ADVANCES IN *IN VIVO* EPR TOOTH BIODOSIMETRY: MEETING THE TARGETS FOR INITIAL TRIAGE FOLLOWING A LARGE-SCALE RADIATION EVENT

Ann Barry Flood^{1,*}, Benjamin B. Williams^{1,2}, Wilson Schreiber¹, Gaixin Du¹, Victoria A. Wood¹, Maciej M. Kmiec¹, Sergey V. Petryakov¹, Eugene Demidenko³, Harold M. Swartz^{1,2} and the EPR Center Tooth Dosimetry Project Team[†]

¹EPR Center for the Study of Viable Systems at Dartmouth, Radiology Dept., Geisel School of Medicine at Dartmouth, Hanover, NH, USA

²Division of Radiation Oncology, Dept. of Medicine, Dartmouth-Hitchcock Medical Center, Lebanon, NH, USA

³Dept. of Biomedical Data Science, Geisel School of Medicine at Dartmouth, Hanover, NH

*Corresponding author: Ann.B.Flood@Dartmouth.edu

Several important recent advances in the development and evolution of *in vivo* Tooth Biodosimetry using Electron Paramagnetic Resonance (EPR) allow its performance to meet or exceed the U.S. targeted requirements for accuracy and ease of operation and throughput in a large-scale radiation event. Ergonomically based changes to the magnet, coupled with the development of rotation of the magnet and advanced software to automate collection of data, have made it easier and faster to make a measurement. From start to finish, measurements require a total elapsed time of 5 min, with data acquisition taking place in less than 3 min. At the same time, the accuracy of the data for triage of large populations has improved, as indicated using the metrics of sensitivity, specificity and area under the ROC curve. Applying these standards to the intended population, EPR *in vivo* Tooth Biodosimetry has approximately the same diagnostic accuracy as the purported ‘gold standard’ (dicentric chromosome assay). Other improvements include miniaturisation of the spectrometer, leading to the creation of a significantly lighter and more compact prototype that is suitable for transporting for Point of Care (POC) operation and that can be operated off a single standard power outlet. Additional advancements in the resonator, including use of a disposable sensing loop attached to the incisor tooth, have resulted in a biodosimetry method where measurements can be made quickly with a simple 5-step workflow and by people needing only a few minutes of training (which can be built into the instrument as a training video). In sum, recent advancements allow this prototype to meet or exceed the US Federal Government’s recommended targets for POC biodosimetry in large-scale events.

Electron Paramagnetic Resonance (EPR) tooth dosimetry has been well recognised for many years as an accurate method to assess whether people

potentially exposed to ionising radiation received a clinically significant dose^(1–3). Although teeth (measured *in vivo* or *in vitro*) can be used to assess exposures many months or years after the fact (see Miyake *et al.*’s report⁽⁴⁾ that assessed dose several years after a radiation event using EPR *in vivo* tooth dosimetry on people living nearby to the 2011 nuclear power plant accident in Fukushima), the focus of this paper is on individualised biodosimetry assessments needed within hours or days of the event. Especially apropos to the situation of a large-scale terrorist event involving radiation, where hundreds to thousands of people have been potentially exposed, the current EPR *in vivo* tooth biodosimetry device can be transported to the areas where people are gathering and can provide rapid noninvasive assessments designed to facilitate appropriate and immediate triage to receive (or not) life-saving medical care to treat or mitigate the effects of acute radiation syndrome (ARS).

There have been several important recent developments at Dartmouth to design, manufacture and test an EPR *in vivo* tooth dosimetry prototype capable of meeting the demands of triaging victims of a

[†]EPR Center Tooth Dosimetry Team includes (alphabetical order within category): [*human factors and clinical studies*] Holly K. Boyle, Ruhong Dong, Shireen Geimer, Lesley A. Jarvis, Kyo Kobayashi, Roberto J. Nicolalde; [*software engineering*]: Jason Crist, Ankit Gupta, Timothy Reynolds; [*electrical and mechanical engineering/MRI*]: Spencer Brugger, Pawel Budzioh, Brandon Carr, Matthew Feldman, Barjor Gimi, Oleg Grinberg, Vladimir Krymov, Piotr Lesniewski[‡], Michael Mariani, Paul M. Meaney, Kevin M. Rychert, Ildar Salikhov, Dmitriy S. Tipikin, Mark Tseytlin; [*project and administrative management*]: Brian R. Edwards, Christopher D. Herring, Catherine Lindsay, Traci Rosenbaum. *Academic partners by principal investigator at site*: Arif Ali (Emory University), David Carlson (Yale University), Wojciech Francisz (Jagellonian University, Poland), Hiroshi Hirata (Hokkaido University, Japan), Jason Sidabras (Medical College of Wisconsin), Steven G. Swartz (U of Florida). *Consultants (project leader)*: Diamant Engineering Design (Paul Calderone), Farm Design, Inc. (Jamie Kennedy), GE Global Research (Joseph Ianotti), MID Labs, Inc. (Eric Elder), and RQMIS, Inc. (Barry Sands). [‡]Deceased

large-scale radiation event at the point-of-care (POC). This report summarises these recent developments up through 2015 and their readiness to undergo advanced developments and prototype finalisation

BACKGROUND: SPECIFICATIONS FOR AN EFFECTIVE POC BIODOSIMETRY METHOD

By way of describing the expectations for such devices, the US government provides guidance for standards that biodosimetry methods should be capable of achieving. Of particular interest here are the targeted specifications for POC biodosimetry methods intended to be used for large radiation events. It is important to note that POC devices are defined in these US standards as biodosimetry methods that are (a) carried out in their entirety, i.e. from taking a sample or making *in vivo* measurements to reporting results and (b) occur nearby to the event without needing specialised medical facilities or experts. POC biodosimetry methods need to be (c) capable of being carried out in the full context of federal plans for medical response and evacuation in a large-scale radiation disaster, including being transportable, operating in temporary or improvised facilities without requiring access to external power or water, and meeting high demands for usage but without needing trained or specialised operators to do so⁽⁵⁾.

These guidelines describe several scenarios for medical response to a large-scale disaster involving radiation, including the scenario used in this paper, i.e. denotation of an improvised nuclear device (IND) in a terrorist attack. The threshold dose for recommending an individual be triaged in the IND scenario is set so as to identify and triage people for urgent ARS-related care whose exposure is high enough to warrant receiving effective (and potentially life-saving) ARS care but not provide urgent care to those with no exposure or without life-threatening exposures. The threshold for triage is generally defined as 2 gray (Gy)^(6, 7), although some have argued that people with combined injuries, i.e. additional trauma or burns, may require the threshold to be lower (~1 Gy) to still be life-saving^(8–10). In addition, an initial triage method should have high sensitivity (so as to not falsely turn away people from receiving medical attention whose lives could have been saved or significantly improved) while also achieving high specificity (i.e. correctly identifying those who truly need medical care in order to optimise use of scarce resources).

Sullivan *et al.*⁽⁷⁾ (see Table 2 in 7) list the full set of target profile requirements set by the Federal Government via Biomedical Advanced Research and Development Authority (BARDA). These requirements include: the accuracy of the result produced by a POC biodosimetry method need only be qualitative,

i.e. it needs only to accurately differentiate doses as being above or below the threshold; in contrast, other biodosimetry methods must be quantitative, i.e. the dose estimate needs to be presented quantitatively and be accurate along the full range of clinically meaningful doses, e.g. the dose should be accurate to within 0.5 Gy along the range from 0 to ~10 Gy.

The US Food and Drug Administration (FDA)⁽¹¹⁾ recently issued recommended guidelines for appropriately assessing the performance of biodosimetry methods in anticipation of obtaining 510(k) approval for their intended use, including defining what is needed in the case of qualitative methods, i.e. those that need to accurately estimate doses as being below or above a cutoff for triage. The FDA, acknowledging the difficulty of carrying out research to truly assess biodosimetry performance in the context of measuring one million people in a few (~6) days and under chaotic conditions, suggest that the specificity and sensitivity of the method can be assessed, using a statistically valid but much smaller number of cases, where the 'true' dose delivered to the sample is known and validated independently. The FDA guidelines suggest that blinding the person performing the dose estimate to the true dose is sufficient to evaluate performance of biodosimetry in small statistically valid studies and extrapolated to its performance in their intended use in large-scale radiation events. (This performance assessment, however, does not take into account the logistical needs for performing one million assays in a few days.) See Flood *et al.*^(12, 13) for a framework to compare biodosimetry methods, focusing on such logistical and time-dependencies, and their application to simulate likely performance capacity in a large-scale disaster. While not detailed here, several have also compared and contrasted the different classes of biodosimetry methods, including delineating the strengths and limitations of several of the most promising candidates for biodosimetry in large-scale events^(3, 6–8, 12, 13).

As discussed above, BARDA further lists as US performance targets that any POC method be easy to operate with minimal complexity, requires only minimal training and has no separate sample preparation. BARDA also defines the targeted goals for POC devices as being capable of assessing one million people within 6 days after the event and that each person/sample should not take longer than 15–30 min to process from start to result⁽⁷⁾.

While some critics suggest that BARDA's target to assess one million victims in less than one week is excessive, several rationales undergird this target: (1) it is easier to adapt when you are prepared for a large event than to try to scale up from planning to handle only a modest-sized event. (2) Terrorists would most likely detonate a small (10 kt) IND in a large urban area where the need to assess one million people may be realistic. (3) The triage step at POC is

designed to solve two problems: (a) quickly find the few thousand whose lives can be saved with prompt care and (b) reach and reassure the majority of the population nearby the event who will be very worried about exposures but, with measurements, can be reassured that their exposure is not life threatening and does not require immediate care. The latter will help preserve limited resources and reduce panic.

For context regarding how many people could potentially be appropriate to assess if a small IND were exploded in a 'large urban area', there are 538 urban areas in the world with over one million people⁽¹⁴⁾. Among these large urban areas, 53 are in the USA (New York City is the largest with 22 million), 52 are in Europe¹ (London is the largest at 14.4 million) and 14 are in Japan (Tokyo is the largest at 39.5 million). If an IND were exploded in any of these cities, the plan to assess dose and triage for care or reassure one million victims would assume that only 2.5% of the people living in Tokyo, 4.5% in New York City, or 6.9% in London would need to be assessed with biodosimetry.

ADVANCEMENTS IN *IN VIVO* EPR TOOTH DOSIMETRY THAT MEET OR EXCEED US TARGETS

Since the authors' most recent publication focused on EPR tooth dosimetry performance⁽¹⁵⁾, there have been several advancements in the device and additional tests that show that its performance meets or exceeds the federal targets. These advances are briefly reviewed below.

Performance targets: accuracy of dose in the allowed timeframe to produce results

Following the initial major test of the performance of the authors' EPR instrument based on mouth models and as reported in Williams *et al.*⁽¹⁵⁾, the authors have made several improvements to their hardware and software that improved the measurement throughput (i.e. reduced the time from start of measurements to results available for triage), while increasing the repeatability and accuracy of their dose estimates and improving the overall ease of operation.

One major hardware change made recently is an improved magnet that increased the size of the gap for placing the head during measurements from 16.5 cm in the original *in vivo* magnet to 20 cm. In addition to improving comfort and access, the new magnet was mounted on a rotational base that permitted it to rotate $\pm 5^\circ$ degrees total around the subject's stationary incisors. This feature, with rotation being fully automated and controlled by the software,

replaced the need for a skilled operator to repeatedly remove and replace the resonator at the same location on the tooth, in order to obtain several independent sets of spectra during a measurement for averaging instrumental noise. Also of importance, automation significantly reduced the total time to complete a measurement.

Refined data acquisition and analysis software streamlines the operator interface, automates tuning of the bridge and resonator, evaluates instrumental feedback parameters to verify validity and discarding of the collected data if needed. The software also controls the magnet rotation, reducing the need for several operator actions. For these reasons, the total time for a measurement (including replacement of the resonator vs. rotation of the magnet) was reduced by almost a third (specifically, from about 15–20 min, with 6 min of total data acquisition, in the results reported in Williams *et al.*⁽¹⁵⁾, to become about 5–6 min, with 3 min of data acquisition), without significantly compromising dosimetric accuracy. Of note, both the original 15–20 min total time and especially the new ~5 min total time meet or exceed even the *minimum* targeted time for throughput from start of measurement/sampling to completed dose estimate of 15–30 min per measurement/assay.

Performance assessed using mouth models

Simultaneously with significantly reducing the throughput time needed, the accuracy of the estimates was improved. Table 1 presents the data from a test of performance conducted *in vitro* by the clinical operators, i.e. by the non-engineering staff trained to perform *in vivo* measurements on healthy and patient volunteers. These data were based on measurements of both upper central incisors using five mouth models. The mouth models used the four upper incisors (two lateral and two central) from the same donor, in order for each measured tooth to have neighboring teeth that received the same dose; see further details about the mouth models in Kobayashi *et al.*⁽¹⁶⁾. Each mouth model was measured four times at each added dose, i.e. at baseline (0 Gy added) and then following serial irradiation to a total of 1, 3 and 5 Gy added, using the same linear accelerator as used for radiation therapy at Dartmouth–Hitchcock Medical Center. Although the automated features do not allow for operator discretion to influence the dose estimates, the operators were kept blinded from knowing exactly when the serial doses were added to the mouth models they were measuring, to the extent allowed by this study design. Similarly, the analysts were blinded to the actual dose added when creating the quantitative and qualitative estimates reported in Table 1.

Although intended primarily as a POC device, Table 1 presents both the quantitative performance

¹Includes Eastern Europe but not Russia.

Table 1. Performance of EPR tooth dosimetry based on measuring upper central incisors of 5 mouth models, serially irradiated using the linear accelerator for patients.

Dose added (Gy)	Number of measurements	Quantitative dose estimate		Qualitative dose estimate	
		Mean (Gy)	SEP (Gy)	# at ≤ 2 Gy	# at > 2 Gy
0	40	0.05	0.4	40	0
1	40	0.97	0.4	40	0
3	40	2.90	0.4	1	39
5	40	5.00	0.5	0	40
Total	160	–	0.43	81	79

data and their uncertainties, plus the qualitative estimates relative to the cutoff for triage. Uncertainty is assessed by the Standard Error of Prediction (SEP) (also referred to in this context as the Standard Error of Inverse Prediction or SEIP⁽¹⁷⁾).

Of particular relevance for assessing the accuracy quantitatively, the overall uncertainty associated with the quantitative point estimate was 0.43 Gy after correcting the calibration for age and tooth width. Note: The linearity of the calibration curve for EPR measurements in teeth across the range of interest, i.e. from 0 to ~12 Gy, has been previously reported⁽¹⁵⁾; though not detailed here, the authors again performed a test of linearity on these data and found no evidence of any non-linearity across these doses.

Table 1 also presents the qualitative data, i.e. the number of dose estimates that were correctly identified, using a cutoff for triage of 2 Gy. Only one measurement out of 160 was incorrectly identified, i.e. one sample at 3 Gy was misidentified as below the 2 Gy threshold; in other words, there was one false-negative and no false-positives in this dataset.

Figure 1 presents a density plot of the quantitative data for each of the 160 measurements. The actual estimates in Gy are portrayed in vertical lines at the bottom of the graph. These same estimates are also superimposed on a separate normal distribution for each ‘true’ added dose. This plot illustrates that the distribution of estimates around the true added dose is quite narrow, i.e. with the majority of points being very close to their true added value. In addition, the relative narrowness of each distribution provides evidence of the uniformity in accuracy for estimating dose across the range of doses, i.e. from 0 to 5 Gy in this data set.

Performance assessed in vivo using unirradiated volunteers

The authors also assessed the performance of their advanced EPR tooth dosimetry device *in vivo* using 10 healthy volunteers without any prior exposure to radiation therapy involving the teeth. Volunteers were screened to ensure they had two upper central incisors whose front surfaces were not covered by a

Figure 1. Relative density plot of estimated dose above background for 160 *in vitro* EPR measurement sessions: 10 extracted central incisors in a mouth model; each tooth was measured for 3 min at a given Gy, with serial irradiation to an added dose of 0 Gy (leftmost), 1 Gy (2nd from left), 3 Gy (2nd from right), or 5 Gy (rightmost).

permanent non-enamel cap and that they were willing to come in on different days to complete four measurements on each central incisor during a two week period.

Information about dental exposures and other medical exposures to ionising irradiation (such as computed tomography scans of the head) was obtained; however, no one was excluded unless they had had very high exposures (>20 Gy) to the head and neck. Teeth were examined and measured by dental experts but no one was excluded on the basis of their teeth except if capped or their teeth had a large resin on the front surface that could not be avoided when placing the resonator. Potential confounders such as tooth characteristics (e.g. size of the labial surface) and demographics (e.g. age) were also collected but were not used to select volunteers.

From an original pool of 31 volunteers who responded to recruitment, 27 met these criteria and

10 (the original targeted sample size) were selected arbitrarily to be included in the study and to represent a range in ages and both sexes. Of these 10, 7 were female and age ranged from 22 to 60. Because the volunteers' teeth were not irradiated, the analysis assumed that the variation in the EPR signal amplitude that is used to detect radiation, for these subjects, reflects the usual range in background signal (which consists of a native EPR signal in enamel and background signals related to environmental and medical exposures to ionising radiation involving the head and teeth in particular).

For a given measurement, the total elapsed time was constrained by the software to be no greater than 10 min, including both data acquisition time, automated tuning between sets or scans if needed, and automated rotation of the magnet. This resulted in an average ~ 11.5 sets of scans acquired per measurement. Eighty measurements were made (20 teeth, each measured 4 times). However, two of these 80 were determined to be invalid based on noise levels that were 3-standard deviations above the expected value. This '3-sigma' rule (adapted from continuous quality improvement methodology for performance) was incorporated into the software as a check to identify and remove outliers based on instrumental performance. To identify outlier measurements that are unacceptable due to disproportionate noise, the standard deviation (SD) in the EPR signal amplitude across the sets was calculated at the end of each measurement and any measurement where the SD was greater than 3 SDs (3 sigmas) outside the expected value was rejected.

Figure 2 reports the estimated dose in Gy for these 78 measurements, after correcting for demographics and tooth size. These estimates are displayed in the small vertical lines along the x -axis; these same points are superimposed on a normal distribution to show their relative density/relative frequency. As expected most estimates of exposure are clustered around 'zero', which is calculated based on the mean signal for subjects whose teeth were not irradiated above normal background sources. The quantitative measurement of uncertainty for these 78 *in vivo* measurements is an SEP of 0.66 Gy. The qualitative measurement of performance reveals that no measurement was misidentified, i.e. all 78 estimates were below the cut-off of 2 Gy.

Assessing sensitivity and specificity in large populations with unknown true positive rates

Williams *et al.*⁽¹⁸⁾, building on the statistical framework that has been used to assess screening methods in large populations (such as mammography used to screen all symptomless women over the age of 50), provide a more complex framework to assess biodosimetry methods in their true intended use in a

Figure 2. Relative density plot of estimated dose above background for 78 valid measurements made *in vivo* in 10 unirradiated volunteers.

large-scale disaster. They argue that the simple qualitative and quantitative measures of performance typically reported in the literature are insufficient to judge the performance of biodosimetry methods for their intended use and lead to inappropriate comparisons.

In particular they argue that statistical measures such as sensitivity and specificity rates and receiver operating characteristic (ROC) curves need to be presented in the context of the likely population of victims in a disaster. This disaster-population not only is significantly larger but it is projected to consist overwhelmingly of people whose exposure is below the cut-off (so will have a very high proportion of true negatives) and whose distribution of doses are continuous across the likely range rather than the discrete added doses used in clinical studies of biodosimeter performance.

Taking Buddemeier's⁽¹⁹⁾ estimates of the population in a large urban area who would be likely to have received a life threatening but treatable exposure in a 10 kt IND explosion, they apply the published performance results from studies of three biodosimetry methods based on small samples to the true intended population. They argue that this framework, which explicitly includes the additional statistical challenges in conducting a mass screening in a population with low rates of true positives, provides a more comparable and defensible estimate of the performance of biodosimetry methods.

Williams and his colleagues started with published performance data for three examples of biodosimetry: EPR tooth dosimetry; dicentric chromosome assay (DCA) which is commonly referred to as 'the gold standard' of biodosimetry when used for small populations, and a genetic assay: quantitative PCR

(qPCR). Applying these data after also taking into account the intended use in a very large population simulated by Buddemeier's data, they compare these three biodosimetry methods via ROC analysis and provide estimates of the areas under the ROC curves (AUC) and compare achievable sensitivity and specificity pairs. Applying Williams' approach to these metrics, EPR *in vivo* tooth dosimetry performs nearly as well as the DCA assay and better than qPCR in identifying victims correctly for triage in a large-scale event. In particular, their reported comparisons based on estimated AUC were EPR = 0.997, DCA = 0.998, qPCR = 0.991. AUC may be interpreted as the probability that a randomly chosen subject with a dose above the threshold will be evaluated to be at higher risk than a randomly chosen subject with a dose below that threshold. With sensitivity values at 99% for all three methods, the corresponding specificity values for EPR and DCA were comparable (94.2% and 96.5% respectively), while the specificity for qPCR was considerably lower (84.5%).

Other performance targets: transportability, operation at POC temporary locations, and ease of operation with minimal training needed for users

Some of the advances related to ease of operation were described above, including advances made to the software, automation of the magnet, and elimination of replacing the resonator between sets. In addition to these advancements, all of the components that control the EPR dosimeter and facilitate EPR data collection were miniaturised. (Note: the magnet needs to fit around the subject's head and so it, and features like the chair for the subject to sit on, cannot be miniaturised.) The authors refer hereafter to the collective instrumental components of the spectrometer that can be miniaturised as the 'hardware rack'.

Figure 3 illustrates the old rack of required instruments (see Williams *et al.*⁽¹⁵⁾) and the new fully operational integrated instrument which replaces the complete functionality of those in the old rack. Table 2 presents comparisons by size, weight, and power needs of the old and new hardware racks.

Miniaturisation was accomplished with two principal strategies. First, the previous analog bridge with RF connectorised modules was replaced with a digital RF bridge designed and constructed on a series of easily manufactured printed circuit board (PCB) substrates. Second, off-the-shelf instruments were replaced with components that meet specific needs and have the capacity needed for tooth dosimetry, e.g. the computer and lock-in amplifier were miniaturised for data acquisition and specific device control capabilities; sweep and modulation coil amplifiers were consolidated into a unified field controller; all power supplies were consolidated into one

Figure 3. The old hardware rack with a touchscreen monitor (top) and the new (miniaturised) box is shown at its base (with a ~6.7 cm diameter tennis ball for comparison). The new rack is also shown in front with the cover removed to show the components (digital bridge, data acquisition card, lock-in amplifier, and power supply) with the monitor in front.

medical grade power supply and regulated accordingly.

These changes had four important consequences:

(1) The instrument rack is much easier to transport, including being carried by one person. (2) The instrument is more easily automated and controlled by the specialised modular software. (3) Miniaturised components paved the way to develop a prototype that integrated the instrument rack into a single-component

Table 2. Comparing the weight, size and power needs of the new instrument rack to the old instrument rack⁽¹⁵⁾.

Comparisons	Old	New	% Change
Weight ^a (kg)	79.4	9.1	–89
Depth (cm)	68.6	31.8	–54
Height ^a (cm)	106.7	13.2	–88
Width (cm)	50.8	34.3	–33
Max power (Watts)	1100	600	–45
Standby power (Watts)	200	75	–63

^aWithout including monitor on old rack; with including monitor in new rack.

Both devices are fully capable of operating on a single standard household outlet or generator power.

device that also contains the magnet and resonator, as illustrated in Figure 4. (4) The increased specialisation of dedicated components and modularised software also set up the path for mass production.

Integrated instrument: table top version or fully self-contained with chair and table

Figure 4 shows the computer-aided design (CAD) representation of the prototype constructed by Farm Design, Inc. While not fully operational at this time, the physical prototype has been constructed for preliminary testing. This model has moving parts and is designed to be fully representational of the magnet and the resonator/coupler and its placement holder. It also has the interior space to accommodate all of the miniaturised instrument components.

The patient (person being measured) on the left in Figure 4 is using the ‘table top’ version, which can be used with any standard height chair and secured to any standard height table. (Though not illustrated here, the authors have also developed a fully self-contained version that has a built-in chair and holding platform for the entire EPR instrument.)

The operator stands in front of the device and patient, i.e. to the right in Figure 4. The current workflow has only five simple steps for the operator to perform. At Step a, the operator adjusts the height of the device to allow the patient to maintain a comfortable sitting position during the 5 minute measurement. At Step b, the operator confirms that the patient has placed his/her teeth on a disposable ‘bite block’ that is held in place so it will hold the patient’s incisor teeth in position in the isocentre of the magnet. The bite block is designed to be comfortable to rest the upper teeth on, while also helping to prevent the teeth from moving and gently keeping

Figure 4. Table Top Model of EPR Tooth Device: 95% male height patient is shown on left. Operator stands on right to perform 5 steps: (a) adjust height of magnet stand, (b) adjust support of neck and forehead, (c) adjust resonator/coupler to centre on tooth, (d) raise magnet to fit around head and (e) start data collection. The ‘hardware rack’, i.e. the miniaturised bridge and electronics, is contained in the base. Table top version uses any standard chair and small table. Both models operate using one standard electrical outlet including via generator power.

the lips open and away from the resonator/coupler. Note that at this point, the magnet is swung away from the patient’s head, allowing easy visual access for both the patient and operator.

At Step b, the operator also adjusts the neck strap so that the patient’s forehead is held firmly against a cushion and the neck is comfortably supported during measurements. (There is a quick release on the neck support that the operator or patient can use if needed.)

At Step c, the resonator/coupler is moved forward and adjusted with a simple tuning knob. If needed, the knob can be easily turned to adjust the resonator/coupler up or down, left or right to locate the resonator/coupler on front of the two incisors. As reported in Schreiber *et al.*⁽¹⁵⁾ a ‘wireless resonator’ can be used in conjunction with an appropriate coupler to reliably obtain dosimetric information, i.e. the ‘wireless resonator’ is previously placed on the incisor tooth and then the resonator/coupler can be used without regard to its exact placement over the wireless resonator and without regard to

adjusting for any imperfect anatomical angles of the incisor in the jaw.

At Step d, the operator swings the magnet up to fit around that patient's head and then (Step e) starts the software using a small monitor located on the operator side. Note that this same monitor can be used initially to present a ~15 min training session for new operators or to display software prompts to the operator during measurements, e.g. to tell the operator to repeat the measurement (if needed) or to replace the coupling loop (if needed). The results are available immediately after the measurement is finished and can be printed or sent electronically to the triage decision maker.

These changes are in advanced development but have not been fully operationalised and tested. However, they have been designed to be as simple as possible so that an operator with minimal training (after watching the ~15 min video) and no expertise can operate the EPR *in vivo* tooth dosimetry system.

Additional developments and future challenges

In addition to finalising the prototype illustrated in Figure 4 (and finalising the wireless resonator as described in Schreiber *et al.*⁽²⁰⁾), the instrument will be specified and tested to be able to fully meet GMP manufacturing requirements and others as required by the FDA for 510(k) status. In addition, further clinical studies involving patients undergoing total body irradiation, total skin irradiation or head and neck cancer radiation involving the incisors and healthy volunteers will be used, both to test the equipment and to further develop evidence of any confounders that can be simply obtained in the field and which can improve the accuracy of the dose estimates.

The authors have already investigated some such factors including age, gender and tooth size as well as the potential contributions associated with exposure to UV light and/or heavy stains. While the authors have not included children under 18 in their clinical studies, children from about age 8 onwards have the potential to measure 'adult' upper central incisors and so adaptations to include them would focus mostly on small stature. The authors' current prototypes have been designed to accommodate from 5% female sizes to 95% male sizes (height and weight).

The authors have also performed tests of the instrument under high use (both in the studies reported in the literature and in intense 1.5 d measurements in a tent operating under generator power) and have performed simulations of the capacity of their instruments to successfully measure thousands of victims at POC within a few days following a major radiation event^(13, 21).

The ultimate challenge, true for all methods of dosimetry intended for use in large-scale radiation events involving civilian targets, is to offer sufficient flexibility and transferability to be prepared to operate effectively across a range of unknowable conditions. Each method must be prepared to fit seamlessly into the larger and very complex political/logistical decision-making system to deal with the short and long-term social, financial and medical consequences of such a major public health disaster. While the special characteristics of EPR tooth dosimetry offer many unique capabilities to provide POC dosimetry in large-scale disasters, practical and logistical challenges will confront it and every other method as well. Thus the larger plans for response need to prepare to address these contingencies by having a multi-pronged arsenal of methods, rather than by relying on a 'one-fit-for-all' solution.

CONCLUSIONS

The current status of *in vivo* EPR Tooth Biodosimetry already meets or exceeds the US targeted requirements for accuracy and ease of operation and throughput. The authors also have advanced designs and specifications to improve their precision and accuracy, to be inclusive of measuring a very large majority of potential victims, and to be prepared to move toward approval as a FDA 510(k) device to use for POC triage in a large scale radiation scenario.

DISCLOSURES

A.B.F. and H.M.S. are owners of Clin-EPR, LLC, which manufactures EPR devices for clinical applications.

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