quantification.

The availability of various imaging modalities has influenced the use of various dosimeters. For example, Fricke Xylenol gel dosimeters which had fallen out of favour because iron species diffusion limited the readout time to the order of an hour [47, 48], are now readily imaged within this constraint when optical scanning is available [49, 50]. It may be that the development of on-line imaging on treatment units may also widen the availability of dosimetric imaging. Recently, Bong *et al* investigated whether cone beam CT imaging on a treatment unit CBCT system could be used for dosimetric imaging [51]. The preliminary experiments confirmed the difficulty of image quantification with CBCT, but pointed to a potential development in the clinic as cobalt and x-ray linac treatment units are coupled to MRI on-line imaging systems.

4. Some practical considerations

The reproducible and accurate dose measurement with the 3D dosimeters reviewed above does require careful attention to particulars of set procedures [30, 31, 33, 38, 40, 52, 53]. However, such attention to detail is no different to the care required for good dosimetry with systems such as thermoluminescent, film and diode dosimeters which have been long, and regularly, used in the clinic. The perception in

Table 2. A broad overview of some typical time constraints in the use of the various 3D dosimeters. In some cases these are set by convention for convenient dosimetry (e.g., the maximum time from preparation to irradiation), in some cases (e.g. polymer gel stabilization after irradiation) the constraints are required for stable reproducible readout. It is assumed that the dosimeters are stored appropriately (in dark, cool storage) to maintain performance.

Dosimetry System	Time Needed /Constraint				
	Preparation	Wait between Preparation and Irradiation	Time for Irradiation	Wait Post irradiation to readout	Period for stable localization
Fricke Xylenol	45 min – 1 hr	12 hrs -1 week	< 20 min	30 min - 1.5 hrs	~ hrs or less
Polymer Gel	45 min – 1 hr	12 hrs -1 week	No limit	> 12- 24 hrs required for reactions to stabilize	years
PRESAGE	Commercially available	Can be weeks	No limit	Minutes (readings are f(t) but well behaved)	See text
Radiochromic Micelle Leucodye	45 min – 1 hr	24 hrs -1 week	No limit	> 20 min to hrs	See text
Silicone gels	1hr	12 hrs -1 week	No limit	> 2-3 hrs	See text

the community that the constraints for reliable 3D chemical dosimetry are more onerous is misplaced. What is required is a careful characterization and understanding of the conditions which need be faithfully maintained in the dosimetric procedures. Conditions such as temperature during preparation, storage in cool dark environments, and temperature control during irradiation may be of variable importance depending on the system used. But it would be best practice to maintain these conditions within established tolerances for the particular dosimeter being used in order to ensure reproducibility. Similarly, the timing of the stages in the dosimetry are important (see Table 2). In particular, when prepared in house, the dosimeters need some time to stabilize and set before irradiation. Because of auto-oxidation, it is usually good practice not to prepare the dosimeter too far in advance of irradiation. Afterwards the time between irradiation and readout should be controlled: for Fricke systems it cannot be too long or the spatial integrity of the dose information will degrade through diffusion; for polymer systems the time cannot be too short as the system needs time to develop as the radiation induced polymerization reactions proceed. The spatial integrity of the 3D dose distributions in polymer gels, some formulations of PRESAGE and the new leucodye micelle gels seems stable from months to years, indicating promise for dose delivery validation over multiple fractionations or for use in IMRT delivery validation by mailed phantoms from an external credentialing group such as the Imaging and Radiation Oncology Core-Houston (IROC-H) [52-54]. It should be noted that some of the leucodye radiochromic systems do change colour and darken over time after irradiation, but this behaviour is well behaved and can be characterized [55-57]. Furthermore, as the dose quantification typically proceeds with calibration samples or phantoms with the same time course, the dosimetry remains consistent and spatially stable [56].

5. Clinical role (reprise)

The strength of 3D dosimetry as described in this review is particularly realized in cases where the dosimetry provides distinct benefits of isotropic high resolution dose measurement that may not be achieved with other dose measurement tools. The clinical role of 3D dosimetry has been long promoted and discussed [5, 14, 24, 29-31]. It has been noted that gel dosimeters mimic tissue extremely well and can be designed for insertion into cavities in anthropomorphic phantoms that can be used to to evaluate new techniques that are being brought on-line (see figure 5). Oldham [24] and Schreiner and

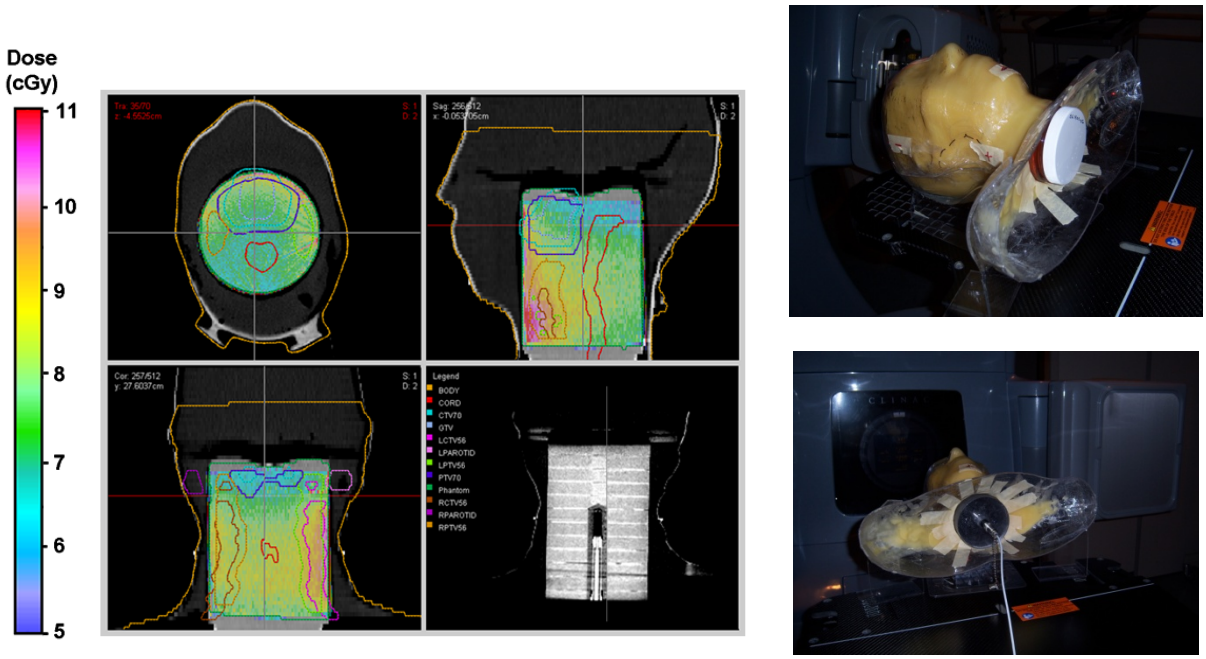


Figure 5. An illustration of a unique implementation of 3D dosimetry in Kingston. (left) A visualization of the radiation dose delivered to an in-house customized head-and-neck phantom containing an FXG gel dosimeter insert (top right) by an average of 5 full bowtie 100 kVp CBCT scans prior to an OBI upgrade. The dose is viewed in the CERR environment and is overlaid on the planning CT data. The bottom right corner of the CERR image frame shows a coronal CBCT slice of an acrylic insert in the wax-filled Rando reproduction (bottom right) containing an ionization chamber for dose readout over multiple CBCT scans. Roughly an order of magnitude reduction in the mean dose was observed following the upgrade of the Varian CBCT software (using gel dosimetry). This was verified at a single point using the acrylic-ion chamber measurement phantom.

Olding [31] have reviewed well multiple applications of 3D dosimeters in clinical validation. Their reviews include applications to small field dosimetry in radiosurgical dose delivery and in the characterization of brachytherapy seeds, to validation of IMAT and VMAT delivery prior to patient irradiation, to the assessment of SABR dose delivery under tumour motion, etc.. Much of this work has also been described in the proceedings of past and present IC3D conferences readily available in the Journal of Physics: Conference Series.

Two recent developments add further to the clinical potential for 3D dosimetry: the investigation of reusable dosimeters and of deformable systems. The results of such studies have not yet been reviewed as extensively since the investigations are recent, but results in both areas are presented in these proceedings [57-59]. The development of reusable dosimeters [54] may make commercial supply of dosimeters economically viable, which would likely extend clinical interest to groups that are currently reluctant to prepare dosimeters in-house. The development of commercial supply with appropriate manufacturing processes and quality control should also make the dosimeters themselves

more consistent, and may help establish protocols that would increase the reliability and reproducibility of the dosimetry. The development of deformable dosimeters [57, 59-61] extends 3D dosimetry to areas currently limited to the domain of the treatment planning algorithms being implemented to account for anatomical changes as tissues respond to treatment as the Adaptive Radiation Therapy proceeds over multiple fractions. Initial reports by Juang, Oldham, *et al* [60, 61] suggest that there needs to be considerable additional validation of commercial deformable image registration packages before they are fully adopted in the clinic.

As noted in the introduction it is clear that the requirements for the validation of patient specific dose delivery at the treatment unit, and for the quality assurance of the radiation therapy processes, have increased over the years with the implementation of IGART. It has been suggested in the past, and in these proceedings, that clinical quality assurance should not be limited to specific steps in the process but that it should also include end-to-end process validation [12, 29, 54, 62]. Presently, this type of quality assurance is typically performed only when working with an external credentialing group such as IROC-H using phantoms they provide [54]. The task could be well executed in-house using 3D dosimeters inserted into an anthropomorphic phantoms which would then be passed on through the radiation delivery team to undergo the adaptive process to be tested [12, 29]. The phantom would be imaged by the CT therapists and contoured by the radiation oncologist. A treatment plan would be developed by dosimetrists and the treatment plan and phantom images transferred to the treatment unit. Setup verification would be completed through the use of on-board cone beam CT imaging on the linear accelerator, with adjustments made as necessary. Once positioning has been verified the planned dose delivery would be given by the treatment therapists. All the steps in the ART process under evaluation (say a dose correction on fraction 11) would be performed fully as specified in the adaptive protocol being tested. Once the protocol has been completed, the physics group would remove and image the 3D dosimeter, register the dose data with the planned deliveries, and evaluate the results. The ability to mimic a patient and measure dose throughout a full ART process, including the various adaptive steps, is a unique and key advantage provided by 3D dosimetry techniques.

We have been attempting to implement such an end-to-end QA in Kingston; a significant challenge has been to design and manufacture suitable opaque phantoms so that the interior is not easily observed without using the treatment localization tools that are part of the test. This work is still underway. One major step forward in the past year has been the development of 3D dosimetry tools in the open software suite Slicer-RT [63, 64]. This has reduced the analysis time for our work considerably. The development of process QA is a challenging task involving a number of health care personnel on the treatment team. But 3D dosimetry has matured sufficiently that the tools for process quality assurance and evaluation are no longer the limitation to the work.

Finally, 3D dosimeters may also have an important role in evaluating other dosimeter systems used in the clinic, especially in establishing their limitations. Most commercial dosimetry systems for clinical IMRT and VMAT delivery validation are complex [19, 20] and typically confined to specialized proprietary software to generate the dosimetric data and to analyse agreement with planned deliveries. For example, some pseudo 3D ion-chamber array systems interpolate or back project 3D dose distributions into regions outside the volume of the measurement points. 3D dosimeters can help in the evaluation of these systems through comparative dose measurements. It is important that the user understand the limitations of all delivery validation tools completely [19, 20, 66] and 3D dosimeters can help greatly in that assessment [67].

6. Authors note

The references are a selective list meant to point to select papers over a long history. The list forms an initial set of references on which the reader can build.

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