J Korean Soc Ther Radiol Vol. 4, No. 2 December, 1986

Dose-Response Curves of Mouse Jejunal Crypt Cells by Multifractionated Irradiation*

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Using as assay for jejunal crypt stem cell survival, dose-response curves for the reproductive capacity of crypt stem cells of mouse jejunum exposed to multifractionated gamma-ray irradiation (single, 2, 3, 4, 5, 8, 10, 12, and 16 fractions) were analyzed and single-dose survival curve of these cells was constructed.

The following conclusion were drawn:

1) Survival curves for higher numbers of dose fractions were displaced to higher dose, and characterized by increasingly shallower slopes.

2) The single-dose survival curve had broad shoulder, Dq=460 cGy, remaining near-exponential over initial dose range 0 to 300 cGy, with initial slope 1Do=474 cGy.

3) At fractionated dose in the range of 180 to 450 cGy, the average recovered dose per fraction interval was approximately 50% of the dose per fraction.

4) The value of α/β ratio by using of linear regression analysis for the reciprocal dose plots was 8.3 Gy which lied in the range of 6-14 Gy for early-reacting tissues.

5) The linear-quadratic model for dose-response formula offers valid approximations for all doses to be used in radiotherapy, only two parameters to be determined, and considerable convenience in practical applications.

Key Words: Radiation, Fractionation, Jejunal crypt.

INTRODUCTION

The response of gastrointestinal system has been critical in radiotherapy. However, modern day treatment regimen is protracted sufficiently long period that repopulation by surviving stem cells during course of therapy minimizes the mucosal injury and the dose is limited by damage that leads to late complications such as adhesion, strictures, and fistulae. Neverthless, the radiobiological characteristics of stem cells of mucosa are of interest from the standpoint, not only of radiation biology, but also of radiotherapy.

The low-dose response of rapidly proliferating cell renewal systems, such as gut, skin, and testis may be inferred from their response to multiple small dose fractions which cumulatively produce a response which can be assayed by the microcolony technique[1,2,3]. The response of jejunal mucosa to multifraction irradiation will be affected by the repair capacity of crypt stem cells from sublethal injury during fractionation intervals, and by their regenerative capacity[4]. The number of fractions was limited by two factors: first, that the overall time was short enough that porliferation was negligible, and second, that the time between dose was long enough that intracellular repair processes were complete[5]. We assumed that effects such as incomplete repair, repopulation and redistribution may contribute to alteration in the survival curve between fractions, and use a linear regression model to test for equality of these combined effects over all fractions.

There is a renewed interest in non-standard fractionation (hyperfractionation and accelerated fractionation) in radiotherapy in the past few years. It has become clear that early and late reactions respond differently to changes in dose per fraction because repair depends upon the state of proliferation of the tissue concerned.

*This work was supported in part by research grants from Kyung Hee University.

The purpose of this article is to describe the results of experiments designed to measure the single-dose survival curve of jejunal crypt cells using microcolony assay of cell survival after multiple, equally spaced, identical dose of radiation. A mathematical model of response to multiple doses with incomplete repair between doses is used to analysis the results.

An understanding of stem cell response to multifractionated irradiation may allow us modification of treatment regimens to minimize acute damage in the gastrointestinal system during clinical radiotherapy and may provide radiobiological data that may be extrapolated to other tissues.

MATERIALS AND METHODS

1. Mice

Specific pathogen free male and female C3H mice were irradiated without anesthesia using gamma-ray of Co-60 when they were 8-10 weeks old.

2. Irradiation

A Co-60 teletherapy unit was used for all experiments, the unanesthetized mice with adequate opening for ventilation were exposed to single or multiple doses (2, 3, 4, 5, 8, 10, 12, and 16 fractions) of whole body irradiation in acrylic box which was divided into 6 compartments, each capable of holding one mouse. The set-up allowed 6 mice to be irradiated at a time. Fractionation radiation dose were spaced at 12 hours interval for 2 fractions, 6 hours for 3, 4, 5 fractions, 4 hours for 5, 8, 10 fractions, and 3 hours for 12, 16 fractions (Table 1). The selection of time intervals between doses was governed by two factors: the first concern was that influence of repopulation of survivors should be minimized, and the second one was sufficiently long interfractional intervals for complete repair of sublethal damage.

3. Assay of Cell Survival

The technique employed has been described previously[1,6]. Briefly, colonies of regenerating crypt cells were counted in histological cross sections of the jejunum on approximately 3 1/2 days after irradiation. Two separate cross sections per mouse were counted. When multiple fractions were used, the interval between irradiation and sacrifice was shortened so that the average colony size was similar in all specimens. Lines were fitted to the geometric means of the data for each

Table 1. Experimental Design of Fractionated Irradiation for Mouse Jejunum

N (number of fractions)	Range of dose per fraction (cGy)	Total dose (cGy)
1	1,000 – 1,600	1,000 – 1,600
2	750 – 950	1,500 – 1,900
3	600 – 800	1,800 – 2,400
4	450 – 600	1,800 – 2,400
5	380 – 510	1,900 – 2,550
8	260 – 380	2,080 – 3,280
10	210 – 330	2,100 – 3,300
12	200 – 290	2,340 – 3,500
16	160 – 230	2,560 – 3,680

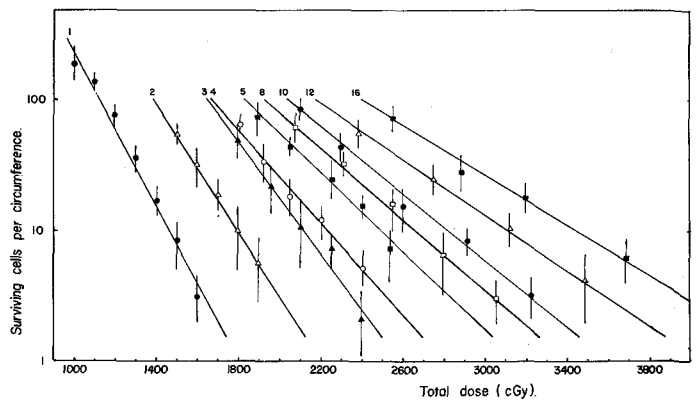

Fig. 1. Relationship between total dose and survival of clonogenic jejunal crypt cells in mice exposed to single dose or multiple equal dose fractions. Number of fraction is shown on each curve.

dose using a least squares regression analysis in which points were weighted according to the inverse of their variance.

4. Data Analysis to Estimate of Single-dose Survival Parameters

Survival parameters were estimated from least square fits of the single-dose surviving fractions to standard survival models the linerar-quadratic (LQ) and two-component (TC) models were used in this paper, their functions are $SF=e^{-(\alpha D+\beta D^2)}$ and $SF=1-(1-e^{-D/D_0})^n$, respectively.

To obtain α/β ratios, the dose required to produce equivalent damage with different fractionation schedules were obtained from experiments.

RESULTS

1. Survival Curves for Single and Multiple Doses Fractions

Survival curves for jejunal stem cells irradiated with single dose or up to 16 equal-sized exposures given at varying time intervals are presented in Fig. 1. Cellular survival is plotted as a function of total dose. The total dose required for a certain effect increased as the number of fractions was increased, although the dose per fraction was less as higher fraction numbers. Not only are the survival curves for higher numbers of dose fractions displaced to higher dose, but they are also characterized by continual reduction in slope of survival curves.

2. Effective Single-dose Survival Curve

After all of the points corresponding to each fraction number were plotted for the survivors per circumference, and constructed the single-dose survival curve for jejunal crypt shown in Fig. 2. The estimates of survival parameters are shown in Table 2. The quality of the fit is good for both models, so that it is not possible to distinguish between them on the basis of survival data.

3. Recovery Per Fractionation Interval

The shift of multifrationated dose-survival curves to higher doses, may be dose increment per fractionation interval required to achieve any particular level of cellular survival, that is, (Dn-D1)/(n-1), where Dn is the total dose given as n frac-

Table 2. Survival Parameters for Mouse Jejunal Crypt Cells

Model	Parameters	Estimate (conf. interval)
LO	α	1.049 (1.002, 1.086) Gy^{-1}
	β	1.442 (1.413, 1.473) Gy^{-2}
	${}_1D_0$	475 (452, 498) cGy
	${}_nD_0$	209 (198, 223) cGy
TC	n	23.9 (21.5, 26.3)
	D_0	145 cGy
	D_q	460 cGy

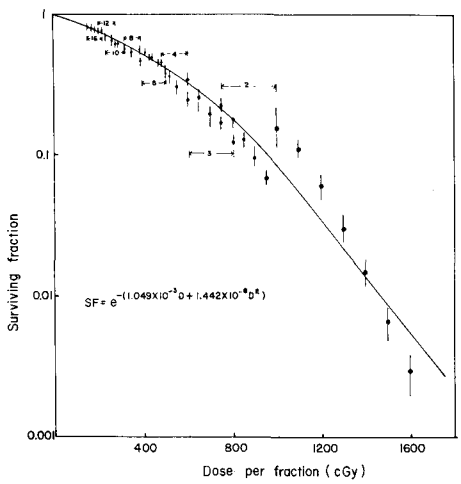

Fig. 2. Effective single dose survival curve of clonogenic cell of jejunal crypts of mice after fractionated irradiation.

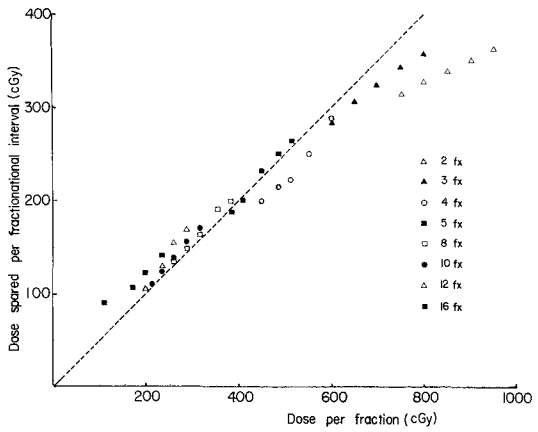

Fig. 3. Recovered dose per fractionation interval $(Dn-D_1)/(n-1)$ as function of dose per fraction (survival to 10 clonogens per circumference). Dashed line indicates recovery equivalent to 50% of dose per fraction.

tions which reduced survival to the same level as the dose D_1 given as a single exposure shown in Fig. 3. At low dose in the range of 180~450 cGy, the average recovered dose per fractionation interval was approximately 50% of dose per fraction, and at doses of 600 cGy or more, recovery was equivalent to 50% or less, of each dose fraction. Since these are the experiments in which regeneration may contribute to recovery the values of 50% may slightly overestimate the recovery attributable to repair of sublethal injury. In Fig. 2 it may be seen that the survival curve begins to bend downward in the range of 400 to 600 cGy, the region of "flexure" in which the ratio, spared per interval/fractional dose, begins to decrease.

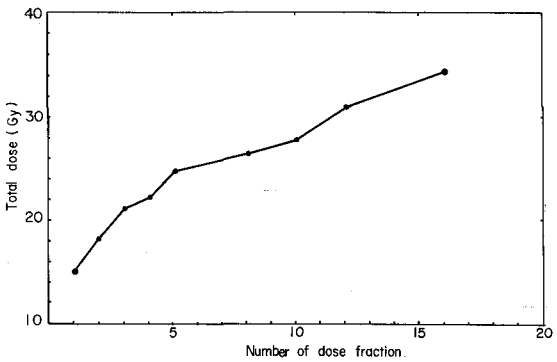

Fig. 4. Isoeffect curve relating total dose to number of dose fractions. The plot illustrates the importance of regeneration in determining the multifraction response jejunal mucosa.

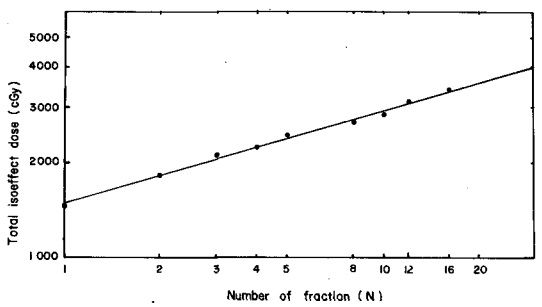

Fig. 5. Iso-effect curve relating total dose to number of dose fractions. The origin of the curve is at 1 : the slope is 0.29.

4. Iso-effect Curves

The relationship between total dose for iso-effect of 10 surviving cell/circumference and number of dose fraction is plotted against linear coordinates in Fig. 4 and logarithmic scales in Fig. 5. The slope of curve in Fig. 5 may be described by the formula: total dose = single dose $\times N^{0.29}$ where N is the number of dose fractions.

5. Estimation of α/β Ratio

The reciprocal total dose required for as iseoffect (10 survivors/circumference) is plotted against dose per fraction shown in Fig. 6. Estimates of the intercept α/E and the slope β/E can be obtained by linear regression of 1/Dn against $\times n$, and the ratio $\alpha/\beta = (\alpha/E)/(\beta/E)$ can be calculated at the chosen level of effect. The intercept was 0.257 Gy^{-1} and the slope was 0.031 Gy^{-2}, therefore the α/β ratio was estimated for 8.3 Gy on Table 3.

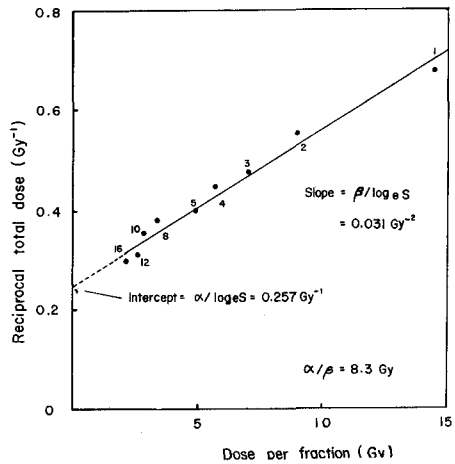

Fig. 6. Reciprocal total isoeffect dose (10 survirors/circumference) of mouse jejunal crypts in multifraction experiment.

Table 3. Values of α and β for Jejunal Clonogenic Cells

Method	α (Gy^{-1})	β (Gy^{-2})	α/β (Gy)*	References
Split dose	0.13	0.04	3	Hendry (1979)[36]
Multifraction	0.23	0.02	12	Thames (1981)[5]
Multifraction	0.26	0.03	8	Present data

* Early reactions 6-14 Gy Late reactions 1-5 Gy

DISCUSSION

Initially, radiotherapists adjusted treatment schedules by producing identical acute skin reaction. The moist desquamation of skin was the limiting factor in kilovoltage era, therefore, isoeffect studies were based on producing identical reactions with various treatment schedules. With megavoltage, skin reaction is no longer a limiting factor because of build-up. Late complication, specific organ complications, and nonspecific fibrosis, are now the limiting factors[7]. When conventional radiotherapy treatment schedules have been altered to fewer fractions of larger dose per fractions, a marked increase in late complications has ensued with little or no difference in the severity of acute responses[8~11]. Similarly, experimental studies of early and late radiation response in pig skin indicated that the severity of late response (contraction) cannot be adequately judged from early skin reactions (erythema and desquamation) when changing to larger dose per fraction[12,13]. From clinical and experimental data there is evidence of dissociation between acute and late radiation responses with changes in dose per fraction[7].

The most general statement of difference of cell survival curves of target cells for acute and late responses is that the difference between the slopes of single-dose and multifraction responses is greater for late responses[7].

The important parameter is the dose per fraction rather than the number of fractions, but of course two are related. Dutreix et al[14] first pointed out that only small changes in total dose were necessary for equal clinical skin reactions, provided that the dose per fraction were lower than a certain value. Withers et al.[4] subsequently elavorated this concept, defining D_R as the additional dose required per fraction when changing to larger number of smaller fractions. It is a measure of extra-repair which occurs when smaller instead of larger dose per fraction are used. The total dose has been called Extrapolated Total Dose (ETD) by Barendsen[15]. The corresponding limiting dose per fraction was defined by Withers[16] as "flexure dose", Df, the dose per fraction at which a significant departure from initially straight to curved dose-response curve can be detected as dose per fraction is increased. This flexure occurs gradully rather than at a precise dose. In order to accomodate this impression, Withers[16] and Masuda et al.[17] quoted range of value from Df which were 100~300 cGy for a number of normal tissues, depending upon the resolution of each experiment. The point is of practical importance because this range includes the dose per fraction normally used in conventional radiotherapy. The value of Df for late reacting tissues tends to be consistently smaller than those for early-reacting tissues, which is likely in some tumors, it is then obvious that therapeutic advantage might be obtained in principle by use of dose per fraction between the flexure dose for tumors and late reacting normal tissues[7,18,19].

The clarity has been much helped by the application of mathematical model which are better than the time-honoured cube root law, or Strandqvist's slope of 0.22 or Ellis' NSD and TDF slope of 0.24 with a time exponent of 0.11, or even Kirk's CRE formula, all of which have been extremely useful in their time[20]. It was unfortunate that reliable data about different normal tissue reactions did not become widely accepted. A comprehensive analysis of fractionation data available for normal tissues which express early reactions and those which express their late damage has been demonstrated[7,21]. This difference can be detected either as steeper slope on a log-log plot of total isoeffect dose versus number of fractions or as a difference in relative magnitude of linear (α; single-hit, irrepairable kill) and quadratic (β; multi-hit, repairable kill) terms of dose effect curve described by the equation: $E=n(\alpha D+\beta D^2)$ where E is a measured effect, n is the number of fraction and D is dose per fraction. The shape of dose-response curve can be analysed in a number of ways[20]: the formulae that should be considered include the linear-quadratic (LQ) model, the multi-target two-component (TC) model, and repair-misrepair (RMR) model[22]. Newer nodels include the use of dose-reponse formula to qualify the effect of each fraction, with the shoulder attributed to repair factors. The LQ model has been found to give better fit to in vitro data for human cell lines than multi-target or multi-hit models[23]. The LQ model provides good fit to experimental data in shoulder region, at least to several grays per fraction[20]. At higher doses many data continue to fit well, but other data fit better a straight exponential curve of slope $1/Do$[20]. The final part of survival curve of LQ model although not straight, can rarely be distinguished from straight Do curve, for values of α and β relevant to mammalian tissues[24]. In authors' case it was good fit to experi-

mental data in initial and shoulder regions, but there was slight difference in final part of survival curve.

Iso-effect curves which describe the response of tissues to fractionated doses are characterized in current literature increasingly by the value of ratio (α/β) or its reciprocal[7,20]. The absolute value is deduced from linear relationship of dose per fraction and the reciprocal total dose resulting in a given level of injury. To obtain α/β ratios, the dose required to produce equivalent damage with different fractionation schedules have been obtained from experiments. The "Fe" analysis derived by Douglas and Fowler[2] was then used reciprocal total dose was plotted as function of dose per fraction. If the data were consistent with linear-quadratic model, they should then have falled on straight line described by the equation: $\frac{1}{nd}=\frac{\alpha}{E}+d\frac{\beta}{E}$ where E is proportional to the level of damage at measured effect. The intercept represents α/E and the slope β/E. There is no sharp division between the values of α/β ratio for late and early responding tissues but a range of uncertainty exists from 5 to 8 Gy[20]. No use is made of relationship between the incidence of functional failure of tissues and the dose, although the steepness of dose incidence curves used to calculate the values of LD_{50} should be related in some way to absoulte values of α and β, in terms of respectively Gy^{-1} and Gy^{-2} which describe the dose survial curve for target cells that in many tissues, determine the observed degree or incidence of tissue damage[25].

The ratio is especially useful for predicting likely clinical effects. A curvy dose-response curve will obviously have a small value of α/β and a rather straight one will have a large value of α/β. Low values of α/β ratio (1.5-5 Gy) indicate that survival curves are bending rapidly at low dose per fraction, and hence within and below the useful clinical dose range (2-4 Gy) variations in fraction size should have a marked influence on isoeffect dose [7,15,18]. By contrast, high value of α/β ratio (6-14 Gy) indicates greater predominece of linear (α) term, so that changes in fraction size have a lesser effect on iso-effect dose. Author's result was 8.3 Gy of α/β ratio which showed rather stratight dose-response curve and had greater predominence of linear (α) component.

Fertile and Malaise[23] have used linear quadratic equation to analyze the available data on human cell lines irradiated in vitro. From their results Williams et al.[26] have calculated the α/β ratio, and for 40 cell lines studied, values of 2.1-92.0 were obtained. It should be remembered that cells and tissues in vivo tend to show greater repair capacity than cells in vitro[27], and the values of α/β ratio may therefore be overestimated. There was a tendency for highest α/β ratios to occur in the most radiosensitive tumors. However, high α/β ratios were observed in clinically radioresistant tumors, which might be therfore benefit from hyperfractionation[26]. It is difficult to know how these ratios would change if they could be assessed in situ in human tumors.

Fowler et al.[21] proposed the use of 0.1 α/β ratio as practical definition of flexure dose, where α and β are coefficents of linear and quadratic terms in relevant dose-response equation. The choice of factor 0.1 implies that difference of 10% total iso-effect dose can be detected with acceptable significance in two schedules with different fraction numbers[26]. The value of 0.1 α/β ratio obtained for both late (0.15-0.5 Gy) and acutely responding normal tissues (0.6-1.4 Gy) are all below the current clinical range of fraction size (2-4 Gy), this implies that hyperfractionation will indeed spare all normal tissues, but late responders even more than acutely responding tissues[27]. It is unknown whether the tumor response is reduced as well as the skin or mucosal response when total dose is reduced to avoid late damage; although this is likely since tumor would be expected to response more likely fast-proliferating than slowly proliferating tissues, and indeed experimental tumors have been found to have dose-response coefficients like proliferating tissues[28].

It has been suggested that tumor will respond like acute responding tissues at that is one reason to expect the therapeutic gain from hyperfractionation relative to late effects in normal tissues[7]. If we consider using a large number of smaller fractions, then late injury should be spared if equal early reactions are achieved. Alternatively the total dose should be increased more than this to yield equal late damage but to cause more damage to early-reacting tissues, probably both tumors and normal tissues[20]. There are of course uncertainties among the advantage claimed for hyperfractionation[7,15,18,19,29], but multiple small fractions have been and should continued to be investigated in clinical trials[30~33]. It is established that prolongation of overall time can lead to less tumor control[34], and that a small number of larger

doses causes excessive late damage if used for radical curative treatment[34,35]. The prolongation of treatment is undesirable, because rapidly proliferating tumor cells will escape treatment[34], so that the use of multiple daily fractionation (MDF) becomes necessary in order to use hyperfractionation. Multiple fractions experiments on animal tumors cannot be interpreted in terms of dose curves unless reoxygenation, as well as repopulation, is eliminated[26]. Two types of experiment minimize reoxygenation: those using clamped-off tumors and those using high dose of misonidazole. Williams et al.[26] have reviewed the available data and found unequivocally high values of α/β ratio for tumor response.

The low values of α/β for jejunum and spermatogonia were calculated from split-dose data, in contrast to higher values for these same tissues calculated from fractionation data[25]. It should be noted that split-dose data were not fitted directly to conventional LQ equation but to three-parameter equation[36]. It is well known that high-LET radiation acts with much larger α component than low-LET radiation: i, e., it has a larger one-hit or irrepairable component[20]. Joiner et al[37] found that α was increased by a factor of 7.2 in changing from x-rays to 3 MeV neutrons used to irradiate mouse skin, but β remains unaltered. How constant β will turn out to be, for various tissues and quantities of radiation, is a matter of interest for the future. The ratio of values derived from these experiments yielded theoretically limiting RBE at even lower dose per fraction, which was 7.2 ± 1 for mouse skin[37]. Radiation and cis-platinum cause damage to mouse intestinal crypt stem cells mainly by independent mechanism[38]. In addition, cis-platinum tends to inhibit sublethal damage repair in these cells. If this finding holds true in humans as well as for other types of mucosal epithelium, it is important factor to consider in designing new treatment protocols where both agents are used[38].

The use of linear regression analysis for reciprocal dose plots may be sensitive in practice, but in principle the quantities plotted against each other (nd vs d) are not completely independent so that analysis is strictly not valid. In practice, a visual indication of spread of α/β values of course provided by derivation of points from the line drawn through them.

Improved clinical results are being sought by hyperfractionation, by accelerated fractionation, or by continuous low dose rate irradiation as interstitial implants. New clinical trials are investigating these approach in many institutes, which have been suggested by the accumulation of radiobiological data.

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국문초록 =

다분할조사에 의한 마우스공장소낭선 세포의 선량반응곡선

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Co-60 치료기로 마우스 전신에 다분할조사(단일 2, 3, 4, 5, 8, 10, 12, 16회 분할 조사)후 공장소낭선세포측정법으로 소낭선세포의 재생능력에 대한 선량반응 곡선을 작성하고, 단일선량생존곡선을 분석하여 다음과 같은 결론을 얻었다.

1) 분할조사회수가 증가함에 따라 생존곡선은 고선량으로 이동하고 경사도는 점차 낮아졌다.

2) 단일선량생존곡선에서 Dq=460 cGy로 비교적 broad shoulder를 가지며 initial slope($_1$Do)는 475 cGy이였다.

3) 180~450 cGy까지 분할조사한 경우 분할조사간격당 평균회복선량은 분할조사선량의 약 50 %이었다.

4) 등가효과를 나타내는 분할조사선량과 이에 해당하는 총선량의 역수를 산출하여 선형회귀분석한 α/β 값은 8.3 Gy로 조기반응조직의 범위(6-14 Gy)에 속하였다.

5) LQ model은 방사선치료에 사용되고 있는 모든 선량에 적용이 가능하고, α, β 두 요소만 필요하므로, 실질적으로 편리하게 적용할 수 있다.

다분할조사에 대한 stem cell의 반응을 이해함으로써, 실제방사선치료시 위장관에 대한 급성손상을 극소화시키는 변형된 치료방법을 도입하고 다른 조직에도 응용할 수 있는 방사선생물학적 자료가 될 것으로 사료된다.