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Determination of Fractionation Scheme Based on Repair Effect Using Equivalent Uniform Dose (EUD) Model

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Abstract

Radiotherapy treatment planning is required to obtain an optimal balance between delivering a high dose to target volume and a low dose to organ at risks. In this planning, it is also necessary to determine the appropriate fractionation scheme for each patient. One of the commonly used methods to determine the fractionation scheme is calculating the Normal Tissue Complication Probability (NTCP) and Tumor Control Probability (TCP) parameters. In this study, the Equivalent Uniform Dose (EUD) model is used to calculate NTCP and TCP. This model is based on a non-uniform dose distribution that is sensitive to the biological factors of cells. The biological factor examined in this research is the repair effect, which is the ability of cells to repair themselves after being radiated. Thus, the objective of this research is to determine the fractionation scheme based on NTCP calculations using the EUD model while taking into account the repair effect. The data used in this study were obtained from 10 patients with glioblastoma brain cancer in the form of cumulative DVH (dose-volume histogram) and total time of radiation. Based on the NTCP calculations, the average risk of organ complication for each patient appears to be close to zero, with a range of values from 2×10^{-6}% to 1×10^{-1}%. These results indicate that the treatment planning conducted is proven to be safe and there are no complications for the patients. Furthermore, based on the NTCP and TCP calculations, the best fractionation scheme is hypofractionation, which remains safe while considering the dose limit for each normal organ surrounding the target.

Keywords: Equivalent uniform dose, Fractionation scheme, Normal tissue complication probability, Repair effect

INTRODUCTION

Radiotherapy is a medical method on tumor treatment by using high energy ray and radioactive substances to halt growth tumor cells. Radiotherapy using ionizing radiation could be able ionize substances which ray goes through. In other words, ionizing radiation could form the ion and could make the tumor cells receive the ray and keep energy from the radiation to impair DNA of tumor cells resulting in death of tumor cells [1]. The impairment of DNA of these tumor cells could be lethal or sub-lethal. If the impairment is sub-lethal it means that either tumor cells or normal cells around them may repair themselves after the cells are given the ray.

Before the patients undergo the radiotherapy, treatment planning should be carried out. Treatment planning involves main consideration some of which are radiation dose prescription and dosage distribution of the ray [2]. This dosage distribution is commonly named fractionation scheme which mean administrating the total sequence of the dosage. The common fractionation scheme are standard fractionation, hypo-fractionation, and hyper-fractionation. The differences among three of them are frequency of the treatment total dosage of the treatment [3]. A good treatment planning gets tumor cells have the right dosage which mean that the tumor cells will be profusely treated while the normal organ will insignificantly be affected by the treatment.

The best fractionation scheme to minimize the side effect of the ray towards normal organ around the tumor cells is to give the effective and secure treatment to the patient by determining several

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parameters. These parameters include NTCP, normal tissue complication probability and TCP, tumor control probability. NTCP is used to count response of the surrounding normal cells while, the other parameters, TCP focuses on cessation of the tumor cells [3].

There are many ways to count NTCP and TCP. Interestingly, EUD focuses mainly on biological effect of the cells and it is easily applied with radiation technique which is often recently used [4]. EUD model simplifies the dosage of distributed radiation in three-dimensional planned treatment. Calculation in model EUD have the benefit to estimate the impact of the dosage of treatment by considering the factor of biological cell which have many types.

The four factors of biological cells after radiation process are repair, reoxygenation, repopulation, and redistribution. Among four factors mention above, repair is the most dominant and the most commonly detected in normal organ surrounding tumor cells [5]. According to previous study [6], determining the fractionation based on the effect of repair in EUD model use only the calculation of TCP. Besides, the calculation of NTCP is essential to determine fractionation to make a treatment planning carried out safe toward patients.

With the summary of determination of fractionation scheme based on repair effect using EUD model and the elaboration of limited problems mentioned, this study is to determine the ultimate fractionation scheme by calculating the repair effect using EUD model based on calculation of NTCP and TCP.

THEORY/CALCULATION

Biology cells can repair themselves after radiotherapy in certain circumstances. Therefore, fraction is necessarily made by dividing the dose. Frequency and dose of fractionation is divided into three types, one of which is standard fractionation. This type is carried out five times in a week, its treatment requires the dose as much as 1.8 Gy - 2.5 Gy. The second type is hypo-fractionation which treatment is administered once or four times in a week with the dose as much as 3 Gy - 5 Gy. The last one hyper-fractionation where the treatment is done twice a day with the dose of 1 Gy - 1.5 Gy. What should be noted in this fractionation is that the interval time between the first and second treatment should be 8 – 10 hours with the total dose is more than the standard fractionation and hypo-fractionation [3].

The concept of equivalent uniform dose assumes that two types of dose distribution can be considered equal if those two types have the same radiobiology effect [4]. That effect becomes surviving fraction where there are still surviving cell fraction after radiation.

$$SF(EUD) = SF(D_i) \tag{1}$$

During the development of the EUD model, It is divided based on assumption after cells are radiated leading to three types. The first type, cell killing based equivalent uniform dose (cEUD) and the second type, linear quadratic cell killing based equivalent uniform dose (cEUD-LQ). The last type, repair effect equivalent uniform dose (rEUD) which in this study is modified by repair [6].

In model cEUD, the assumption used is when cells are radiated by radiotherapy, radiated cells will thoroughly be corrupted because of the lethal corruption. In this EUD model, the surviving fraction equation is stated in exponential as follows:

$$SF(D_i) = \sum_i v_i e^{-\alpha D_i} \tag{2}$$

D_i, v_i components can be obtained from dose volume histogram (DVH) data to distribute uniform dose in volume of the target which indicate the amount of dose received (D_i) by sub volume (v_i). In the equation (2) only α component presents means that the calculation of this radiation only causes lethal corruption. The cEUD equation can be calculated as follows:

$$cEUD = \left| \frac{\ln SF(D_i)}{\alpha} \right| \tag{3}$$

Meanwhile in cEUD-LQ model, the assumption in LQ model shows that cells can be lethal (α) and cells around the target which is known as sub-lethal (β) cells still possible to reproduce during the treatment. The surviving fraction is cEUD-LQ model, is stated in linear quadratic model as follows:

$$SF(D_i) = \sum_i v_i e^{-\alpha D_i - \beta D_i^2} \tag{4}$$

The EUD calculation with cEUD-LQ model can be use in the following equation:

$$cEUD_{LQ} = \left| \frac{-\alpha - \sqrt{\alpha^2 - 4\beta \ln SF(D_i)}}{2\beta} \right| \tag{5}$$

Then, there is rEUD model which is modified so that it can count repair effect besides cEUD and cEUD-LQ model. This modification uses Lea-Cathcheside equation that depends on repair time of the cells after radiated and on total time of therapy. The Lea-Catcheside equation is shown as follows:

$$G(\tau_R) = 2\left(\frac{\tau_R}{T}\right)^2 \left(e^{-\frac{T}{\tau_R}} - 1 + \frac{T}{\tau_R}\right) \quad (6)$$

Lea-Catcheside parameter depends on repair time of the cells whose value specifically found in every tissue (τ_R), with total time of radiotherapy depending on fractionation scheme chosen at the process of radiotherapy (T).

The research carried out by Brenner in 1995 stated that repair effect on the calculation of surviving fraction can substitute Lea-Catcheside so that repair effect can be calculated as follows:

$$SF(d_i) = \sum_i v_i e^{-\alpha d_i - \beta G(\tau_R) d_i^2} \quad (7)$$

The calculation of rEUD model can be calculate using following equation as follows:

$$rEUD = \frac{-\alpha + \sqrt{\alpha^2 - 4\beta G(\tau_R)\ln[SF(d_i)]}}{2\beta G(\tau_R)} \quad (8)$$

Given in n times of dose fraction in radiotherapy, D_i dose distribution is stated to be equivalent dose as much as d dose in each fraction (d_i) it is determined to be equation (9) as follows [7]:

$$d_i = D_i \frac{\frac{\alpha}{\beta} + \frac{D_i}{n}}{\frac{\alpha}{\beta} + d} \quad (9)$$

As for NTCP calculation, it can be calculated through equation as follows:

$$NTCP = \frac{1}{1 + \left(\frac{TD_{50}}{EUD}\right)^{4\gamma_{50}}} \quad (10)$$

TD_{50} is the probability of complication in normal tissue amounted of 50% and γ_{50} is the slope of the response curve on 50% NTCP. While EUD value is obtained through previous equation EUD model such as cEUD, cEUD-LQ, and rEUD.

EXPERIMENTAL METHOD

The study is first carried out with radiotherapy treatment planning on 10 patients who suffers glioblastoma brain cancer in Santosa Hospital in Bandung. The treatment planning uses IMRT (intensity modulated radiation therapy) technique. The report of radiotherapy is shown in cumulative DVH and in total radiotherapy span to count NTCP in the next step. NTCP can be counted by using equation (10), after rEUD model is calculated so that effect repair can be counted. Analysis is done in NTCP calculation by using EUD model which is already modified. Variation of fractionation scheme is further calculated which produce: standard fractionation, hypo-fractionation, hyper-fractionation.

In this study, each patients receive the dose of radiation prescribed amounted 60 Gy given in in 30 fraction with 2 Gy per fraction. Meanwhile, the maximum limit dose for each organ at risk (OAR) value based on the QUANTEC recommendation is shown in table 1 as follows [8]:

Table 1. Maximum dose limit on OAR

OAR	D_{max} (cGy)
Brainstem	6000
Chiasm	5500
Optic Nerve	5500
Lens	700

The EUD and NTCP calculation is done in excel software with the parameter shown in table 2 as follows:

Table 2. Parameters to be used in NTCP calculation

Parameter	Value	Reference
d	2 Gy	[9]
TD_{50}	60 Gy	
γ_{50}	3.2	[10]
α_{lens}	0,0666 Gy^{-1}	[11]
β_{lens}	0,0572 Gy^{-2}	
$\alpha_{optic\ nerve}$	0,0586 Gy^{-1}	
$\beta_{optic\ nerve}$	0,0195 Gy^{-2}	
α_{chiasm}	0,0586 Gy^{-1}	
β_{chiasm}	0,0195 Gy^{-2}	
$\alpha_{brainstem}$	0,0491 Gy^{-1}	
$\beta_{brainstem}$	0,0294 Gy^{-2}	
τ_R	4 hours	[12]

RESULTS AND DISCUSSION

DVH curve is obtained from the treatment planning of 10 patients who suffers from glioblastoma brain cancer and whose organ normal are observed surrounding the target after the radiation. The dose data of DVH is use as an input value to count NTCP by using modified EUD model counting repair effect before deciding one of the 3 types of fraction scheme. The lowest value of 3 fractionation scheme is chosen. Graph below shows the example of DVH curve on patient 1,

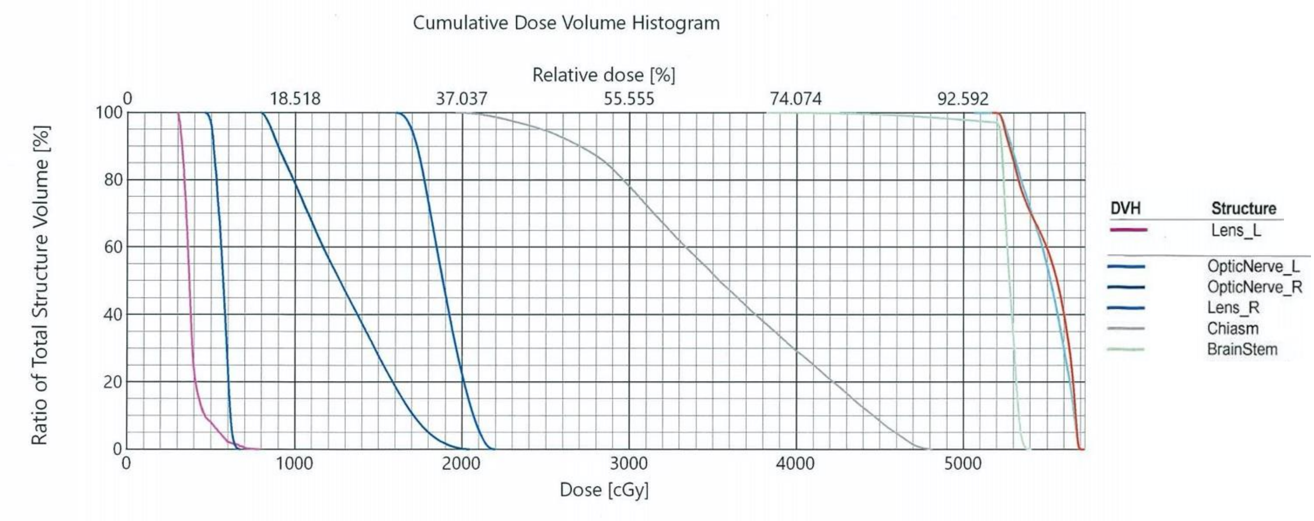

Fig. 1. Dose Volume Histogram (DVH) for patient 1

Figure 1 is example of data in DVH form from patient 1. There is difference in dose value for each normal organ surrounding the target cells. This difference is determined by the value of the radiation dose constrain OAR which is stipulated by QUANTEC stated in table 1 and by the location of tumor. As can be seen in table 3, the dose value for left and right lens of the eyes for patient 1 are different because the location of the tumor appears.

Table 3. Data of the dose values radiated to the normal organs surrounding the target from patient 1

Organ	Volume (cm^3)	Max Dose (cGy)
Left lens	0,4	794,2
Left optic nerve	0,5	2196.7
Right optic nerve	0,6	2047,9
Right lens	0,6	675,7
Chiasm	0,9	4817,1
Brainstem	18,3	5408,6

The result of the calculation of NTCP using rEUD model for each related organ can be seen on table 4. Based on table 4, the average value of NTCP of 10 patients whose organ at risk including lens, optic nerve, chiasm, and brainstem in the case of glioblastoma brain cancer is at 2 x 10^{-6} – 1 x 10^{-1} %. Those values are considered very low nearing to zero. This shows that the treatment planning which calculates with NTCP calculation using rEUD model is safe and optimal. This also indicates that the treatment planning is safe and optimal even though there's an organ receiving higher dose than the

Table 4. The result of NTCP calculation using the rEUD model

rEUD	Left Lens (%)	Right Lens (%)	Left Optic Nerve (%)	Right Optic Nerve (%)	Chiasm (%)	Brainstem (%)
Patient 1	2×10^{-7}	3×10^{-10}	2×10^{-5}	7×10^{-6}	5×10^{-2}	2×10^{-14}
Patient 2	1×10^{-7}	2×10^{-6}	2×10^{-3}	3×10^{-3}		5×10^{-10}
Patient 3	9×10^{-7}	2×10^{-8}	1×10^{-1}	2×10^{-5}	1×10^{-19}	1×10^{-4}
Patient 4	8×10^{-9}	9×10^{-10}	4×10^{-7}	4×10^{-2}	2×10^{-4}	7×10^{-11}
Patient 5	2×10^{-16}	2×10^{-19}	3×10^{-4}	6×10^{-6}	3×10^{-7}	5×10^{-13}
Patient 6	1×10^{-5}	1×10^{-5}	3×10^{-7}	1×10^{-11}	5×10^{-11}	2×10^{-7}
Patient 7	2×10^{-8}	4×10^{-7}	3×10^{-11}	4×10^{-17}	8×10^{-19}	6×10^{-9}
Patient 8	1×10^{-6}	1×10^{-6}	2×10^{-8}	2×10^{-7}	1×10^{-6}	
Patient 9	1×10^{-6}	9×10^{-1}	5×10^{-3}	2×10^{-1}	3×10^{-1}	
Patient 10	3×10^{-7}	1×10^{-3}	2×10^{-2}	8×10^{-1}	5×10^{-5}	4×10^{-14}
Average	$\mathbf{2 \times 10^{-6}}$	$\mathbf{9 \times 10^{-2}}$	$\mathbf{1 \times 10^{-2}}$	$\mathbf{1 \times 10^{-1}}$	$\mathbf{4 \times 10^{-2}}$	$\mathbf{2 \times 10^{-5}}$

administered dose stipulated by QUANTEC. For example, the left lens of patient 1 who received dose as much as 794.2 cGy considered safe although it exceeds the safe limit which is 700 cGy.

In this study, the fraction scheme is determined considering no complication surrounding the target is found and sufficient dose to corrupt the target cells so that this fraction scheme is optimal based on the least NTCP value calculated using rEUD.

Table 5. Determination of fractionation scheme based on NTCP calculation results for patient 1

Patient 1	rEUD		
	Standard Fractionation (%)	Hypo-fractionation (%)	Hyper-fractionation (%)
Left Lens	2×10^{-7}	7×10^{-8}	3×10^{-7}
Left Optic Nerve	9×10^{-5}	2×10^{-5}	2×10^{-4}
Right Optic Nerve	1×10^{-5}	2×10^{-6}	2×10^{-5}
Right Lens	3×10^{-10}	1×10^{-10}	8×10^{-10}
Chiasm	5×10^{-2}	4×10^{-3}	5×10^{-2}
Brainstem	2×10^{-14}	4×10^{-7}	1×10^{-12}

Based on table 5, on patient 1 case, the result of calculation based on the least NTCP value fractionation scheme is hypo-fractionation for left lens, right lens, left optic nerve, right optic nerve, and chiasm, while for brainstem is standard fractionation. In patient 3 until patient 10, the result of fraction scheme is the same as that of patient 1.

Table 6. Determination of fractionation scheme based on NTCP calculation results for patient 2

Patient 2	rEUD		
	Standard Fractionation (%)	Hypo-fractionation (%)	Hyper-fractionation (%)
Left Lens	2×10^{-6}	6×10^{-8}	2×10^{-7}
Left Optic Nerve	1×10^{-2}	4×10^{-4}	4×10^{-3}
Right Optic Nerve	2×10^{-2}	7×10^{-4}	7×10^{-3}
Right Lens	3×10^{-5}	1×10^{-6}	5×10^{-6}
Chiasm	-	-	-
Brainstem	7×10^{-11}	2×10^{-18}	3×10^{-10}

Meanwhile, based on table 6, on patient 2 case, the optimal fractionation scheme is hypo-fraction for all the organs including left lens, right lens, left optic nerve, right optic nerve, and brainstem but the chiasm organ is not the main concern because it was not radiated.

In other words, there is a difference between the result of fractionation scheme on brainstem on patient 1 and patient 2. This difference of fractionation scheme depends on the different dose given to the organ and on location of the target cells. Besides, the fractionation scheme on patient 1 is fractionation standard on brainstem where the calculation of NTCP is relatively low so that fractionation scheme can be done by using hypo-fractionation. To note, another study done in Netherland stated that hypo-fractionation on brainstem can be done as long as within the dose limit and within the briefest treatment time [13]. Thus, this study stated that hypo-fractionation is safe and appropriate by NTCP calculation.

This study focusing on NTCP is further study of previous study on TCP carried out by Fatimah in 2019 concludes that hypo-fractionation is the best fractionation. The good fractionation, which is the result of treatment planning, should consist of both calculation of NTCP and TCP. From both calculations, it is concluded that the best fractionation scheme is hypo-fractionation. Therefore, the best fraction for glioblastoma brain cancer is hypo-fractionation.

CONCLUSION

Radiotherapy is medical treatment on tumor using high energy ray requiring treatment planning so that the treatment can be safe and effective. Many aspects should be determined in treatment planning one of which is the fractionation scheme based on NTCP and TCP calculations. The EUD model which is modified to calculate repair effect is used in calculating the NTCP and TCP. This study which is based on the data from 10 patients suffering from glioblastoma brain cancer states in the form of DVH and total time radiation. Over all it can be concluded that:

1. The result of NTCP calculation indicates the low risk level with average range value 2 x 10^{-6} % for left lens, 9 x 10^{-2} % for right lens, 1 x 10^{-2} % for left optic nerve, 1 x 10^{-1} % for right optic nerve, 4 x 10^{-2} % for chiasm, dan 2 x 10^{-5} % for brainstem. Based on NTCP calculation the treatment planning that has been done is safe and does not have any complication to the patients. Furthermore, there are different values on NTCP calculation towards each organ because of the different dose given.
2. Based on the least NTCP value among many variations on fractionation scheme together with the TCP calculation done by Fatimah in 2019, the best fractionation scheme is hypo-fractionation for target and the normal organ surrounding the cells. This fractionation scheme is safe by considering dose limit for each normal organ surrounding the target cells.

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