RADIOBIOLOGICAL MODEL APPLICABILITY IN RADIOTHERAPY: SINGLE AND FRACTIONATED IRRADIATION

by

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CERTIFICATE

This is to certify the dissertation entitled

"Radiobiological Model Applicability in Radiotherapy: Single and Fractionated Irradiation"

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DECLARATION

I hereby declare that this dissertation is the result of my own investigations, except where otherwise stated and duly acknowledged. I also declare that it has not been previously or concurrently submitted as a whole for any other degrees at Universiti Sains Malaysia or other institutions. I grant Universiti Sains Malaysia the right to use the dissertation for teaching, research and promotional purposes.

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LIST OF ABBREVIATIONS AND ACRONYMS

CO_2	Carbon dioxide
DMEM	Dulbecco's Modified Eagle's medium
DNA	Deoxyribonuclide acid
PBS	Phosphate-Buffered Saline
DSB	Double strand breaks
EDTA	Ethylenedinitrilotetraacetic acid
LET	Linear energy transfer
LINAC	Linear accelerator
LQ	Linear Quadratic
MT	Multi-target
SLDR	Sublethal damage repair
SSD	Source to skin distance
SSB	Single strand breaks

LIST OF SYMBOLS

Name	Definition
α	The cell kill per Gy of the initial linear component
β	The cell kill per Gy^2 of the quadratic component
cm	Centimeter
cm^2	Centimeter square
D	Dose (LQ model)
Dq	The size of the shoulder of the curve
Do	Dose at final slope
Gy	Gray
ml	Milliliter
MV	Mega voltage
n	The extrapolation number
µl	Microliter
X	Irradiated dose (MT model)
°C	Degree Celcius

ABSTRAK

Pengenalan: Kesan pemecahan telah terbukti secara penyelidikan mampu meningkatkan pecahan kemandirian sel berbanding iradiasi tunggal. Kemandirian sel boleh dihuraikan dengan mengunakan model radiobiologi yang mana bertindak meramal radiokepekaan dan "sublethal" pembaikan kerosakan sel terhadap radiasi. Dalam kajian ini, "linear quadratic (LQ) model" dan "multi-target (MT) model", model-model ini digunakan untuk membandingkan kemandirian sel antara iradiasi tunggal dan iradiasi pecahan. Penggunaan kedua-dua model ini dalam radioterapi akan dikenalpasti.

Kaedah: HeLa sel akan diradiasi menggunakan 6 MV sinar radiasi foton dengan 10×10 cm^2 saiz medan, 100 cm SSD dengan dos yang berbeza. Piawaian pengklonian asei telah digunakan untuk menilai kemandirian sel. Data yang dikumpul akan dipadankan dengan model-model LQ dan MT mengunakan perisian OriginPro 9.2. Parameter radiobiologi telah dinilai melalui padanan lekokan yang terbentuk dari model-model ini.

Keputusan dan Perbincangan: Padanan lekokan yang terbentuk daripada model-model LQ dan MT untuk kemandirian sel bagi iradiasi tunggal dan iradiasi pecahan menghampiri dengan kumpulan data yang diperoleh. Lekokan kemandirian yang dipadankan dengan model-model LQ dan MT menunjukkan cerun yang curam dan bahu lekokan yang kecil bagi iradiasi tunggal. "Sublethal" pembaikan kerosakan lebih bagus dengan iradiasi pecahan dengan bahu lekokan yang besar. LQ model memperoleh nilai parameter α dan nisbah α/β yang besar, manakala MT model menunjukkan nilai n, Do dan Dq yang kecil.

Kesimpulan: Penggunaan setiap model LQ dan MT menunjukkan iradiasi tunggal lebih berkesan dalam mengurangkan bilangan sel hidup. Model MT dinilai lebih tepat dalam menggambarkan radiokepekaan sel terutamanya pada dos yang tinggi bagi iradiasi tunggal dan iradiasi pecahan kerana padanan kumpulan data lebih dekat dengan lekokan. Model yang paling biasa digunakan, LQ menunjukkan padanan yang kurang memuaskan bagi dos yang tinggi.

ABSTRACT

Introduction: The effect of fractionation had been experimentally proven to increase the surviving fraction of the cells instead of single irradiation. Cell survival described by radiobiological models could be used to predict the radiosensitivity and sublethal damage repair of cells to radiation. In this study, the linear quadratic (LQ) and multi-target (MT) cell survival curve models were used to describe the cell survival with single and fractionated irradiation. The applicability of both models in radiotherapy was investigated.

Methods: HeLa cells were irradiated using 6 MV photon beam with 10×10 cm^2 field size, 100 cm SSD at different doses. Standard clonogenic assay was performed to determine the cell survival. The experimental data were fitted to the LQ and MT model using OriginPro 9.2 software. Radiobiological parameters were evaluated from the fitting curves generated from these models.

Results and Discussion: Fitting curve of the LQ and MT models for cell survival with single irradiation were found to be close to the experimental data. The survival curves fitted with LQ and MT model for single irradiation displayed steep initial slope and small shoulder. The sublethal damage repair was better for fractionated irradiation with wider shoulder. The parameters of LQ model showed a larger α and α/β ratio whereas for MT model showed a smaller n, Do and Dq.

Conclusion: The parameterisation of LQ and MT model showed that single irradiation is more effective in reducing the number of cell survive. MT model seem to be more accurate in describing the radiosensitivity of the cells especially at high dose for both single and fractionated irradiations because the experimental data plotted fitted closely to the curve. The most commonly used model, LQ seem to provide unsatisfactory fitting at high dose.

CHAPTER 1: INTRODUCTION

1.1 Radiotherapy

Radiotherapy is a type of therapy for cancer treatment using high energy radiation to kill cancer cell. Basically, there are two types of radiotherapy which are external radiotherapy and internal radiotherapy. External radiotherapy is a type of therapy which is radiation originated from the outside by means from a machine. Internal radiotherapy which is radiation comes from the inside of the body as radioactives implants in the form of seeds, wires or tubes for a certain period of time.

For this study, external radiotherapy is applied for cancer treatment and this treatment is delivered using a machine called linear accelerator (LINAC). LINAC is a machine that is commonly used to treat cancer by emitting ionizing radiation.

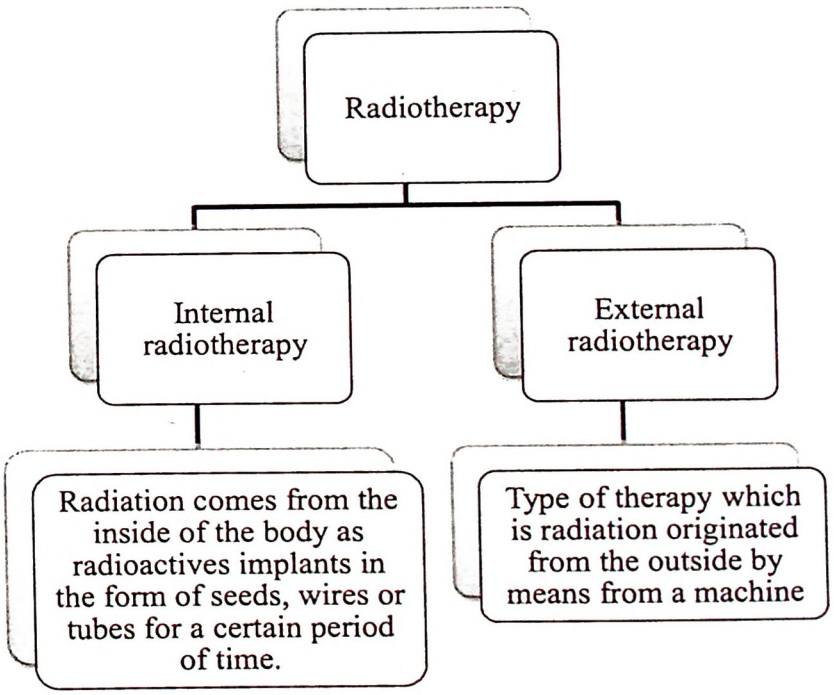

Figure 1.1: Different type of radiotherapy

1.2 Radiobiology

Radiobiology is a branch of science that evaluates the action of ionizing radiation on biological tissues and living organisms, and it's formed by combination of two disciplines which are radiation physics and biology (Suntharalingam et al., 2005). When the cells are actively dividing during mitosis phase, radiation eventually led to cell death. In cell cycle, cells being most radiosensitive in the M and G_2 phase while least sensitive in the late S phase. Radiosensitivity can be defined as the degree of the cell is to be damaged by radiation.

The presence of ionizing radiation will enhance mutation frequency (Beyzadeoglu et al., 2010). Ionizing radiation will damage the cell's deoxyribonucleic acid (DNA) which is the genetic code forming the critical backbone of the cell. Any changes in this code can potentially affect the cell functions and in the extreme condition will prevent it from functioning (Jones et al., 2001).

Radiation action mechanism occurs in two ways which are direct and indirect action. For direct action, radiation affects DNA molecules in the target tissue directly. Energy absorption of atoms via the photoelectric effect and Compton interactions will result in direct ionization of atoms in DNA molecules. When the energy absorbed is enough to remove electrons from the molecule, the bonds are broken and can break one DNA strand or both. Usually, a single strand breaks (SSB) can be repaired by the cell, while double strand breaks (DSB) will result in cell death (Beyzadeoglu et al., 2010).

For indirect action, the energy transfer from radiation causes the formation of free radicals and eventually molecular damage occurs due to the interactions of theses free radicals with DNA. Formation of free radicals happened due to the interaction of radiation with water molecules since the human body consists of approximately 70% water. Free radicals are electrically neutral atoms that contain unbound electrons. They are highly electrophilic and reactive (Beyzadeoglu et al., 2010).

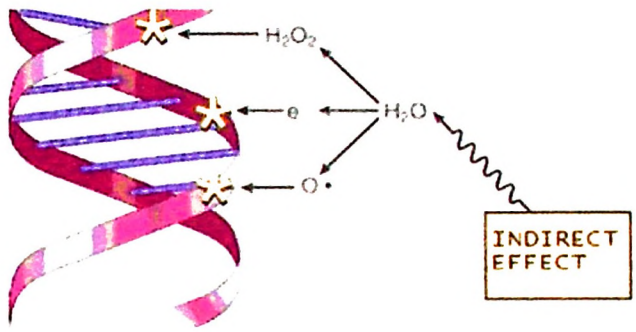

Figure 1.2: Indirect action of radiation. [Beyzadeoglu, M., Ozyigit, G., & Ebruli, C. (2010). Basic Radiation Oncology. Springer Berlin Heidelberg].

Figure 1.3: Direct action of radiation. [Beyzadeoglu, M., Ozyigit, G., & Ebruli, C. (2010). Basic Radiation Oncology. Springer Berlin Heidelberg].

1.3 HeLa cells

The HeLa cell is a human cervical cancer cell taken from Henrietta Lacks. Henrietta Lacks died in1951 of an aggressive adenocarcinoma of the cervix. The HeLa cell appears to be immortal and grow quickly in cell culture and become the first human cell line (Lucey et al., 2009). HeLa cell can spread easily and infect other cells. Nowadays, the cancer cell is widely used in medical research around the world.

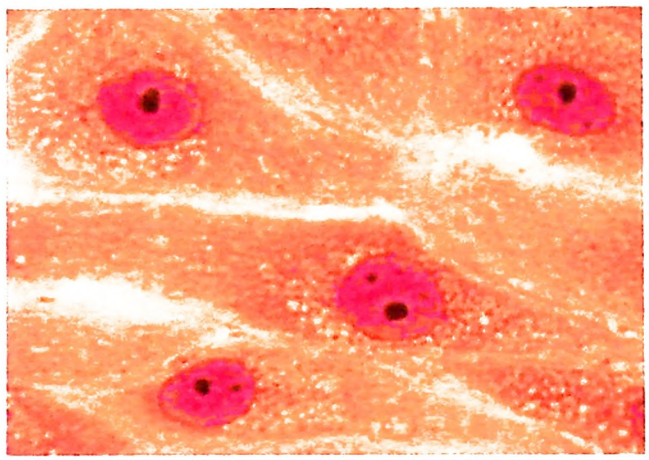

Figure 1.4: The HeLa cell lines (magnification ×40)

1.4 Clonogenic assay

The clonogenic assays become the basis of cellular response studies in tumours and in some normal tissues. The basic idea is to remove cells from the tumour, grow them in a suitable growth environment and test for their ability to produce a sizeable colony of descendants (Joiner, 2009). The clonogenic assay is an in vitro cell survival assay based on the ability of a single cell to grow into a colony. The colony needs to form at least 50 cells. Not only the clonogenic assay can be used to determine cell reproductive death after treatment with ionizing radiation, but can also be used to determine the effectiveness of other cytotoxic agents (Franken et al., 2006).

1.5 Cell survival curve

The first survival curves for mammalian cells were obtained by Puck and Marcus whose work marks the beginning of quantitative cellular radiobiology (Tubiana et al., 1990). A cell survival curve is a plot of surviving fraction against dose (Mayles et al., 2007). Besides, it shows the relationship between the surviving fraction of cells and the absorbed dose. Basically, cell survival curve is plotted on a logarithmic scale of survival. There are two reasons why cell survival curve is plotted in that way:

a) If cell killing is random then survival will be an exponential function of dose, and this will be a straight line on a semi-log plot.

b) A logarithmic scale more easily allows us to see and compare the very low cell survivals required to obtain a significant reduction in tumour size or local tumour control.

(Joiner, 2009).

1.6 Linear Quadratic model

Linear Quadratic (LQ) model is proposed by Douglas and Fowler in 1972. The LQ model is a mechanistic model of cell killing. Now, the LQ model is widely used in both experimental and clinical radiobiology and works well in describing responses to radiation in vitro and in vivo (Joiner, 2009). The LQ model is used globally to model the effect of total dose and dose per fraction in conventionally fractionated radiotherapy (Kirkpatrick et al., 2008).

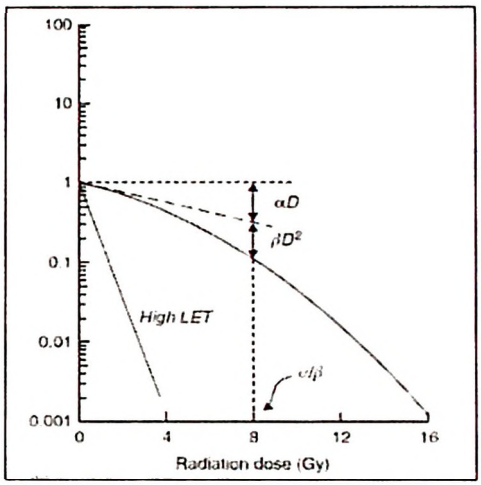

Figure 1.5: The graph shows the relationship between dose and surviving fraction in LQ model. [Joiner, M., & Kogel, A. V. D. (2009).Basic Clinical Radiobiology (4th ed.). Edward Arnold: United Kingdom].

Based on the Figure 1.4, the LQ model consists of two components. The first component is a linear region which is directly proportional to the dose, also a region of low doses and shows linear function. The second component is a quadratic region which is directly proportional to the square of dose. This quadratic region is the region of higher doses.

The LQ model is expressed in formula:

$$S = e^{-\alpha D - \beta D^2}$$

Where, S = surviving fraction

D = the dose delivered in unit Gray (Gy)

α = the cell kill per Gy of the initial linear component (on a log-linear plot)

β = the cell kill per Gy^2 of the quadratic component of the survival curve

As demonstrated by Jones et al (2001), α represents the direct killings of cells while β represents the effect of cell killing from 'double hits'. This model originated from the curvilinear nature of dose-response curves of the log of cell survival. The curvature is presumed to be related to the production of DNA double strand breaks (DSBs) by two different radiation tracks. Two of such DSBs or subset of DSB is required to produce a lethal lesion such as a dicentric chromosome aberration (Brenner et al., 1998).

The LQ model is rather accurate in the classical fractionation region from 1.5 to 4 Gy. However, as the dose range of the radiotherapy application widen the classical LQ model becomes less and less accurate (Brahme, 2011). According to Andisheh et al (2013), LQ model is not suitable in the high-dose region where it underestimates the surviving fraction in the high dose range. Its parameters are essential but to describe more complex treatment, a realistic model is more desirable. Unfortunately, according to the research conducted by Iwata et al (2013), the LQ model only capable to fractional doses of 5 Gy or less.

1.7 Multi-target model

Multi-target model is one of the models that has been developed in which the basic principle involves there are more targets than just one in a cell and inactivation of all the targets leads to the death of the cell. When a dose that causes an average of x hits inside a cell of organism, the survival rate of a cell population is expressed by:

$$S = 1\text{-}\ (1 - \exp^{-DoX})^{n}$$

Where, S = probability of survival

D_o= a dose that causes a mean of one-hit per cell (mean lethal dose)

X = irradiated dose

n = number of targets (required number of hits for cell death)

(Nomiya, 2013).

The MT model provides an alternative description of clonogenic survival as a function of radiation dose. Although this classical model also represents a straight line at high doses, which is "n" supported by the mechanism of the underlying radiobiological processes, the MT model is still valuable because it fits the empirical data well, especially in the high-dose range, thus, compliment the drawback of LQ model deficiency.

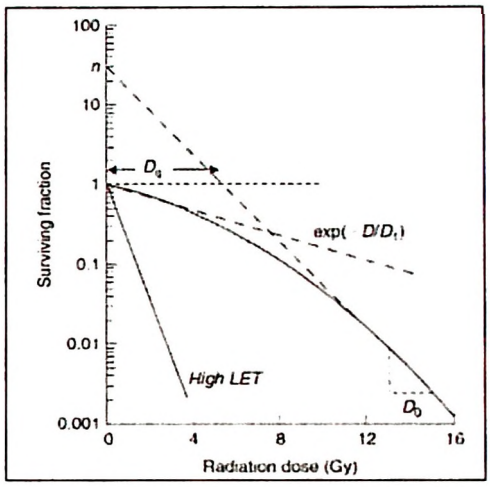

Figure 1.6: The graph shows the relationship between dose and surviving fraction in MT model. [Joiner, M., & Kogel, A. V. D. (2009).Basic Clinical Radiobiology (4th ed.). Edward Arnold: United Kingdom].

1.8 Problem statement and Significance of the Study

Cell survival is normally used to present the radiosensitivity of the cells towards low dose and high dose range. But unfortunately, according to Kirkpatrick et al (2008) LQ model is not applicable for high dose rate radiotherapy. This is happened because LQ model does not accurately explain the observed (in vivo) clinical data and does not consider the impact of the subpopulation of radioresistant clonogens as well. Basically, LQ model is derived largely from in vitro, rather than in vivo, observations and thus does not consider the impact of ionizing radiation on the supporting tissues. The LQ model also creates a "false belief" that this simplified model represents an absolute truth.

The significance of the study is to evaluate the applicability of linear quadratic model in determining the radiosensitivity of HeLa cells with single and fractionated irradiation. The radiosensitivity and radiobiological response of HeLa cells are plotted in cell survival curve by LQ model and then compared to MT model. From this comparison, we can determine which model can describe better about the radiosensitivity and radiobiological response of the cells for energy 6 MV of 2-8 Gy of dose. This study also provided insight towards understanding the relationship between fractionation and repair mechanism of the cells.

1.9 Aim and objectives

Aim:

To study the applicability of radiobiological model in analysing single and fractionated irradiation in radiotherapy.

Objectives:

1) To analyse cell survival curve using Linear Quadratic model and Multi-Target model.
2) To compare cell survival curve for single and fractionated irradiation.
3) To examine the applicability of linear quadratic model to single and fractionated irradiation compared to multi-target model.

CHAPTER 2: LITERATURE REVIEW

In the study by Lucey et al (2009), HeLa cell is the cervical cancer cell of a 30 years old African-American woman, Henrietta Lacks. She died in 1951 of cervical cancer. The cells were cultured by Dr George Gey and his colleagues on February 1951. The cell grew aggressively in cell culture then became the first human cell line. There were some unique characteristics of HeLa cell, which were a robust, immortal cell line, easily propagated over generations in culture and able to contaminate other cell lines. HeLa cells appeared to be immortal and encountered an unlimited number of divisions in an uncontrolled way compared to other cell lines. Until now, HeLa cell was still widely used by researchers around the world especially in medical research.

The cell survival curve presented the relatedness between radiation and surviving fraction. Puck et al (1957) conducted a research and the research was being published for in vitro mammalian cells irradiated with x-rays and demonstrated the connection between the dose delivered and the killing of the cell being the cell survival curve. This curve has been proved as a guideline for many models to determine the effects of radiation. If this curve was considered accurate, then these models can be used to compare various situations in radiotherapy treatment planning for example different dose distributions and fractionation schedules (Jones et al., 2001). In addition, surviving fraction of cells was obtained from the clonogenic assay technique based on the colony form.

Radiobiological models were used to describe the radiation effect at subcellular level by modelling the biophysical events using mathematical approach with parameters that indicate the events. A radiobiological model typically converts a physical quantity (absorbed dose) to a biological quantity (cell survival fraction) (Wang, 2010).

The linear quadratic (LQ) model was most commonly used for quantitative predictions of dose or fractionation dependencies in radiotherapy. Now, the linear quadratic model was globally used in calculating radiotherapeutic isoeffect doses for various fractionation or protraction schemes (Brenner, 2008). As been demonstrated by Brenner (2008), the LQ model had the following useful properties to determine the isoeffect doses. First, as we know, linear quadratic model was a mechanistic and biologically-based model. Second, it had sufficiently few parameters to be practical. Third, various mechanistic model of cell killing predicted the same fractionation dependencies as LQ model. Fourth, it had well documented predictive properties for fractionation and dose rate effects in the laboratory. Fifth, it was reasonably well validated, theoretically and experimentally up to about 10 Gy per fraction and would be reasonable for use up to about 18 Gy per fraction. Until now, there was no evidence of problems when LQ model had been clinically applied.

According to Jones et al (2001), there were a few uses of the LQ model in terms of fractionation regimes. One of the main benefits of LQ model was associated to fractionation effects and able to compare various fractionation schedules. Besides, LQ model was able to simply assess a fractionation schedule which was not necessarily distributed evenly in fraction size or delivery time throughout the entire treatment. Addition to that, the LQ model and its modifications can also be used to consider an inhomogeneous dose distribution that was resulting in fraction sizes which were not consistent through the target volume.

Unfortunately, as mentioned by Kirkpatrick et al (2008), the LQ model was not applicable for high dose rate radiotherapy and beneficial for conversion between relatively low radiation doses as used in conventional radiotherapy. In his study, he highlighted some reasons why linear quadratic model was not applicable to high dose rate. The LQ model may be inappropriate for high doses per fraction practiced in radiosurgery because it did not explain accurately the observed (in vivo) clinical data. Second, it was derived largely from in vitro, rather than in vivo, observations and therefore did not consider the impact of ionizing radiation on the supporting tissues. Next, the LQ model did not consider the impact of the subpopulation of radioresistant clonogens. Last but not least it created a "false belief" that this simplified model represents an absolute truth.

Based on the research conducted by Iwata et al (2013), this model was capable to fractional doses of 5 Gy or less. According to research by Shibamoto et al (2012), she also stated that the LQ model was not being applicable with high doses per fraction. This happened because dose-survival curves for cultured cells cannot be fitted well by the LQ model in high-dose ranges. The LQ model showed the cell survival curve continues to bend downwards at high dose did not seem to fit the actual curves at high doses.

There were 5 assumptions regarding the LQ model based on Alpen (1997). The first one is the assumption that this model had certain critical molecules in the cell which was important for the survival of the reproductive function of the cell. Second, these critical molecules were assumed to be double-stranded DNA and thus, the critical damage was predicted to be a double-strand break in the DNA molecules. Besides, the mechanism of radiation, either direct or indirect, was considered to be damaging the molecular bond in DNA strands (lesion).

Other than that, the lesions in DNA were able to express the varying degrees of repair under certain conditions of being repaired and modifications of radiobiological effects. Lastly, the repairing process of DNA includes physiochemical recombination, charge transfer process, chemical restitution and enzymatic repair.

Target theory became one of the crucial concepts for understanding radiobiology. Multi –target single-hit model was most commonly used and had assumption that the cells had several targets, each requiring one hit for inactivation (Spring & Holmberg, 1968). An experiment was conducted on the effects of radiation on bacteria and viruses and the results from the experiment demonstrated that the survival of irradiated organisms decreased exponentially with increased in radiation dose (Lea & Coulson, 1949; Lea et al., 1941; Lea, 1946; Nomiya, 2013).

There are four presumptions regarding the MT model. The first one was there are n targets in the cell. Next, each target had the same probability q, of being hit. Then, one hit was adequate to inactivate each target but not the cell. Last but not least, in some general cases, there will be a hit survival function as in the single-hit formulation (Alpen, 1997).

Alpen (1997) stated six properties of the MT model. The first properties is each log curve for surviving fractions below about 0.1 becomes a straight line at which time the shoulder region has no more effect on the curvature. The second properties is the extrapolation of this straight line portion of the plot back to the zero dose ordinate yields a value for n, the target multiplicity. However, except for the remarkable case of n = 1, in which circumstance the relationship degenerates to the single-hit form, every curve has a shoulder that increases in breadth with the multiplicity, n. The curves will have zero slope at zero dose for any n greater than 1. The fifth properties is q has the dimensions and nature of the inactivation coefficient as in the single-hit case and the last properties 1/q is the dose for 1/e (37%) survival in the linear portion of the survival plot, and it is called the D_0. The D_0 has the dimensions of dose.

CHAPTER 3: MATERIALS AND METHODS

3.1 Materials

3.1.1 Cell culture

3.1.1.1 HeLa cell

Cancer cells that continuously grown in cell culture and become the first human cell line grown in vitro. HeLa cell is an epithelial type of cell in cervix cancer tissue. This HeLa cell is widely used in medical research especially in cancer research because the cell was said to be remarkable, durable and prolific compared to many other cell line that being used in research.

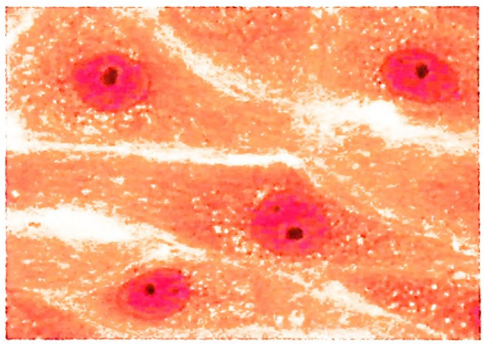

Figure 3.1: The HeLa cell lines (magnification ×40)

3.1.1.2 Culture flask

Culture flask played an important role in cell culture as a place for cell to grow and spread. Culture flask was available in 3 different sizes, which are 25, 75 and 175 cm.

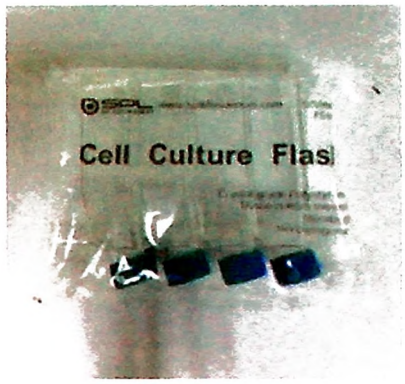

Figure 3.2: Cell culture flask

3.1.1.3 Eppendorf tube

Function of eppendorf tube as a place to put the cultured cells and being transferred from culture flask by using pipette. Eppendorf tube consists of several different size and the size used was depends on the volume of the cells.

Figure 3.3: Eppendorf tube

3.1.1.4 Pipette

Pipette was used to withdraw and dispense cells, medium and also reagents. Pipette also consists of various sizes and size chosen was based on volume transferred. Pipette was set to desired volume in order to obtain accurate measurements and pipettes fit tips that were specific for the specific volumes. The tips were kept in color-coded sterile boxes and will be disposed after used.

Figure 3.4: Pipette

3.1.1.5 Cell culture hood

Cell culture hood is a place to prepare the cell in clean working area to prevent contamination of the cells. Cell culture hood is equipped with a UV light to sterilize the materials that will be used. UV lamp must be turned off before working in the hood to prevent exposed to hazardous UV light. Wipe down the inside surface of the hood with alcohol before starting work to ensure that the hood is always clean. All equipment and supplies used inside the hood must be cleaned and wiped with alcohol.

Figure 3.5: Cell culture hood for preparing cells

3.1.1.6 Incubator (CO_2 Series Sheldon Mfg. Inc)

Incubator provided the appropriate environment for the cells to grow by controlling the growth factors of cells including temperature, humidity, CO_2 level and ventilation. Incubator was set to a specific temperature suitable to the cells. For mammalian cells, the temperature was kept at 37.0° C and humidity of 35% to function properly. CO_2 gas was needed to keep the pH balanced, that's why incubators are connected to a CO_2 gas tank. CO_2 level was maintained at 5%.

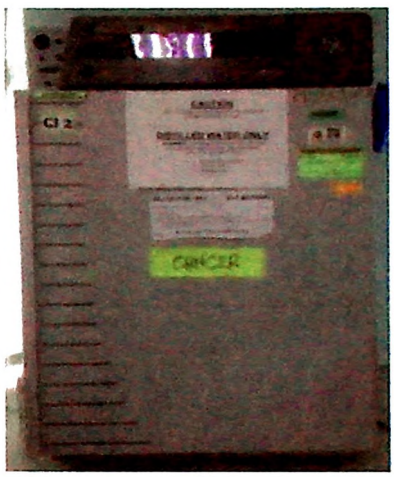

Figure 3.6: Incubator for cancer cells

3.1.1.7 Surgical gloves

Surgical gloves gave protection for users from biohazard of other substances. It can be sanitized by spraying them with 70% isopropanol and allowed it to dry for 30 seconds before used it.

Figure 3.7: Surgical gloves

3.1.2 Cell irradiation

3.1.2.1 Siemens Primus Linear Accelerator (LINAC)

Linear accelerator (LINAC) is the machine that is commonly used that provides external beam radiation treatments for patients suffering cancer. Linear accelerator that has been used in this research is Siemens Primus Linear Accelerator. One of the unique features of this linear accelerator is, it can produce both photon and electron beam with various energy. Besides, it was used to treat all parts of the body by delivering high energy radiation to cancer site.

Figure 3.8: Siemens Primus LINAC for irradiation process

3.1.2.2 Bolus

Bolus was used for tissue compensation. In addition, bolus can be used in modifying dose at skin surface and at a depth. Bolus often used to increase the surface dose. Sometimes, it was also used to make up for a missing tissue and provide build-up of dose to the skin surface. Bolus was made up from a tissue equivalent material such as wax that was sufficiently flexible to conform to the patient's surface and also durable.

Figure 3.9: Bolus