A Theoretical Study for Estimation of Oxygen Effect in Radiation Therapy

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Purpose: For estimation of yields of DNA damages induced by radiation and enhanced by oxygen, a mathematical model was used and tested.

Materials and Methods: Reactions of the products of water radiolysis were modeled as an ordinary time dependant equations. These reactions include formation of radicals, DNA damage, damage repair, restitution, and damage fixation by oxygen and H-radical. Several rate constants were obtained from literature while others were calculated by fitting an experimental data. Sensitivity studies were performed changing the chemical rate constant at a constant oxygen number density and varying the oxygen concentration. The effects of oxygen concentration as well as the damage fixation mechanism by oxygen were investigated. Oxygen enhancement ratio(OER) was calculated to compare the simulated data with experimental data.

Results: Sensitivity studies with oxygen showed that DNA survival was a function of both oxygen concentration and the magnitude of chemical rate constants. There were no change in survival fraction as a function of dose while the oxygen concentration change from 0 to 1.0×10^7. When the oxygen concentration change from 1.0×10^7 to 1.0×10^{10}, there was significant decrease in cell survival. The OER values obtained from the simulation study were 2.32 at 10% cell survival level and 1.9 at 45% cell survival level.

Conclusion: Sensitivity studies with oxygen demonstrated that the experimental data were reproduced with the effects being enhanced for the cases where the oxygen rate constants are largest and the oxygen concentration is increased. OER values obtained from the simulation study showed good agreement for a low level of cell survival. This indicated that the use of the semi-empirical model could predict the effect of oxygen in cell killing.

Key words: Free radical, Cell survival, Radio-sensitizer, Oxygen, OER

Introduction

Ionizing radiation produce ionized and excited molecules and free subexcitation electrons when it interacts with biological material. The excited and ionized water molecules that are formed during irradiation results in the production of reactive free radicals such as hydroxyl(OH·) and hydrogen(H·) radicals that are able to diffuse far enough to reach and damage the critical targets[1]. When the radiation interacts directly with critical target such as DNA, the target itself is excited and ionized, thus initiating the chain of events that leads to biological modification in DNA[2-6]. These interactions occur during the physico-chemical and chemical stages. Biological effects such as cell killing, somatic, and genetic effects result from the direct and indirect action of radiation. These effects occur in the time frame of days to years.

There are a number of theoretical and experimental studies on the yields of DNA damages induced by ionizing radiation[7-12]. These studies showed that there were several modifying factors that change radiosensitivity of cells. These include the oxygen which increases sensitivity in hypoxic cells and halogenated pyrimidines which increase the sensitivity to ionizing radiation in proliferating cells[13-15].

Oxygen effects were investigated experimentally by irradiating cell in the presence and absence of oxygen[16-20]. Oxygen enhancement ratio (OER) was calculated to evaluate the effectiveness of oxygen in cell killing[21,22]. Palcic et al[23]., measured the OER values at high radiation doses and found that OER values were between 2.5 and 3.0 for sparsely ionizing radiation such as x-rays. This indicates that cells are much more sensitive to x-rays and that cell killing by radiation is enhanced in the presence of oxygen. The effects of oxygen on cell killing are still not fully understood due to the limitation in measuring technique that oxygen must be present during the irradiation. However there is general agreement that oxygen acts at the level of the free radicals.

A model was previously developed which described the radiochemical interactions in the absence of oxygen and demonstrated that the model could be used as a tool to estimate the effects of radiation on cell killing[24]. In the present study, the previously developed semi-empirical model was modified to incorporate the oxygen effect on cell killing. The interaction between oxygen and damaged organic molecule($R\cdot$) which produces an organic peroxide($RO_2\cdot$) was modeled as an irreversible damage. This interaction only take place in the presence of oxygen and results in increased radiosensitivity. This observed radiosensitizing effects of oxygen was simulated as a function of oxygen concentration and OER values were calculated using the semi-empirical model at a various cell survival level. These values were compared to experimentally determined values that were obtained from literature.

Materials and Methods

The radiochemical reactions that are modeled in this study are listed below.

(G1) Radiation + $H_2O \rightarrow H\cdot$ (1)
Radiation + $H_2O \rightarrow e^+ + H\cdot \rightarrow H$ (2)
(G2) Radiation + $H_2O \rightarrow OH\cdot$ (3)
(G3) Radiation + $RH \rightarrow R\cdot$ (4)
(R1) $OH\cdot + OH\cdot \rightarrow H_2O_2$ (5)
(R2) $H\cdot + H\cdot \rightarrow H_2$ (6)
(R3) $OH\cdot + H\cdot \rightarrow H_2O$ (7)
(R4) $OH\cdot + RH \rightarrow R\cdot + H_2O$ (8)
(R5) $H\cdot + RH \rightarrow R\cdot + H_2$ (9)
(R6) $H\cdot + R\cdot \rightarrow$ RH(Repair) (10)
(R7) $H\cdot + O_2 \rightarrow HO_2\cdot$ (11)
(R8) $RH + H_2O_2 \rightarrow R\cdot$ (12)
(R9) $HO_2\cdot + HO_2\cdot \rightarrow H_2O_2 + O_2$ (13)
(R10) $RH + HO_2\cdot \rightarrow R\cdot + H_2O_2$ (14)
(R11) $R\cdot + O_2 \rightarrow RO_2\cdot$ (damage fixation) (15)
(R12) $RO_2\cdot + RH \rightarrow R\cdot + RO_2H$ (16)

Equations (1) through (4) show direct interactions of radiation with either water or organic molecule which yield chemically active species such as H radical, OH radical, and excited or ionized water. These reactive species are removed by the reactions (5) through (10). Equations (11), (12), (15) and (16) are included for oxygen effect. The formation and decay of the initial products that are formed during physico-chemical stage of radiation interactions in the presence of oxygen are modeled as time dependent differential equation. The following eight time dependent differential equations are used to describe the combined effects of oxygen concentration and X-rays on cell survival curves.

$$\frac{d[OH\bullet]}{dt}=G_2\phi-R_1[OH\bullet]^2-R_4[OH\bullet][RH]-R_3[OH\bullet][H\bullet] \qquad (17)$$

$$\frac{d[H\bullet]}{dt}=G_1\phi-R_5[H\bullet][RH]-R_6[H\bullet][R\bullet]-R_7[H\bullet][O_2]-R_2[H\bullet]^2-R_3[OH\bullet][H\bullet] \qquad (18)$$

$$\frac{d[H_2O_2]}{dt}=R_1[OH\bullet]^2+R_9[HO_2\bullet]-R_8[R][H_2O_2]+R_{10}[R][HO_2\bullet] \qquad (19)$$

$$\frac{d[HO_2\bullet]}{dt}=R_1[H\bullet][O_2]-R_9[HO_2\bullet]^2-R_{10}[R][HO_2\bullet] \qquad (20)$$

$$\frac{d[R]}{dt}=-G_3\sigma_r[R]\phi-R_4[OH\bullet][R]-R_5[H\bullet][R]+R_6[H\bullet][R\bullet]-R_8[R][H_2O_2]-R_{10}[R][HO_2\bullet]-R_{12}[RO_2\bullet][R] \qquad (21)$$

$$\frac{d[R\bullet]}{dt}=G_3\sigma_r[R]\phi+R_4[OH\bullet][R]+R_5[H\bullet][R]-R_6[H\bullet][R\bullet]+R_8[R][H_2O_2]+R_{10}[R][HO_2\bullet]-R_{11}[R\bullet][O_2]+R_{12}[R0_2\bullet][R] \qquad (22)$$

$$\frac{d[RO_2]}{dt}=R_{11}[R\bullet][O_2]-R_{12}[RO_2\bullet][R] \qquad (23)$$

$$\frac{d[RO_2H\bullet]}{dt}=R_{12}[RO_2\bullet][R] \qquad (24)$$

The dose delivered to cells by X-rays was calculated using the same equation used by Lee et al.,[24].

$$\dot{Dose}=[1.6\times10^{-8}]\times E\times\mu_m\times\frac{1}{\rho}\times\phi \qquad (25)$$

In the equation, a dose rate of 100 rad/min and an initial DNA concentration of 1.0 x 10^{10} cells/cm^3 are used to calculate the radiation flux (φ). The calculated flux of incident radiation is 5 x 10^{10}. The rate constants known from literature are summarized in Table 1[25] and the unknown rate constants are obtained by fitting the experimental data. Fig. 1 shows the cell survival curve obtained experimentally[16] and used to determine the unknown constants. In the figure, the curve labeled with the oxygen number density of 8.4 x 10^{12} which represents hypoxic conditions was used as a baseline for the curve fitting.

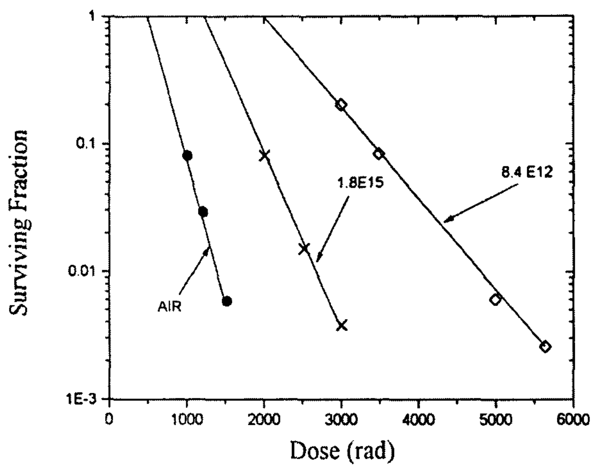

Fig. 1. Survival curve used to determine the unknown variables with oxygen equation(Experimental data were obtained from Elkind et al.,[16]).

The observed radiosensitizing effects of oxygen is simulated as a function of oxygen number density. The solubility of oxygen depends on many factors including temperature and atmospheric pressure. Thus, it was not possible to determine oxygen concentration in cell simply from the knowledge of the oxygen concentration to which the cell were exposed. Several studies on the effects of oxygen tension on cell killing showed that the dependence of radio-sensitivity as a function of oxygen concentration has little effect if the partial pressure of oxygen exceeds about 30 mmHg which corresponds to an oxygen number density of 3.3 x 10^{16} [26,27]. Based on these observations, the oxygen number density used in

Table 1. A summary of chemical rate constants used to evaluate the oxygen effect on cell survival curve (Simonson[25]).

Reactions		Rate Constants (cm^3/sec)
$OH\cdot + OH\cdot$	H_2O_2	R1 = 1.8 x e^{-11}
$H\cdot + H\cdot$	H_2	R2 = 4.1 x e^{-11}
$H\cdot + OH\cdot$	H_2O	R3 = 8.3 x e^{-16}
$H\cdot + O_2$	$H_2O\cdot$	R7 = 7.5 x e^{-11}
$HO_2\cdot + HO_2\cdot$	H_2O_2	R9 = 1.8 x e^{-14}

this study was smaller than the number density which corresponds to 30 mmHg. A baseline value of 1.0 x 10^{11} was used as the oxygen concentration in cell if the cell is exposed in air.

Sensitivity studies were performed to evaluate both the effect of oxygen concentration and the effect of the rate constants contained in equations (14), (15), and (16) which described the mechanism by which oxygen act as a radiosensitizer. For the sensitivity studies, oxygen concentration was varied from 0 to 1.0 x 10^{13}. OER is calculated at 37% cell survival level that are calculated while rate constants for R10, R11, and R12 were varied from 1.0 x 10^{-12} to 1.0 x 10^{15}.

OER values calculated using the semi-empirical model at a various cell survival level are compared to experimentally determined values that are obtained from literature. The expression for the OER is as follows:

$$OER = \frac{D_{N_2}}{D_{O_2}}$$

where D_{N2} is the dose in N_2 for a given survival fraction and D_{O2} is the dose in O_2 for the same level of survival faction. Fig. 2 shows the experimental data used to determine the unknown constants[28]. The unknown values of yield and rate constant were calibrated against the hypoxic data.

Results

The rate constants determined by fitting the experimental data are listed in Table 2. The oxygen concentration is varied by a factor of one thousand and then by an even greater factor as shown in Fig. 3. There are no changes in survival fraction as a function of dose while the oxygen concentration change from 0 to 1.0 x 10^7. When the oxygen concentration change from 1.0 x 10^7 to 1.0 x 10^{10}, there is significant decrease in cell survival. Fig. 4(A) and 4(B) shows the effect of varying the chemical rate constants. In Fig. 4(A), the rate constants R10, R11, and R12 are increased by a factor of ten while in Fig. 4(B),

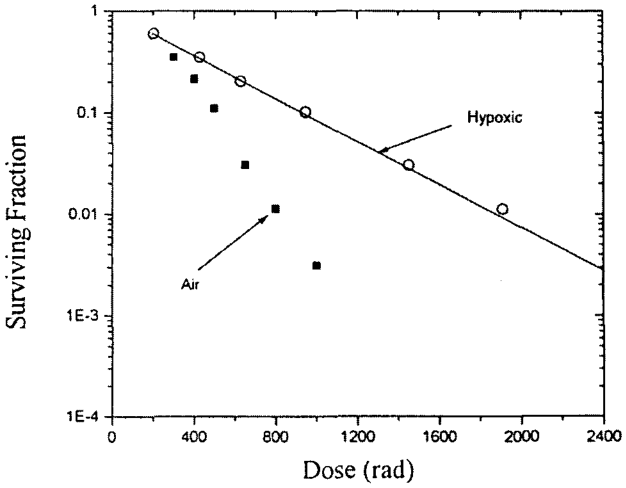

Fig. 2. Survival curve used to determine the unknown variable for calculation of OER values (Experimental data were obtained from Nias et al.[28]).

Table 2. Summary of the fitted rate constants to reproduce the cell survival curves and to perform sensitivity studies in the presence of oxygen.

Reactions		Constants
H-radical yield		G1 = 0.030 (#/cm)
OH-radical yield		G2 = 0.018 (#/cm)
Damaged DNA yield by direct effect		G3 = 0.003 (#/cm)
$OH\cdot + RR\cdot$		R4 = 1.0 x e^{-14}(cm^3/sec)
$H\cdot + R\ R\cdot$		R5 =2.0 x e^{-14}(cm^3/sec)
$H\cdot + R\cdot R$		R6 =2.0 x e^{-16}(cm^3/sec)
$H_2O_2 + R$	$R\cdot$	R8 = 2.0 x e^{-14}(cm^3/sec)
$HO_2\cdot + R$	$R\cdot + H_2O_2$	R10 = 1.5 x e^{-13}(cm^3/sec)
$R\cdot + O_2\ RO_2\cdot$		R11 = 1.5 x e^{-13}(cm^3/sec)
$RO_2\cdot + R$ `	$R\cdot + RO_2H$	R12 = 1.5 x e^{-13}(cm^3/sec)

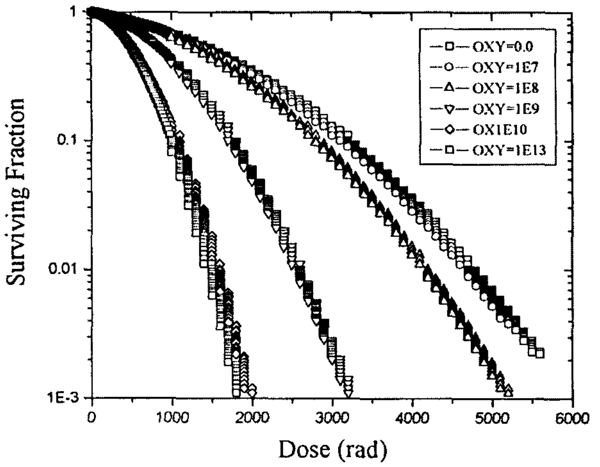

Fig. 3. DNA survival curve at a various oxygen concentration (Unknown constants were obtained by fitting the hypoxic curve of the cell survival curve from Elkind et al., 1965).

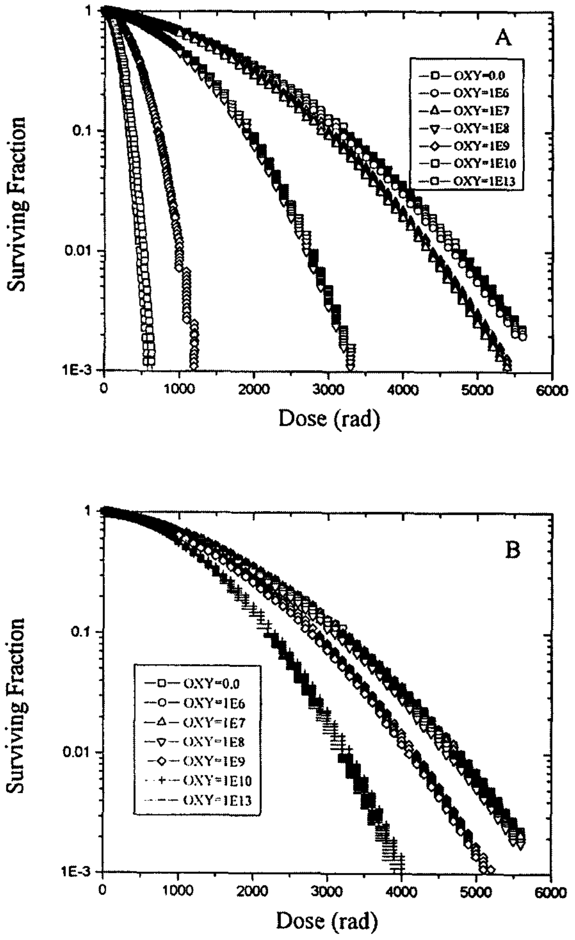

Fig. 4. The effect of varying the chemical rate constants for R10, R11, and R12. In (A): R10 = R11 = R12 = 1.0 x 10^{14} and (B): R10 = R11 = R12 = 1.0 x 10^{12}.

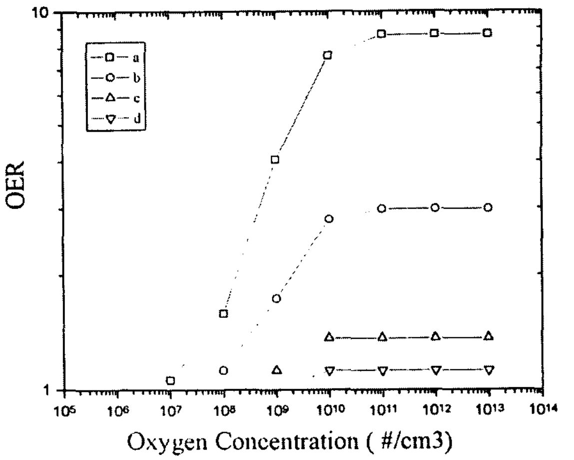

Fig. 5. The dependence of radiosensitivity on oxygen concen -tration as the rate constant varied. a: R10 = R11 = R12 = 1.5 x 10^{-12}, b: R10 = R11 = R12 = 1.5 x 10^{-13}, c: R10 = R11 = R12 = 1.5 x 10^{-14}, d: R10 = R11 = R12 = 1.5 x 10^{-15}

the same constants are decreased by a factor of ten. The trend evident from experimental data are reproduced with the effects being enhanced for the case where the rate constants are largest.

Fig. 5 shows the OER values at 37% cell survival level that are calculated while rate constants for R10, R11, and R12 are varied from 1.0 x 10^{-12} to 1.0 x 10^{-15}. As the rate constants increased so did the OER values. The range of oxygen concentration which shows the oxygen effect is varied when the rate constants are varied. The rapid change of radiosensitivity occurred as the oxygen concentration increased from 1.0 x 10^{7} to 1.0 x 10^{10}, 1 x 10^{8} to 1 x 10^{11}, 1 x 10^{9} to 1 x 10^{10}, and 1 x 10^{9} to 1 x 10^{10} when the rate constants R10, R11, and R12 were 1 x 10^{12}, 1 x 10^{13}, 1 x 10^{14} and 1 x 10^{15} respectively. Above an oxygen concentration of 1 x 10^{10}, there is no change in each case.

Table. 3 shows the unknown rate constants and radical yield determined using the experimental data for 300 keV X-rays from Nias et al.,[28] and Fig. 6 is the result of a simulation study in which the oxygen concentration is varied from 10^{7} to 10^{12}. The effects of oxygen in enhancing cell killing when low LET(lineat energy transfer)

Table 3. Summary of the fitted rate constants to reproduce the cell survival curves without oxygen.

Reactions		Constants
H-radical yield		G1 = 0.035 (#/cm)
OH-radical yield		G2 = 0.02 (#/cm)
Damaged DNA yield by direct effect		G3 = 0.015 (#/cm)
$OH\cdot + R$	$R\cdot$	R4 = 3.5 x e^{-14}(cm^3/sec)
$H\cdot + R$	$R\cdot$	R5 =7.0 x e^{-14}(cm^3/sec)
$H\cdot + R\cdot$	R	R6 =7.0 x e^{-16}(cm^3/sec)
$H_2O_2 + R$	$R\cdot$	R8 = 7.0 x e^{-14}(cm^3/sec)
$HO_2\cdot + R$	$R\cdot + H_2O_2$	R10 = 3.8 x e^{-13}(cm^3/sec)
$R\cdot + O_2$	$RO_2\cdot$	R11 = 3.8 x e^{-13}(cm^3/sec)
$RO_2\cdot + R'$	$R\cdot + RO_2H$	R12 = 3.8 x e^{-13}(cm^3/sec)

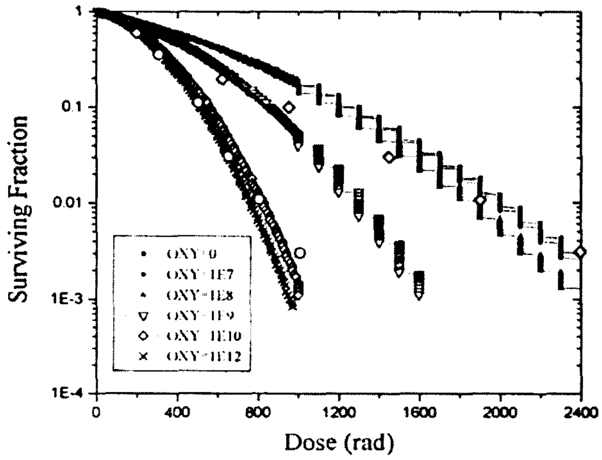

Fig. 6. The effects of oxygen concentration on cell survival simulated with oxygen equation. (Unknown constants were obtained by fitting the hypoxic curve of the cell survival curve from Nias et al., 1973).

radiation is used is apparent.

OER values are calculated from the simulation study and compared to those obtained from the experimental data. For this calculation, the oxygen concentration for the hypoxic condition and for air were taken as 0.0 and 10^{12} respectively. Table 4 shows the OER values that are simulated in this study and determined from experimental data. As shown in Table. 4, the OER values decreased as the percent of cell survival increased in both cases. As the end point approached to 1%, the difference between experimentally obtained data and simulated data were less than 2%.

Discussion and Conclusion

The effect of oxygen has been generally found to be one that can be described as a dose modifying agent. That is, there is a constant ratio of surviving fraction in aerobic and hypoxic conditions regardless of the level of the dose when the target is irradiated. In order to study the effects of oxygen in cell killing semi-empirically, the model developed by Lee et al.,[24)] is modified to include the radiochemical reactions that are known to be present in the presence of oxygen. One of the important mechanism is the interaction between damaged organic molecule with oxygen. This reaction is known to be the chemically irreparable damage[29)]. To include these reactions, three more equations are written. Five rate constants are obtained from the literature[25)] and the yield constants and seven unknown constants are determined by fitting to experimental data[28)].

The effects of oxygen number density on cell survival were studied. Simulated results shows that radiosensitivity increase linearly as the oxygen concentration increased and reaches a maximum as the oxygen number density approached 1 x 10^{10} cm^{-3}. Gary et al.,[26)] studied the effects of oxygen concentration on cell killing and showed that the OER increased as the oxygen concen -tration increased and reached maximum at 10 ~ 20 mmHg and that the OER value was about 2 when oxygen tension was 3 ~ 5 mmHg. Elkind et al.,[16)] varied the oxygen concentration from 10 ppm or 0.0075 mmHg which corresponds to hypoxic conditions to 10^6 ppm or 750 mmHg which corresponds to oxygen tension in air. These studies show that there is a rapid increase in cell killing as the oxygen concentration increased from 10 ppm to 2200 ppm.

Hall[29)] summarized these data and showed that the OER values reached a maximum value of 3 as the oxygen concentration increased from the hypoxic condition until the oxygen concentration increased by a factor of 10^4. If this is compared qualitatively with the simulation data, a similar trend is obtained when a value of 1.5 x 10^{13} ^{i}s used for the rate constants R10, R11, and R12 (Fig. 5). The radio-sensitization occurred when the oxygen number density increased by a factor of 10^4 and OER value is 3. However, when these rate constants are increased or decreased by a factor of ten, the slope of the linear range vary significantly. This may indicate that radiosensitivity in the presence of oxygen depends not only on oxygen concentration but also on the rate constants between radicals and DNA which means the cell type.

In conclusion, radio-chemical reactions in the presence of oxygen is modeled as a time dependent differential equation in order to provide theoretical tool for estimating combined effects of oxygen and x-rays on cell survival curves. The significance of this study was that this model would allow the investigator to differentiate oxygen effect from other mechanism. In order to use this model in real clinic, further work is needed to determine the unknown constants experimentally.

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방사선 조사시 산소가 세포에 미치는 영향의 이론적 분석

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목적: 방사선조사에 의해 형성된 DNA 손상정도가 산소에 의해 변화되는 추세을 이론적 모델을 이용하여 평가 및 분석하였다.

방법 및 대상: Water radiolysis(물의 방사성분해)시 생성되는 유리기 들간의 반응, 손상된 DNA의 형성, 손상의 복구, 및 산소에 의한 손상의 고정들을 시간 미분 방정식을 이용하여 표현하였다. 문헌에 나와 있는 반응상수(rate constants)들은 그대로 사용되었고 알려지지 않은 상수들은 실험에서 얻어진 데이터에서 얻은 곡선을 대입하여 얻었다. 화학반응상수 변화와 산소농도변화에 따른 세포 생존도를 구하였다. 모델을 통해 얻어진 세포 생존도와 방사선량의 상관관계를 세포 생존곡선으로 표시하였다. 산소에 의한 손상의 fixation(고착화)과정과 산소농도가 세포생존에 미치는 영향을 분석하여 보았다. 산소가 세포생존에 미치는 정도를 정량화 하기 위하여 산소증가효과비(Oxygen Ehhancement Ratio, OER)를 계산하여 실험치와 이론치를 비교하였다.

결과: 산소에 대한 민감성 연구에서 DNA생존도는 산소의 농도와 화학반응속도상수에 영향을 받았다. 산소의 농도가 0에서 1.0 x 10^7 으로 변화할 때 세포 생존도에는 변화가 없었다. 그러나 1.0 x 10^7 에서 1.0 x 10^{10} 변화할 경우 세포의 생존률이 감소하였다. 모의연구에서 얻은 OER치는 10% 세포생존시에는 2.32, 45% 세포생존시에는 1.9 이었다.

결론: 산소의 감수성 연구에서 보여주듯이 방정식을 이용하여 얻어진 새포생존곡선은 실험에서 얻어진 세포생존곡선을 재연할 수 있었다. 또한 방사선조사시 생성되는 손상된 세포의 양은 산소 반응상수가 가장 크고 산소농도가 증가되는 경우에 증가됨을 알수있었다. 모의연구에서 얻은 산소증가효과비는 세포생존이 low level인 경우 높은 일치성을 보여 주었다. 따라서 본 연구는 세포살해시 산소의 효과를 semi-empirical 모델을 사용하여 예측할수 있다는 것을 보여주고 있다.

중심어: 자유기, 세포생존, 방사선감작제, 산소, 산소증가효과비