Optimization of time-dose fractionation radiotherapy scheme by simulated annealing with consideration of biological factor

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Abstract. Ionizing radiation for cancer treatment also known as radiotherapy has undergone development for more than century. Radiation kills cancer by giving partially or entirely all of the energy to the tumor tissue, especially in the DNA. If tumor or a cancer is irradiated by radiotherapy, there is no way to avoid the tissues near cancer will be affected by the radiation. As a result, the healthy tissues near tumor will lose their functionality, or worse, there may appear a new tumor in that tissues. Therefore, it should be done some improvement in the quality of radiotherapy, one of the examples is optimization of time-dose fractionation radiotherapy scheme. To optimize the fractionation dose, is made a program in MATLAB using simulated annealing as the optimization method. The objective function is Biologically Effective Dose of cancer, with constraints are Biologically Effective Dose of the healthy tissues around cancer. After obtaining the optimum dose per fraction, the data will be analyzed for the total and fractionation time. Thus, it would be obtained the optimum of time scheme and dose fractionation of cancer. The result of this research will show the dose per fraction from the total time in 10 until 60 days in both of the treatment schemes, the value of Biologically Effective Dose of the cancer, and the optimum of dose per fraction from both of the treatments.

1. Introduction
For more than century, the ionizing radiation for cancer treatment or radiotherapy has undergone a massive development. Radiation is an energy emitted by the electromagnetic wave or particle stream. Radiation can break the DNA in the cell which has a function to control the growth and the division of cells. When the DNA of the cell is broken, the tumor can not grow and split, and by the time, the tumor cell will be dead. While the tumor is irradiated by radiotherapy, the healthy tissues around the tumor will be affected by the irradiation. As a result, the comp lication of the healthy tissues will rise. For years, the technologies have been developing on the aspect of radiation distribution that has an aim to widen the therapy window to decrease the effects in the healthy tissues while improving the effects in the target (tumor).

In general, there are three methods to improve the radiotherapy quality: (1) improve the quality of dose distribution; (2) optimize the time scheme-dose fractionation in the radiotherapy; (3) modify the response of the radiation in the tumor (radiosensitizers) and/or in the healthy tissue (radioprotection). By using the latest clinical implementation in radiotherapy, such as Intensity-Modulated Radiotherapy (IMRT), nowadays, it can be obtained the optimum dose distribution in the radiotherapy treatment. The second method, the optimization of time scheme-dose fractionation, can be done by many ways, such as using the biological aspect.[2]
The application of the radiobiology in the field of clinical radiotherapy is still in the primitive stage. To make the optimum design of the patient treatment and the proper usage of the potential research in the radiobiology that has developed for years, it will be a good advantage to improve and develop inverse optimization technique using time-dose fractionation. This will not only be increasing the comprehension of the impact of the biological parameter in the radiotherapy treatment for the tumor, but also provide the practical tools to get the optimum result in total dose, fractionation scheme, dose per fraction and overall treatment time. One of the fundamental formulation in the radiobiology to describe the link between time-dose fractionation scheme in the tissue is linear-quadratic. Linear-quadratic is used to predict the dose isoeffect from radiotherapy when the schedule of the fractionation is changed. This formulation becomes the most commonly used formula, because linear-quadratic can describe a model that will calculate tumor control and healthy tissue complications when a dead cell occurs.

Simulated annealing or SA is an optimization method which is included in stochastic methods. A stochastic method is a mathematical method based on probability or randomness. The main advantage of SA is that the method can find the global optimum from all the evaluated area. In other words, SA can remove itself from local minima in the evaluated area. Another advantage of SA is that the method can work in a non-linear model, a model that has many noises, and has many constraints. The disadvantage of this model is that SA needs parameter calibration to get the optimum result. In addition this method is a time-consuming method. Furthermore, because SA is the one of stochastic methods, so sometimes this method do not find the true optimum, but just an approximation of the optimum value.[8][9][15]

This work will optimize the time scheme and dose fractionation by simulated annealing in the tumor which can be divided into two categories. The first one is called late effect tumor, this kind of tumor has very long proliferation time that can be more than a month. The second category is early effect tumor, this tumor will proliferate in short time, only a couple of days or weeks. The optimization has constraints in the form of organ at risk (OAR) around the target (tumor). Similar to the tumor, OAR also has two categories. So, this optimization will vary both of the tumor and OAR, as well as the other parameters such as kick-off time, resensitization time, and repair time to analyze the optimum time scheme and dose fractionation.

2. Materials and Methods

2.1. Linear-Quadratic Radiobiology (LQR)

Linear-quadratic is a fundamental tool in radiobiology, because this formula can calculate the tumor control probability (TCP) and normal tissue complication probability (NTCP). This formula also can predict the isoeffect dose from radiotherapy when the fractionation schedule has changed. The first formula and the famous one in the linear-quadratic is survival factor. Survival factor explains the ratio between the broken cell (dead cell) with the survived cell that happened from two unrelated processes, which is from the physical mechanism by single-hit and double hit.

\[ S = \exp\left[-(\alpha D + \beta D^2)\right] \] (1)

The constant alpha explains about the damage caused by the ionization events that lead to lethal damage in DNA directly, whereas the beta is a constant that appears as a result of the damage in the cell caused by two ionization event which does not have any repair in the sublethal damage, so the damage becomes lethal damage. The D represents total dose which is given in the radiotherapy treatment.

In the clinical radiobiology, it is known a term called 4R radiobiology. 4R radiobiology is biological factors that affect tumor and healthy tissues responses from a fractionation radiotherapy treatment. The first one, called repair, is a biology mechanism that will fix or repair the sublethal damage caused by radiation. Secondly, the redistribution, this phenomenon is affected by the distribution in proliferation cell population that happened during the fractionation radiotherapy through cell cycle that will increase
the dead cell. The next is reoxygenation from the cell which has hypoxia condition, at first the cell is resistant to radiation then as day by day the cell becomes more sensitive to the dose of radiation. The last one, called repopulation, this phenomenon happened when cell duplicates itself during the treatment of radiotherapy.

\[
S = \exp \left\{ \sum_{i=1}^{i_d} \left[ -a d_i - \beta G_i(\tau_r) \frac{1}{2} \sigma^2 G_i(\tau_s) d_i^2 \right] + \right\} \frac{H(T_{tot}, T_1)(T_{tot} - T_1)}{T_{pd}} \]

(2)

\[H(x, x_0) = \begin{cases} 0, & \text{if } 0 \leq x < x_0 \\ 1, & \text{if } x \geq x_0 \end{cases} \]

(3)

Equation 2 is called linear-quadratic radiobiology or LQR. This formula calculates the effects of the 4R radiobiology mentioned before. The G, usually called Lea-Cactheside time factor, will calculate the effect of the fractionation or protraction of the treatment radiotherapy. The first one, G(\tau_r), is a Lea-Cactheside time factor in a function of repair and the second one, G(\tau_s), is a Lea-Cactheside time factor in a function of resensitization, consisting of reoxygenation and redistribution. The (1/2)\sigma^2 is the variance of Gaussian Distribution of \sigma. The last term, repopulation, is in the heaviside factor, where T_{tot} is overall treatment time, \tau_1 is kickoff time of accelerated proliferation, and T_{pd} doubling time of tumor.

\[G_i(\tau) = 1 + \frac{2}{\sigma} \sum_{j=1}^{i-1} d_j \prod_{k=j}^{i-1} \exp \left( -\frac{\Delta k}{\tau} \right) \]

(4)

For an arbitrary fractionation with interval fractionation (\Delta t_1, \ldots, \Delta t_t, \ldots) and radiotherapy fractional dose (d_1, \ldots, d_t, \ldots), which d_i represents the ith fractional dose and \Delta t_i as a time interval between fraction i and i+1. For normal tissue calculation, the formula only considers the cell killing and incomplete repair of sublethal damage, or in other words only the first two in Equation 2 are included.

2.2. Objective function and constraints

In the optimization problem, the objective function is a mathematical formulation which will determine the best solution that has been obtained. The minimum possible solution (or maximum, depends on the optimization) from an objective function is called optimum solution. Whereas, a constraint is a condition on the optimization problem and the solution must satisfy some conditions.

This paper uses an objective function in the function of BED (Biologically Effective Dose), which can be written

\[F = \frac{BED_{tumor-reference}}{BED_{tumor}} \]

(5)

From the Equation 5, it can be said that on this research will find the minimum value of the objective function, i.e it will be found the maximum value of the BED tumor. The constraints of the problem are:

\[BED_{organ} \leq BED_{organ-reference} \]

(6)

The reference schedule for this research is standard fractionation with a total dose 70 Gy and dose per fraction is 2 Gy/fraction. While, in this research, it will be used two kinds of schedule, standard fractionation and hyperfractionation. On this paper, there are only two patterns of the interval: five fractions per week (interval=1 day) with a weekend break (standard fractionation) and ten fractions per week (interval between two fractions in the same day is 8 h) with the overnight and weekend breaks (hyperfractionation). The overall time is two weeks until eight weeks for fast proliferation, and two weeks until six weeks for slow proliferation. For each overall treatment time, the optimization program
will optimize the dose per fraction using simulated annealing that will maximize the tumor BED with constant or lower healthy tissue BED.

From Equation 5 and 6, it is known that the optimization problem has constraints. The problem can be solved by linear algebra and geometry, and the result will usually be complicated and technical. In this research, it will be introduced basic technique, that will change a constraint problem into unconstraint problem. This technique is called penalty technique, it will penalize a treatment plan that has BED-organ bigger than BED-organ-reference.

\[
F = \left\{ \frac{BED_{tumor-reference}}{BED_{tumor}} + \sum_{n=1}^{N} k \times \max(0, BED_{organ-n} - BED_{organ-ref-n}) \right\}
\]

By using the Equation 7, an optimization problem that has a constraint at first will become unconstraint. The value of k in the Equation 7 is positive, therefore if the BED organ is bigger than the BED organ reference, the objective function will be bigger and the objective function is not an optimum solution. In other words, the solution is penalized by penalize function. Otherwise, if the BED organ is less than the BED organ reference, the penalize function will be zero, and the objective function remains the same.

The organs and tumor are divided into two parts, which is early effect tissue and late effect tissue. Those two parts will have different parameter value as shown in the table below.

| Table 1. Parameter of fast and slow proliferating tumor and tissues |
|---------------------------------------------------------------|
| Parameters | Fast proliferating | Slow proliferating |
| α tumor (Gy⁻¹) | 0.35 | 0.1 |
| α/β tumor (Gy) | 10 | 1.5 |
| Tumor doubling time (day) | 3 | 40 |
| Tumor kick off time (day) | 28 | 300 |
| Tumor resensitization time (day) | 1 | 2 |
| Tumor repair time (hour) | 0.5 | 1.9 |
| Variance of gaussian distribution | 0.02 | 1/3 β |
| α of late responding tissue (Gy⁻¹) | 0.315 | 0.315 |
| α/β of late responding tissue (Gy) | 3 | 3 |
| Late responding tissue repair time (hour) | 4 | 4 |
| α of early responding tissue (Gy⁻¹) | 0.315 | 0.315 |
| α/β of early responding tissue (Gy) | 10 | 10 |
| Early responding tissue repair time (hour) | 0.5 | 0.5 |

3. Results and Discussion

3.1. Fast proliferation and slow proliferation tumor

Figure 1 shows the ability of simulated annealing to reproduce the same value of BED tumor. Simulated annealing can reproduce with an accuracy more than 0.1% in fast proliferating tumor as illustrate in Figure 1(a). However, on the case of slow proliferating tissue in the Figure 1(b), simulated annealing fails to reproduce the value of BED tumor. As shown in Figure 1(b) the poor accuracy of reproducibility is obtained, that is less than 12%. It is happened due to the sensitivity of changing dose per fraction in slow proliferating tumor is higer than fast proliferating tumor. Therefore, if the simulated-annealing mechanism changes the dose per fraction in order to find the optimum BED tumor, a little change in dose per fraction will change large amount of BED tumor in slow proliferating tumor. Nevertheless, simulated annealing can be upgraded or improved by simple method as the result which is shown in
Figure 1. Reproducibility of BED tumor (a) Standard Fractionation. (b) Hyperfractionation with a normal simulated-annealing. (c) Hyperfractionation with an improve of simulated-annealing.

Figure 1(c). This improvement will re-iterate after doing the first iteration of simulated annealing with an early dose of the second iteration is the optimum dose of the first iteration, the iteration will continue until five iteration. As shown in Figure 1(c), the accuracy of reproducibility is increase, with the accuracy more than 1.1%. In spite of the accuracy is not as accurate as the fast proliferating tissue, but it is acceptable.

As illustrates in Figure 2, the BED tumor in standard fractionation will rise in the early of total treatment time and in the middle of the total treatment time, the BED tumor will decrease as the treatment time increases. It is known that the kick-off time (the time when tumor is proliferating) is the main factor of this effect. After the treatment time pass through the kick-off time, the tumor will proliferate or doubled the cell rapidly. It will decrease TCP (Tumor Control Probability) as well as the BED tumor, the TCP decreases because many cells have proliferated or doubled rapidly eventhough the cell is dead due to the treatment radiotherapy. However, the cell dead is way more few than the doubling cell mechanism, therefore the TCP will decrease as the treatment time increases. As a result of the lack of accuracy in slow proliferating tissue, the graphic in Figure 3 (slow proliferating tissue) is not as smooth as Figure 2 (fast proliferating tissue). Trend of the graphic of slow proliferating tumor is not as the same as the fast proliferating tumor. BED tumor in slow proliferating tumor will increase steeply in the early of the treatment time, but after some time the BED tumor will be more sloped. It is due to the long kick-off time of the slow proliferating tumor, hence the BED tumor will not decrease until it reaches the kick-off time of tumor which is 300 days, but as the time goes by, the increasing of the treatment time will not be more effective as in the early treatment time in order to prevent the loss of the healthy tissue functionality or the appearance of the new tumor.
Figure 4 and 5 show the dose per fraction of the slow proliferating tissue and fast proliferating tissue. In the treatment of fast proliferating, it is shown that the dose will be delivered every day to optimize the radiotherapy, but in the slow proliferating tumor the best dose per fraction is not delivered every day, but 2 or 3 days per fraction, known as hyperfractionation. In the slow proliferating tumor, the given dose is a maximum dose that can be given in the linear-quadratic formulation which is 5 Gy, while in the fast proliferating tissue the dose per fraction is around 2-3 Gy per fraction which is a normal dose for standard fractionation.

3.2. Effect of parameter tumor and healthy tissue
Resensitization is a combination of repair and reoxygenation which will affect the radiosensitivity of the tumor and/or healthy tissue. This characteristic should be analyzed because it is one of the important effect of the radiotherapy scheme. As can be seen in the Figure 6 and 7, the different resensitization will have the different BED tumor. As a resensitization increases, the BED tumor will decreases, both in standard fractionation and hyperfractionation. The resensitization will change the radiosensitivity of the tumor, and makes the tumor more sensitive. Hence, as the resensitization time increases, the time for the tumor to change to be more sensitive will be longer, therefore tumor will have more resistant cell if
the resensitization time is large. Otherwise, when the resensitization time is small, the tumor will change to be more radiosensitive rapidly, therefore many tumor cell will be dead as the treatment time increases.

Figure 8 and 9 illustrate the effect of the variance in kick-off time and doubling time of the tumor respectively. As shown in those figures, both of the parameter will have not affected the BED until the treatment time pass the kick-off time of the tumor. Kick-off time will affect the BED by decreasing the BED tumor if the treatment time exceeds the kick-off time. As kick-off time increases, the BED tumor will increase longer than if the kick-off time is small. It is obvious, because if the treatment time is shorter than the kick-off tumor, there is no doubling mechanism of the cell. However, if the treatment time is longer than the kick-off tumor, there will be doubling mechanism of the tumor cell and will decrease the TCP as well as the BED tumor. The other parameter that should be considered is doubling time of the tumor. As can be seen in the Figure 9, the doubling time affects the BED tumor. The longer the doubling time of the tumor, the larger BED tumor that will be obtained. It is due to the doubling mechanism of the tumor cell accelerates the reduction of the BED tumor. If the doubling time of the tumor is 1 day, the BED tumor will go to 0 in near treatment time of 50 days, it means that there will be no reduction of the tumor cell, instead there will be an increasement of the cell tumor.

3.3. Dose per fraction

Besides the BED tumor, another important output that should be analyzed is dose per fraction. As shown in the Figure 10, there are 4 different types of the dose per fraction scheme in the fast proliferating tumor. Figure 10(a) and 10(b) are the optimum scheme for standard fractionation, which is a schedule that gives a fractionation dose one per day. As shown in the figure, every first and last day of the week, the fractionation dose is higher than the other days. It is due to the effect of the repair time and resensitization time of the tumor and healthy tissue. In the Figure 10(a), the resensitization is zero, which means the radiosensitivity of the tumor will always increase everytime. The difference between Figure 10(a) and 10(b) is that the resensitization is not zero in Figure 10(b), but 1 day. It means that the resensitization in Figure 10(b) is slower than in Figure 10(a). As a result, the dose per fraction will be lower in the middle of the week for the Figure 10(a).
On the other hand, the Figure 10(c) and 10(d) represents hyperfractionation but it has different dose per fraction. In Figure 10(c), the dose per fraction vary randomly, with a dose per fraction in first and last week is higher than the others. In constrast, Figure 10(d) has almost constant dose per fraction every day. In the Figure 10(d), the constancy the dose per fraction is due to the zero value of all the parameters (repair time and resensitization time), which means there are no difference between the mechanism of the repair and resensitization of the tumor and healty tissue. The main factor that affects the optimization is alpha and beta of the tissue which is constant for all the treatment scheme. Whereas, Figure 10(c) is affected by the repair and resensitization time of the healthy tissue, therefore the dose per fraction vary with high dose per fraction in the first and last day of the week.

4. Conclusion
Ordinary simulated annealing is not accurate to predict the BED tumor optimum of the slow proliferating tissue. The simulated annealing is then modified to increase the accuracy of the optimization method. The increasing accuracy is about 10%. The trend of the slow proliferating tumor and fast proliferating tumor is different one and another. Fast proliferating tumor will increase at the early treatment time, and then at near the kick-off time, it will decrease because of the tumor cell will doubled rapidly. While in the slow proliferating tumor, due to the long kick-off time, there will usually be no reduction in BED tumor. However, after some time, the BED tumor will remain almost constant, in order to prevent the loss of the healthy tissue functionality or the appearance of new tumor near the healthy tissue.

The mechanism of the cell when it is irradiated by radiotherapy, such as repair, repopulation, reoxygenation, and redistribution should be considered as the parameters of optimization in radiotherapy scheme. As can be seen in the Figure 6, 7, 8, and 9, all of the mechanism affect the BED tumor. The optimum BED tumor should be analyzed and calculated with consideration of the cell mechanism in order to optimize the dose perfraction as well as the BED tumor. Besides the BED tumor, another parameter that should be analyzed is dose per fraction. As can be seen in Figure 10, the cell mechanism affects the optimum dose per fraction and it should be optimized to get the optimum effect of radiotherapy.
Figure 10. Dose per fraction for different tumor and/or healthy tissue characteristics. (a) standard fractionation with repair time of healthy tissue is 12 hours and resensitization time of tumor is 0 h (b) standard fractionation with repair time of healthy tissue is 12 hours (c) hyperfractionation with healthy tissue repair time is 4 hours and resensitization of tumor is 1 day (d) hyperfractionation with healthy tissue and tumor parameter (repair and resensitization time) is zero.

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