Tumor Control Probability (TCP) and Normal Tissue Complication Probability (NTCP) with Consideration of Cell Biological Effect

Rany Nuraini and Rena Widita
Biophysics Research Group, Departemen of Physics Faculty of Mathematics and Natural Sciences, Institut Teknologi Bandung

Corresponding Author : ranynuraini25@gmail.com

Abstract. In radiotherapy, Tumor Control Probability (TCP) is a parameter used to calculate the percentage of tumor killing, while its effect on normal tissue damage describe by Normal Tissue Complication Probability (NTCP). Both TCP and NTCP depend on fractionation and cell biological effects such as repopulation, repair, redistribution and re-oxygenation. It also depends on the statistical distribution model used. One model that can review the biological effects of cells is the Poisson model. In this research, we modified the Poisson model by considering the four biological effects mentioned above on TCP and only the effect of repair on NTCP. The objective of this research is to investigate the most dominant effect that influences TCP value and the effect of repair on NTCP. The results show that the effect of repair and repopulation cause tumor cells cannot be erased completely while the effects of resenitization (re-oxygenation and redistribution) can facilitate tumor cells to die. It can be seen that the most dominant biological effect is the repair effect on the tumor. This effect can be minimized by reducing the length of dose delivery time. Furthermore, the repair effect on normal tissue can reduce the value of NTCP about 9% compared with other models. By using the ISO-NTCP curve we also get the spinal cord repair time after 15 hours.

1. Introduction
Generally, the purpose of radiotherapy is to remove all the tumor cells in the certain area completely, but this condition is difficult to achieve because it is impossible to give a high dose without seeing the effect on the surrounding normal tissue. There are two factors that need to be considered to maximize doses in tumor tissue. The first are the probability of tumor cells that can be controlled to the radiation dose given or better known as Tumor Control Probability (TCP). Another one is the response of normal tissue in the surrounding tumor area which is known as Normal Tissue Complication Probability (NTCP). Both TCP and NTCP depend on cell biological effects such as repopulation, repair, redistribution, and re-oxygenation [1].

The biological effects mentioned above are found in tumor tissue, whereas in normal tissue only repair effect that can be considered. Repopulation occurs due to cell proliferation. Proliferation represent the ability of cells to multiply and form the new populations. This effect important in the case of malignant tumors, namely tumors that have rapid cell multiplication [2]. Repair effect occurs in tissue that have sub-lethal damage. As it is known that beam radiation cannot distinguish between normal tissue and tumor tissue, both of them will be damaged. When the damage is not lethal damage the cell
has the possibility to repair itself. Re-oxygenation occurs in cells that experience hypoxia. If the remaining tumor cells that survive after therapy become hypoxic (lack of oxygen), then the cell becomes radio-resistant to radiation. Hypoxic cells undergoing this process will have better radiosensitivity than cells that do not experience re-oxygenation. Therefore, re-oxygenation is expected to exist in the fractionation scheme [3]. Redistribution happen when cells undergo a phase of cell division (mitosis). Giving doses in this phase can be optimized because cell tends to be radiosensitive to dose radiation. Furthermore, re-oxygenation and redistribution are usually incorporated into one parameter, namely reoxygenation [4].

In addition to cell biological effects, TCP and NTCP depend also on the statistical model used. One model that examines these biological effects is the model using Poisson distribution. This is the first model used in calculating TCP values [5]. The Poisson model has some advantages over other models, which can explain in detail the influence of biological factors on the determination of TCP. This is because the model is based on the survival fraction of cell. The survival fraction itself usually uses a well-known linear quadratic model that can be modified by adding to the four biological factors [6]. In previous study, the calculation of TCP used the Poisson model, Zaider Minerbo, and EUD model and obtained the program to calculate TCP name RADBIOMOD [7]. In this program the biological effect (repopulation, radiosensitisation, re-oxygenation) are considered but the repair effect does not take into account.

Based on this issue, the objective of this research is to modify the Poisson model by reviewing the four biological effects on TCP and only repair effect on determining the NTCP value. More specifically in cases of head and neck cancer.

2. Tumor Control Probability (TCP) and Normal Tissue Complication Probability (NTCP)

2.1. Tumor Control Probability (TCP)

The survival fraction is the key to determining the biological effects of cells on TCP value. If we take into account the biological effects of tumor cells, namely repopulation, repair, redistribution and re-oxygenation, the linear quadratic equation can be modified in the form [2].

\[
S(D) = N \exp\left[ -\alpha D - \beta G(\tau) D^2 + \frac{1}{2} \sigma^2 G(\tau) D^2 + \gamma (T - T_k) \right]
\]

where \( \sigma \) is the variance of \( \alpha, \gamma \) is repopulation tumor specific value which depend on tumor doubling time [8], \( T \) is overall treatment time, \( T_k \) is the kick off time and \( G(\tau) \) is the Lea-Catcheside function, define as follows

\[
G(\tau) = 2 \left( \frac{\tau}{\tau_R} \right)^2 \left( e^{-\tau/\tau_R} - 1 + \frac{T}{\tau} \right)
\]

with \( \tau \) is the repair/resenitization time. Thus for the Poisson model TCP define as

\[
TCP = \exp\left[ -N \exp\left[ -\alpha D - \beta G(\tau) D^2 + \frac{1}{2} \sigma^2 G(\tau_S) D^2 + \gamma (T - T_k) \right] \right]
\]

As for TCP calculations of head and neck cancer using this model, it is necessary to have the data as seen in Table 1.

| Parameters | Value      | Parameters | Value  |
|------------|------------|------------|--------|
| \( \alpha \) | 0.396 Gy\(^{-1}\) | \( T_k \)  | 28 days |
| \( \beta \)  | 0.0396 Gy\(^{-2}\) | \( T_p \)  | 3 days  |
| \( \sigma \) | 0.07       | \( \tau_R \) | 0.5 h   |
| \( \gamma \) | 0.231 days\(^{-1}\) | \( \tau_S \) | 1 days  |
2.2. Normal Tissue Complications Probability (NTCP)

The model used to calculate the repair effect on NTCP is Incomplete Repair (IR). This model suggests that when a typical cell is damaged and not completely repaired the dose per fraction (d) has been given.

It is assumed that the fraction $\theta$ decays exponentially with time $t$.

Then, the linear quadratic model is modified as follows

$$S(d,\theta) = \exp \left[ -\alpha d - \beta d^2 - n \beta h_n(\theta) d^2 \right]$$  \hspace{1cm} (4)$$

Where

$$h_n(\theta) = \left( \frac{2}{n} \theta \left[ \frac{1}{1-\theta} \right] - \frac{1-\theta^2}{1-\theta} \right)$$ \hspace{1cm} (5)$$

$$\theta = \exp(-\mu \Delta t)$$ \hspace{1cm} (6)$$

$\mu$ is the repair constant that depend on the normal tissue repair half time. Thus, using the definition of NTCP as in [9] we can obtain the NTCP value as

$$NTCP = \exp \left( -N_0 \alpha^k \exp \left( -\alpha D - \frac{\beta d^2}{n} - \frac{\beta h_n(\theta) D^2}{n} \right) \right)$$ \hspace{1cm} (7)$$

As for NTCP calculations, we considered the effect of radiotherapy in the spinal cord. It is also necessary to have the data as seen in Table 2.

| Parameters | Value | Parameters | Value |
|------------|-------|------------|-------|
| $\alpha$  | 0.0445 Gy$^{-1}$ | $N_0$  | 90.68 |
| $\beta$   | 0.0135 Gy$^{-2}$ | $k$   | 0.211 |
| $\Delta t$ | 15 h  | $\mu$  | 0.288/h |

3. Results and Discussion

3.1. TCP results

The results of TCP calculation with consideration of four biological effects for 10 patients head and neck cancer and comparison with other models are presented in Table 3 below.

| Data | TCP (%) | Margin (%) |
|------|---------|------------|
| Poisson + cell biological effect | EUD | Zaider Minerbo | Zaider Minerbo | EUD |
| 1    | 92.19   | 82.16      | 93.07      | 0.88       | 10.03 |
| 2    | 95.14   | 80.99      | 88.47      | 6.67       | 14.15 |
| 3    | 82.04   | -          | -          | -          | -     |
| 4    | 85.26   | 81.84      | 93.93      | 8.67       | 3.42  |
| 5    | 95.26   | 80.24      | 86.29      | 8.97       | 15.02 |
| 6    | 86.98   | -          | -          | -          | -     |
| 7    | 95.4    | 83.52      | 90.72      | 4.68       | 11.88 |
| 8    | 91.54   | 81.61      | 87.66      | 3.88       | 9.93  |
| 9    | 94.48   | 81.95      | 91.06      | 3.42       | 12.53 |
| 10   | 94.98   | 82.13      | 93.45      | 1.53       | 12.51 |
| Average Difference | 4.84 | 11.18 |
We can see that the average differences of TCP models that take into account the biological effects of tumor cells with others models, namely the Zaider Minerbo models is around 4.84%. The difference is classified as not too significant because both have similarities, which consider the effects of repopulation. Whereas the difference between the Poisson model which is reviewed and the EUD model looks quite large, namely 11.18%. This is because the biological effects of cells in EUD model is neglected.

On the other hand, the EUD model is depend on tissue specific parameters. The parameter $a$ (in the equation of EUD model) is a tissue specific parameter whose value is negative for tumor cells and positive for normal tissue. In this case, -8 for head neck cancer was taken in [11]. Other references state for non-aggressive tumor the value is -5 while for aggressive tumor around -50 [12]. If the tissue parameters is taken around -5 then the difference is around 4.6%, but the EUD dose is much greater than the dose given. Therefore, in this study the value of $a$ is taken at -8. The difference regarding the value of $a$ is one of the weaknesses of the EUD model. Compare to others models for TCP, this model less accurate.

**Effect of each biological effect on TCP**

The following results are the TCP results obtained from each effect and the combination of two effects by modifying the linear quadratic model.

| Data | LQ  | Repair | Repopulation | Resenitization |
|------|-----|--------|--------------|----------------|
| 1    | 100 | 96.6   | 84.41        | 98.40          |
| 2    | 100 | 97.9   | 90.11        | 99.02          |
| 3    | 100 | 91.7   | 64.95        | 96.15          |
| 4    | 100 | 93.9   | 73.02        | 96.88          |
| 5    | 100 | 97.9   | 90.19        | 99.04          |
| 6    | 100 | 94.1   | 73.74        | 97.27          |
| 7    | 100 | 98.0   | 90.47        | 99.07          |
| 8    | 100 | 96.3   | 83.10        | 91.54          |
| 9    | 100 | 97.6   | 88.59        | 98.88          |
| 10   | 100 | 97.8   | 89.72        | 98.98          |
| Average | 100 | 96.2   | 82.23        | 98.20          |

Table 4 shows that the repair effect decreases TCP about 4% while the repopulation effect has no effect at all on decreasing TCP values. This is because the tumor doubling time is 3 days while the interval between fractions of therapy is only 1 day (standard fractionation). To analyze the effects of resenitization and repopulation, the model must be combined with a repair effect. From the table it is known that when repair is combined with resenitization, TCP increases by about 2% when compared to the model that consider the repair effect only. When repair is combined with repopulation, the TCP value drops by around 14%. It can be concluded that the next effect that inhibits tumor cells to die is the repopulation effect while the effects of resenitization have an effect on accelerating tumor cell death. As for a significant reduction of the combined repopulation and repair effects caused when many tumor cells are repaired (repair time is 0.5 hours), the cell can multiply immediately (after 3 days) so the effects of radiotherapy will decrease due to these two effects. To increase the TCP value, a suitable fractionation scheme is needed.
3.2. NTCP results
The results of NTCP calculation and comparison with other models is shown in Table 5.

| Data | NTCP Poisson + Repair (%) | NTCP without Repair (%) |
|------|---------------------------|-------------------------|
| 1    | 3.64                      | 12.04                   |
| 2    | -                         | -                       |
| 3    | 4.26                      | 13.18                   |
| 4    | 3.47                      | 10.97                   |
| 5    | 3                         | 10.79                   |
| 6    | 5.5                       | 15.39                   |
| 7    | 2.6                       | 9.94                    |
| 8    | 3.2                       | 11.32                   |
| 9    | 3.01                      | 10.79                   |
| 10   | 2.8                       | 10.45                   |
| Average | 3.50                      | 11.65                   |

The results show that the average difference between NTCP model that reviews the repair effect with the EUD model and the LKB model is 9.43% and 9.56% respectively. The difference in the NTCP value is due to the EUD model and the LKB does not review the repair effect. The similarities between the three models are for the smallest NTCP value is in patient 7. This shows that for patients 7 radiation that affects the spinal cord organ is minimized. In the table above also seen when compared with the usual Poisson model, the Poisson model that reviews the repair effect decreases the NTCP value by 8.16%. This is because the effect minimize damage after radiation is given, so this effect needs to be considered.

Previously it was found that the repair effect on NTCP can reduce the value about 8 to 9%. In this case, the fractionation method used is the standard fractionation method where the interval between fractions is 24 hours. To determine whether cell in normal tissue has been repaired or not, an ISO-NTCP curve is applied to this model as shown in Figure 1.

Figure 1. The ISO-NTCP curve of Spinal Cord

The ISO-NTCP curve is a dose per fraction curve with respect to the time lag between fractions where the NTCP value tends to be the same or constant. In this study it was seen that the cell was completely repaired after 15 hours. This is indicated by the constant dose value per fraction. Therefore, for standard fractionation with a delay between fractions 24 hours, the effect of repair on normal tissue needs to be taken into account. Compared to hyper fractionation scheme, which interval between fractions of 8-10
hours the results of NTCP value is smaller. Therefore, if radiation is given with interval between fractions less than 15 hours (the cell has not fully recovered), then the possibility of normal tissue damage will increase.

3.3. Repair effect on radiotherapy
From the results of above, the most dominant effect on the calculation of TCP and NTCP is the repair effect. This effect depends on the repair time, for head neck cancer cells itself around 0.5 hours as for the normal tissue (spinal cord) more than 15 hours. For more optimal therapy, the effect of repair in tumor must be minimized and the effect of repair on normal tissue must be maximized. One way to suppress the effect of repair on tumor is by:

Reduce irradiation time (dose deliver time)
Based on the research in [13], the dose delivery time will affect damage to tumor cells. The longer the dose delivery time, the more cells that experience repair due to sublethal damage. But the shorter the dose delivery time, the more deadly tumor cells die. This is because before the damaged tumor cells undergo therapeutic repair has been given. As for this research, for dose deliver time 45,30, and 15 minutes the TCP value is 95.4%, 97.33%, and 99.37% respectively.

The irradiation time depends on the therapeutic technique taken. For head and neck cancer usually used IMRT where the duration of irradiation is about 15-45 minutes. The reduction of irradiation time has no effect on the normal tissue around it due to the total dose delivered remain constant. This research can be used as a reference for hospitals in providing radiation therapy to patients where the duration of dose deliver time needs to be considered to suppress the repair effect on the tumor.

Increase the dose per fraction
The second method is increasing the dose given. This can increase the TCP value but consequently it will increase the dose in normal tissue. In the end we need to plan again and analyze the DVH data so that it can be determined how much the NTCP value is. Further research is also needed to optimize the dosage in the tumor by minimizing the dose increase in the surrounding tissue.

4. Conclusion
The biological effect in calculation of TCP and NTCP value need to be considered. The repair effect on NTCP can decrease the value about 8%. Based on the NTCP IR model for spinal cord, normal tissue can be repair after 15 hours. So that the repair effect on standard fractionation must be taken into account in order to minimize damage to the spinal cord. The repair effect also is the most dominant effect on tumor cell. To minimize this effect, the irradiation time must be shorter than the repair time of tumor cells.

References
[1] Cappuccio A, Herroro M A and Nuñez L 2009 Tumour Radiotherapy and Its Mathematical Modelling Conteporary Mathematics 492 77
[2] Brenner David J, et al 1995 A Convenient Extension of The Linear-Quadratic Model to Include Redistribution and Reoxygenation International Journal Radiation Oncologi, Biology, Physics 32(2) 379-390
[3] Richard A Popple, Roger Ove and Sui Shen 2001 Tumor Control Probability for Selective Boosting of Hypoxic Subvolume, Including the Effect of Reoxygenation International Journal Radiation Oncologi, Biology, Physics 54(3) 921–927
[4] Kallman R 1997 Facts and Models Applied to Tumor Radiotherapy, International Journal Radiation Oncologi, Biology, Physics 5 1103-1109
[5] Tucker S L et al 1990 How well is the probability of tumor cure after fractionated irradiation described by Poisson statistics Radiation Research 124 273-282

[6] Yang Y and Lei Xing 2005 Optimization of radiotherapy dose-time fractionation with consideration of tumor American Association of Physicists in Medicine, Medical, Physics 32 3666

[7] Joe H Chang et al 2016 RADBIOMOD: A simple program for utilising biological modelling in radiotherapy plan evaluation Physica Medica 32 248–254

[8] Zaider M and Minerbo G N 2000 Tumour control probability: a formulation applicable to any temporal protocol of dose deliver Phys. Med. Biol. 45 279–293

[9] Kehwar T S 2005 Analytical approach to estimate normal tissue complication probability using best fit of normal tissue tolerance doses into the NTCP equation of the linear quadratic model (Department of Radiation Oncology, Postgraduate Institute of Medical Education and Research Chandigarh)

[10] Levin, et al 2000 Effect of Incomplete Repair On Normal Tissue Complication Probability In The Spinal Cord Int. J. Radiation Oncology Biol. Phys. 46(3) 631–638

[11] Wu Qiuwen, et al 2002 Optimization of Intensity-Modulated Radiotherapy Plans Based on The Equivalent Uniform Dose Int. J. Radiation Oncology Biol. Phys. 52(1) 224–235

[12] Wu Qiuwen, et al 2005 Dose sculpting with generalized equivalent uniform dose Medical Physics 32 1387

[13] Sharon, et al 2012 An Estimation of Radiobiological Parameters for Head and Neck Cancer Cells and Clinical Implications Cancers 4(2) 566-580