A biodosimetry using in vivo electron paramagnetic resonance spectrometer for human teeth in accidental radiation event

Jong In Park [a,b], Kwon Choi [a,b], Chang Uk Koo [a,b], Jeonghun Oh [c], Hiroshi Hirata [d], Harold M. Swartz [e], Sung-Joon Ye [a,b,*]

[a]*Program in Biomedical Radiation Sciences, Department of Transdisciplinary Studies, Graduate School of Convergence Science and Technology, Seoul National University, Seoul, 08826, Republic of Korea*
[b]*Biomedical Research Institute, Seoul National University Hospital, Seoul, 03080, Republic of Korea*
[c]*Department of Nuclear Engineering, Seoul National University, Seoul 08826, Republic of Korea*
[d]*Division of Bioengineering and Bioinformatics, Graduate School of Information Science and Technology, Hokkaido University, Sapporo, Japan*
[e]*Geisel School of Medicine, HB 7785 Dartmouth College, Hanover, NH 03755 USA.*

[*]*Corresponding author: sye@snu.ac.kr*

1. Introduction

Electron paramagnetic resonance (EPR) is the one of the spectroscopy techniques which uses the magnetic resonance phenomenon to enable the quantification of the presence of paramagnetic species within the sample. EPR measurements for teeth especially has advantages to strong signal intensity because of the high stability of carbonated radicals in tooth enamel. The absorbed dose and the amount of CO_2^- radicals in tooth are linearly proportional and remain stable permanently [1]. Thus, EPR spectrometer has been widely applied in retrospective analysis of exposures for individuals who were exposed to radiation such as workers of nuclear power plants [2], and people living nearby regions of mass exposure like in Chernobyl [3], Hiroshima and Nagasaki [4]. However, those study uses X-band EPR which is limited only to in vitro dosimetry of extracted teeth. Development of lower frequency (L-band) EPR becomes possible to estimate the irradiated dose with eliminating the need to have extraction of teeth [5]. The use of in vivo EPR tooth dosimeter would remove extra sample processing steps and requirement of specialists in dosimetry and dentist in the emergency for swift first triage purpose [6]. L-band EPR was demonstrated as a on-site in vivo dosimeter for dose estimation for individuals who have received radiation treatment [7] and have potentially received dose from small-scale accidents [8] and radiation event of the nuclear power plant accident in Fukushima [9].
In this study, we developed a EPR spectrometer which can be used as on-site in vivo dosimeter to estimate the dose in accidental radiation event. We performed several experimental measurements using human intact tooth to demonstrate the feasibility of estimation of the irradiated dose. We also tested feasibility of triage with developed EPR spectrometer for a volunteer who had received total body irradiation.

2. Methods and Results

2.1 Development of EPR instrument

We have produced and tested a prototype of a continuous-wave EPR tooth dosimeter designed at L-band of 1.15 GHz based on previous design [10]. This spectrometer uses homodyne detection at carrier frequency of 1.15 GHz microwave which provide suitable penetration depth of microwave signal to cover tooth enamel. The in-vivo EPR dosimeter consists of a magnet, a microwave source, a bridge circuit, a surface coil resonator for signal detection, and appropriate immobilizer to provide support and positioning capabilities for stable measurement. The electronics for EPR detection and magnetic field sweeping are contained in an instrument rack that can be deployable. The components of the bridge were set up on a transportable rack. The EPR spectrometer was configured automatically to obtain the spectrum via data acquisition board (DAQ) and a control software. This software also controls instrumental settings for the lock-in amplifier, bridge circuit, modulation and sweep field systems.

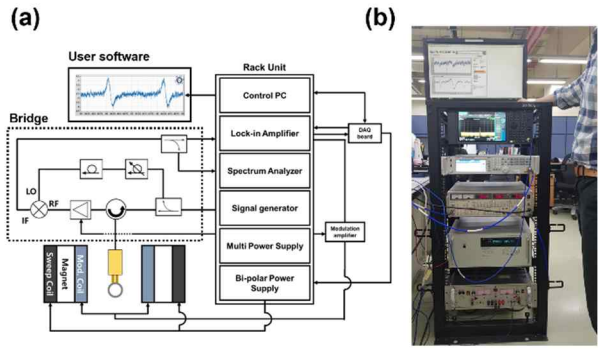

Fig. 1. (a) Simplified block diagram of in vivo continuous wave electron paramagnetic resonance spectrometer (EPR) for tooth dosimetry. (b) The EPR spectrometer assembly installed at laboratory (Magnet part was not shown).

2.2 In-vitro measurements for curve calibration

Fig. 2(a) illustrates a representative result for the incisor (I9) at measured doses ranging from 0 Gy to 30 Gy. The EPR spectrum was fitted from noisy signal. The

amplitude of two peaks along the within RIS region increased as the applied dose was increased as shown in Fig. 2(b). ^{15}N-PDT signal shows measured across all dose points which was used to monitor of reliability of measurement based on linewidth and location of peaks.
The twelve single tooth calibration curves were described in Fig. 3. The EPR intensity of RIS for all measured tooth samples was linearly increased according to irradiated dose with different slope among tooth phantom. Fig. 3 illustrated also twelve single tooth calibration curves with tooth-size adjusted EPR signal of RIS. The EPR signal of RIS was also linearly increased with irradiated dose with consistent slope. Based on the measurements in tooth phantom, the for calibration curve with tooth size-adjusted EPR signal, the dose response had a slope of 0.03511 AU/Gy and intercept of 0.04288 AU ($R^2 = 0.999$). When the average of ten measurement sessions for each tooth was taken, the standard error of inverse dose prediction was observed to be 0.39 Gy across 12 independent tooth phantoms for 6 dose points of 0, 2, 5, 7, 10, and 30 Gy. These processed data were then averaged to obtain the median amplitude for each tooth at each dose point. The inverse prediction was performed when the EPR intensity y is known, and the dose to be predicted is x. Regression standard error was used to evaluate the accuracy of prediction for calibration curve. The standard error of the inverse dose prediction (SEIP) was used to guide error of dose estimation from the measured EPR intensity and parameters of intercept and slope of calibration curve [11]. Previous study achieved SEIP of 0.50 Gy for the in vitro mouth model study, and these protocols are now being applied for in vivo studies [12]. Our calibrated SEIPs were less than 0.5 Gy which is enough for the radiation event.

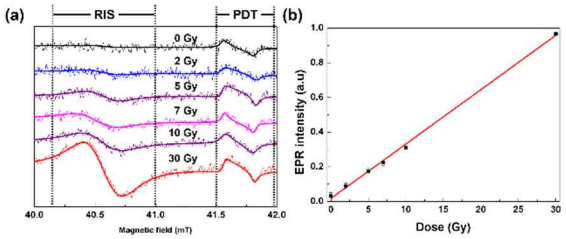

Fig. 2. (a) Spectral fitting of accumulated dose of 0 Gy, 2 Gy, 5 Gy, 7 Gy, 10 Gy, and 30 Gy from incisor tooth phantom (I9). The smooth solid lines are fitted based on nonlinear least square method. Two peaks of radiation induced signal (RIS) was used in terms of peak-to-peak amplitude. (b) The linear relationship between EPR intensity and applied dose ($R^2 = 0.998$).

2.3 Dose estimation test

We tested the feasibility of dose estimation using developed EPR spectrometer. Sixteen unknown tooth phantoms were used for the construction of calibration curve. We used the calibration curve method to estimate the irradiated dose. The results of dose estimation were shown in Fig. 3. We used simple and empirical equation which are only measurable tooth dimensions. Sixteen unknown pre-irradiated tooth phantoms were used for dose estimation. Used tooth phantoms were not included in dose calibration curve. The 95% (Black dashed line) and 75% confidence limit (Black solid line) were described on this graph. Estimated dose across tooth sample was in accordance with dose calibration curve and included within 95% confidence limit of SEIP which is shown as dashed line except one tooth phantom. The dose from used all tooth phantom were estimated above 2 Gy.

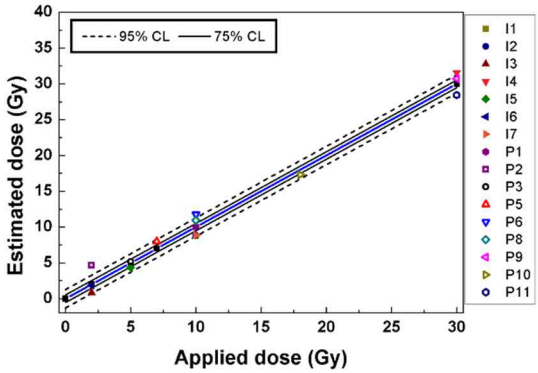

Fig. 3. The used tooth phantoms for dose estimation were not included in calibration curve. The estimated dose across tooth samples was in accordance with dose calibration curve and included within 95% CL for standard error of inverse prediction (SEIP) of calibration curve which is shown as dashed line except one tooth phantom

2.4 Stability of EPR signal

Fig. 4 illustrated the measured results of evaluation for stability of the EPR signal of RIS for 4 incisors (I1, I2, I3, I6) and 2 premolar teeth (P9, P11) which irradiated different dose, respectively. Each tooth sample was measured to obtain 1 data set of 10 scans for 1 day, 3 weeks, and 2 months after X-ray irradiation, respectively. The measured EPR intensity for each tooth sample was median value of the average of the10 scans. Based on these data, results re-stated that the tooth signals remain stable after the first 24-h period post-irradiation. The relative EPR intensity was calculated normalized to EPR intensity of P9 (1 day after).

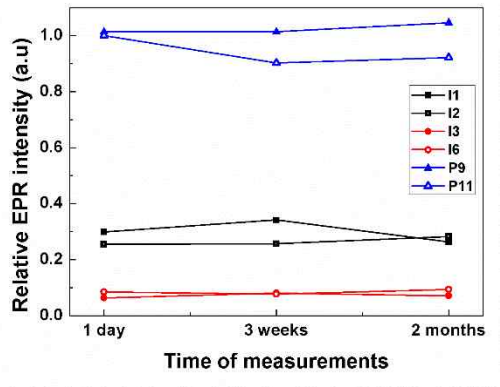

Fig. 4. Each dose measurement was done 3 separated days which are 1 day after, 3 weeks after, and 2 months after. The signal stability was observed during the 2 months for 2 Gy (I3, I6), 10 Gy (I1, I2) and 30 Gy (P9, P11) irradiated tooth phantoms.

2.5 Feasibility test for in vivo measurement with total body irradiation patient

Mean EPR intensity with standard deviation of unirradiated teeth and the TBI patient were 0.016 ± 0.006 and 0.06 ± 0.012. Based on the results, mean EPR intensity was increased 3.8 times for the TBI subject compared to the results obtained from unirradiated samples for the in vitro measurements. A clear difference was observed in EPR intensity between unirradiated teeth and TBI patient. In-vivo calibration curve is required for accurate dose estimation. The estimated dose was could be substantially underestimated when the signal amplitude is applied to *in vivo* measurement.

3. Conclusions

We developed an EPR spectrometer for non-invasive in vivo dosimetry for achieving measurement in situ. Dose calibration curve has been established using joint calibration of premolar and incisor tooth phantoms with geometric consideration. The SEIP of the in vitro dosimetry of intact human tooth phantom was approximately 0.39 Gy which is less than 0.5 Gy that means acceptable level for triage purpose to screen people who irradiated more than 2 Gy. The feasibility of measurement for a TBI patient was also successfully demonstrated to estimate the significant dose with the developed EPR spectrometer.

REFERENCES

[1] P. Fattibene, F. Callens, EPR dosimetry with tooth enamel: A review, Appl Radiat Isotopes, 68 (2010) 2033-2116.
[2] A. Wieser, E. Vasilenko, P. Fattibene, S. Bayankin, N. El-Faramawy, D. Ivanov, P. Jacob, V. Knyazev, S. Onori, M.C. Pressello, A. Romanyukha, M. Smetanin, A. Ulanovsky, Comparison of EPR occupational lifetime external dose assessments for Mayak nuclear workers and film badge dose data, Radiat Environ Biophys, 44 (2006) 279-288.
[3] A.I. Ivannikov, V.G. Skvortsov, V.F. Stepanenko, K.S. Zhumadilov, Comparative analysis between radiation doses obtained by EPR dosimetry using tooth enamel and established analytical methods for the population of radioactively contaminated territories, Radiat Prot Dosim, 159 (2014) 125-129.
[4] N. Nakamura, C. Miyazawa, S. Sawada, M. Akiyama, A.A. Awa, A close correlation between electron spin resonance (ESR) dosimetry from tooth enamel and cytogenetic dosimetry from lymphocytes of Hiroshima atomic-bomb survivors, International Journal of Radiation Biology, 73 (1998) 619-627.
[5] M. Zdravkova, N. Crokart, F. Trompier, B. Asselineau, B. Gallez, E. Gaillard-Lecanu, R. Debuyst, Retrospective dosimetry after criticality accidents using low-frequency EPR: a study of whole human teeth irradiated in a mixed neutron and gamma-radiation field, Radiat Res, 160 (2003) 168-173.
[6] B.B. Williams, R.H. Dong, A.B. Flood, O. Grinberg, M. Kmiec, P.N. Lesniewski, T.P. Matthews, R.J. Nicolalde, T. Raynolds, I.K. Salikhov, H.M. Swartz, A deployable in vivo EPR tooth dosimeter for triage after a radiation event involving large populations, Radiat Meas, 46 (2011) 772-777.
[7] B.B. Williams, R. Dong, R.J. Nicolalde, T.P. Matthews, D.J. Gladstone, E. Demidenko, B.I. Zaki, I.K. Salikhov, P.N. Lesniewski, H.M. Swartz, Physically-based biodosimetry using in vivo EPR of teeth in patients undergoing total body irradiation, Int J Radiat Biol, 87 (2011) 766-775.
[8] M. Iwasaki, C. Miyazawa, T. Chida, F. Takahashi, Y. Onai, Dental ESR dosimetry of a medical physicist who received occupational radiation exposure for almost 40 Y, Health Phys, 83 (2002) 534-538.
[9] M. Miyake, Y. Nakai, I. Yamaguchi, H. Hirata, N. Kunugita, B.B. Williams, H.M. Swartz, In-Vivo Radiation Dosimetry Using Portable L Band Epr: On-Site Measurement of Volunteers in Fukushima Prefecture, Japan, Radiat Prot Dosim, 172 (2016) 248-253.
[10] B.B. Williams, R.H. Dong, M. Kmiec, G. Burke, E. Demidenko, D. Gladstone, R.J. Nicolalde, A. Sucheta, P. Lesniewski, H.M. Swartz, Development of in Vivo Tooth Epr for Individual Radiation Dose Estimation and Screening, Health Phys, 98 (2010) 327-338.
[11] E. Demidenko, B.B. Williams, A.B. Flood, H.M. Swartz, Standard error of inverse prediction for dose-response relationship: approximate and exact statistical inference, Stat Med, 32 (2013) 2048-2061.
[12] B.B. Williams, A.B. Flood, I. Salikhov, K. Kobayashi, R.H. Dong, K. Rychert, G.X. Du, W. Schreiber, H.M. Swartz, In vivo EPR tooth dosimetry for triage after a radiation event involving large populations, Radiat Environ Bioph, 53 (2014) 335-346.