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Modeling and Simulation of the Effect of Radiotherapy on Nasopharyngeal Tumor Volume with the Fourth Order Runge-Kutta Method

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ABSTRACT
Cancer that is benign is often known as a tumor. Currently cancer is a disease that causes death in the world. Cancer can attack all human organs including the nasopharynx. Nasopharyngeal cancer occupies the top 10 most cancers in Indonesia. Various methods have been used to treat cancer, one of which is radiotherapy. The dose of radiotherapy using a fractionated dose and a dose fraction for nasopharyngeal cancer of 1.6 Gy-2.2 Gy. The dosing must consider many things, such as the patient's condition, the duration of treatment and the dose of therapy. Due to the complexity of the metabolic processes of tumor cells, so far it has not been able to reveal the changes in detail. In this research, using mathematical modeling for clinical treatment including cancer treatment. In this study, the modeling used was Gompertz tumor growth and Linear Quadratic (LQ) radiotherapy model. Modeling uses the Rungge-Kutta Order 4 method to solve differential equations and has a higher accuracy than the Heun method. The model was applied to 13 clinical data of nasopharyngeal cancer patients. The results of this study indicate validation with a high level of accuracy using the analysis of the Root Mean Square Error (RMSE) and Mean Absolute Percentage Error (MAPE). RMSE and MAPE were best in 12 patients with values of 0.96 and 2.31%. All models of the 13 patients were consistent with clinical data. Therefore, this mathematical model can be used as a reference for radiotherapy planning models in hospitals.

Keywords: *Cancer, Tumor, Radiotherapy, Runge Kutta Order-4, Dose*

1. INTRODUCTION

Tumor is a general term for an abnormal lump in certain organs. Tumor cell growth occurs abnormally in the body, both those that are benign (benign) and those that are malignant (malignant). Cancer is a term for tumor cells that have malignant properties. Cancer cells grow rapidly and out of control. Some organs are susceptible to cancer [1]. Cancer is one of the leading diseases in the world. In 2018 there were 18.1 million new cancer cases and 9.6 million of which died from cancer occurred globally [2]. Based on preliminary data on cancer diagnosis in 2008-2014 based on Dr.. Sardjito hospital with the top 10 diagnoses of nasopharyngeal cancer ranks fourth with 745 cases [3]. Several treatment methods that can be used for cancer therapy are hormone therapy, surgery, immunotherapy, chemotherapy and radiotherapy. Radiotherapy or radiation therapy is a non-surgical therapy for curative treatment or cure of cancer. Approximately 50% required for radiotherapy annually worldwide are diagnosed with cancer [4]. Radiation therapy is administered according to a fractionated dose rule based on a radiobiological rule. Fractionation studies in radiotherapy began to be developed after it was realized that a single dose of

radiotherapy was ineffective for tumor control and had serious side effects [5]. However, not all fractionated doses provide maximum results. Apart from treating, radiation-exposed tissue has side effects, namely lethal damage (cell death), sublethal damage, and potentially lethal damage. It is also influenced by the overall treatment time and the delay in cell proliferation after irradiation [6].

The complexity of the metabolic process of tumor cells has not been able to reveal the mechanism of change in detail. Therefore, researchers describe in mathematical modeling for clinical medicine including cancer treatment. Some researchers use mathematical models to describe tumor cell development. In previous research [7] through the Gompertz equation with the introduction of simple differential equations to describe the evolution of tumor cells from solid tumor cells. However, modeling in this study is limited to simulating the growth in tumor volume.

Recently, many investigators have begun to study mathematical models of tumor response to radiation therapy [8] with simple mathematical models to simulate tumor volume growth and response to high dose single irradiation fractions. Models can be used to find biological parameters in treatment. However, there is too large a statistical uncertainty because the sample used is too small. Research was continued [9] to prepare a simple mathematical model of the distribution of tumor cells in fractional tumor radiotherapy with computer simulations. The tumor growth model of three cell components in the tumor, namely, dividing cells, non-dividing cells and quiestient cells. The Gompertz tumor model was formulated and applied to fractional radiotherapy with a set of precise parameters. However, the parameters used are limited to the general case assumption of tumor radiotherapy. So, when faced with a particular organ case, further research is needed.

The complexity of biomedical activities and the limitations of the research conditions have resulted in some of the above research models only being used for general tumor growth analysis. In addition, tumor cells also experience interactions with radiation particles in radiotherapy. Modeling and simulation are expected to be able to present an overview of the effect of radiation on tumor cell volume. So that it can be seen the length of therapy and the amount of dose required in radiotherapy to get the tumor cell volume decreases until the cells die. So, it is necessary to do research "Modeling and Simulation of the Effect of Radiotherapy on Nasopharyngeal Tumor Volume with the Rungge-Kutta Method of 4 Order ". The Runge-Kutta method is one of the most popular methods of solving differential equations. Especially the Runge-Kutta Method 4 Order which is often used in numerical calculations. The higher accuracy is the advantage of this method compared to the Euler method and the Heun method [10]. Modeling and simulation in this study are expected to determine and describe the effect of radiation dose on radiotherapy volume of nasopharyngeal tumor cells.

1.1. Cancer

Tumor is a general term for an abnormal lump in certain organs. Abnormal tumor cell growth in the body, both benign (benign) and malignant (malignant) [1]. Cancer cells continue to divide and do not maintain normal growth laws. Cancer can attack various tissues in organs, such as skin cells, liver cells, blood cells, brain cells, breast cells, lung cells, urinary tract cells, and various other body cells. Cancer occurs when cells in a part of the body start to grow and get out of control. This occurs when the DNA is damaged beyond repair [11].

1.1.1. Nasopharyngeal Cancer

Nasopharyngeal cancer grows in the cavity behind the nose and behind the roof of the mouth. Like other cancers, the cause of nasopharyngeal cancer is not certain. However, the onset of nasopharyngeal cancer is closely related to the epstein bar virus (herpes virus) [12]. Nasopharyngeal cancer is a malignant tumor of the nasopharyngeal epithelium. The disease was originally reported in 1901 and clinically characterized in 1922. Nasopharyngeal cancer is a disease with a worldwide geographical and racial distribution. It is a rare malignancy with an incidence of under 1 / 100,000 population per year in Caucasians of North America and other Western countries. The highest incidence was recorded in the Southern Chinese Population of Guangdong, the incidence was 15-25 cases per 100,000. NPC is also called "Canton tumor" in Guangdong Province [8].

1.2. Define Target Volume

Target Volume definition is a prerequisite for 3-D care for accurate dose planning and reporting. International Commission of Radiation Units and Measurement (ICRU) Report No. 50 and 62 define and describe some critical target and volume structures that aid in the care planning process. The following

volumes have been defined as the main volumes associated with 3-D treatment planning [13]:

a. Gross Tumor Volume (GTV)

GTV is the volume of the tumor that can be felt or seen the level and location of the malignant growth that is proven. GTV is usually based on information obtained from a combination of imaging modalities (computed tomography (CT), magnetic resonance imaging (MRI), ultrasound, etc.), diagnostic modalities (pathology and histology, reports, etc.) and clinical examination.

b. Clinical Target Volume (CTV)

CTV is a tissue volume containing GTV and / or subclinical microscopic malignant disease, which must be removed. This volume must be treated adequately to achieve therapeutic, healing or palliative goals. CTV often covers the area around GTV, which may contain microscopic disease and other areas that are considered risky and need treatment (for example, positive lymph nodes).

c. Internal Target Volume (ITV)

ITV consists of CTV plus internal margins. Internal margins are designed to account for variations in the size and position of the CTV relative to the patient's reference frame (usually determined by bone anatomy); that is, variations due to movement of organs such as breathing and bladder or rectal contents.

d. Planning Target Volume (PTV)

PTV is a geometric concept, for selecting the right setting and ensuring that the specified dose is completely absorbed in the CTV. PTV includes internal target margins and additional margins for regulatory uncertainty, tool tolerances, and variation outside of therapy. The PTV is linked to the processing machine's reference frame and is often described as CTV plus a fixed or variable margin (eg PTV = CTV + 1 cm).

e. Organ at Risk (OAR)

Organs at risk are organs that are sensitive to radiation so the dose received from the treatment plan may be more significant than its tolerance, requiring a change in radiation setting or a change in dose. Particular attention should be paid to organs that, although not directly adjacent to CTV, have very low dose tolerance (eg, the lens of the eye during treatment of the nasopharynx or brain tumors).

1.3. Radiotherapy

Radiation is one of the main cancer treatment options for the neck and head, glands, lungs and Hodgkin's disease. However, radiation can also be given to other types of cancer. Radiation therapy can be done either alone or in combination with surgery or chemotherapy. Therapy which has a local effect can be given internally or externally. Internally, namely in the form of radioactive implants that are inserted in the cancer area. Meanwhile, external therapy is by firing radioactive waves at cancer cells [11].

The goal of radiotherapy in general is palliative and radical treatment. Palliative treatment is applied to cases of advanced cancer to relieve symptoms, because it is inoperable and is given in a short period of 1-2 weeks. Meanwhile, radical treatment or primary therapy to shrink the tumor followed by surgery at longer intervals of 4-6 weeks [14].

Ionizing radiation consisting of electromagnetic radiation, or photons, is the type of radiation most commonly used to treat patients with radiotherapy. The damaging effects of this type of radiation arise from their ability to ionize, or remove electrons, from molecules in cells. Nearly all photons are produced by linear accelerators which have sufficient ionization energy. Most of the biological damage is done by the ejected electrons which in turn causes further ionization of the molecule which collides and slows down further. At the end of the electron trajectory, interactions with other molecules become more frequent, giving rise to ionization groups. Ionization can occur in several DNA base pairs [15].

2. MATERIALS AND METHODS

2.1. Research Materials

The equipment and materials used in this study are:

1. Notebook
2. MATLAB software version 2008b
3. Microsoft office Excel 2016 software
4. Examination data of nasopharyngeal cancer patients before and during the review of 13 patients with nasopharyngeal tumor radiotherapy at Shandong Cancer Hospital from January 2014-April 2015 [16].

2.2. Method

2.2.1. Tumor Growth Model

The tumor growth model solves the problem of describing radiation-induced tumor growth and metabolism so that it can be used to improve the optimization of radiotherapy. The tumor growth model can be described in first-order differential equations [17]:

$$\frac{dN}{dt} = f(N) \quad (1)$$

where N is the clogenic number of tumor cells or cells that proliferate i.e. the tumor volume in time t and f (N) is an appropriate function. Exponential growth is described by the differential equation [18]:

$$\frac{dV(t)}{dt} = rV(t) \quad (2)$$

where, the rate of increase in volume dV against dt with volume V (t) times the growth rate r which is assumed to be constant. Tumor interactions that occur with inhibitors and cell nutrition in the body. Both explain dynamic tumor development. These ideas generally include the logistical equation [19]:

$$V' = PV \quad (3)$$

where,

$$P = \lambda\left(1 - \left(\frac{V}{V_{max}}\right)^{\alpha}\right) \quad (4)$$

V is the rate of tumor change for the decrease in factor P from tumor volume V in the slowing down of tumor growth to Vmax which limits when the tumor grows and the tumor carrying capacity or available capacity. The breakdown of the combined deceleration α = 0 and approaches the limit in the form of Gompertz [19]:

$$P = -\lambda\alpha \log\left(\frac{V}{V_{max}}\right) \quad (5)$$

Tumor growth in the Gompertz equation acts as a two-way control process in which the tumor regulates growth or vascular suppression, and tumor blood vessels control tumor growth through nutritional function. Historically, the value of Vmax in equation (8) is the level of carrying capacity for the tumor or K (t) then [19],

$$P = -\lambda\alpha \log\left(\frac{V}{K}\right) \quad (6)$$

Equation (6) becomes:

$$V' = -\lambda V \log\left(\frac{V}{K}\right) \quad (7)$$

or:

$$V' = \lambda V \log\left(\frac{K}{V}\right) \quad (8)$$

Exponential growth kinetics can describe tumor growth well. To account for the dynamically decreasing tumor growth rate in the Gompertz equation. Where the evolution of the number of N tumor cells in volume with the growth rate ρ = λ is described by the following differential equation [20]:

$$\frac{dN}{dt} = \rho\, N\,(t) \log\left(\frac{K}{N(t)}\right) \quad (9)$$

Growth rate ρ and carrying capacity K are defined as the effective vascular support provided for the tumor as reflected by the size of the potentially sustainable tumor. With these equations, one Gompertz growth curve can be simulated for different initial tumor volumes and it is possible to describe clinical stages I to IV in one framework.

2.2.2. Radiotherapy Model

The quadratic linear model has two main components, the first is the linear component. The linear component is described as a straight line / arithmetic, which indicates that cell death is directly proportional to dose (αd). Another component illustrates that cell death is directly proportional to the square of the dose (βd2), which is called the quadratic component. Basic quadratic linear formula *[21]:*

$$E = D(\alpha + \beta d) \quad (10)$$

Where E is the radiation effect received by each fraction of the surviving cells. The total dose is D (n × d) and d is the dose every n fraction. Then to assume the fraction of cells that survive [21],

$$S = e^{-E} \quad (11)$$

Then equations (10) and (11) become,

$$S = e^{-n(\alpha d + \beta d^2)} \quad (12)$$

or,

$$S = e^{-(\alpha D + \beta D^2)} \quad (13)$$

when described against (t) then,

$$\frac{dS(t)}{dt} = -(\alpha D + \beta D^2)dt \quad (14)$$

The LQ model describes the cells that survive being irradiated with a radiation dose. This equation can be described in the differential equation [21]:

$$\frac{dN(t)}{dt} = -(\alpha d(t) + \beta d(t)^2)N(t) \quad (15)$$

In the radiotherapy model approach, the α / β constant is assumed to be ± 10 Gy and d is the dose per fraction. Radiation-induced cell killing is determined by the patient's radiosity parameter which refers to the susceptibility of cells to the effects of radiation. There is a negative symbol on radiotherapy indicating a reduction in tumor growth due to the radiotherapy constant. The two models were combined into a differential formula to model the patient's tumor growth during radiotherapy treatment.

$$\frac{dN(t)}{dt} = \rho\, N\,(t) \log\left(\frac{K}{N(t)}\right) - (\alpha d(t) + \beta d(t)^2)N(t) \quad (16)$$

The constant ρ has a value of 7 × 10-3 with K = 30, for α and β obtained through the estimation of Particle Swarm Optimization (PSO) programming, which is a population-based algorithm for the exploitation of individuals in search. Repetition of α and β on the PSO by providing the minimum and maximum ranges so that an accuracy of> 90% is achieved. The α and β constants that reach the best accuracy will be simulated by equation (19) with the 4th order Runge-Kutta method.

3. RESULTS AND DISCUSSION

3.1 Model Validation

The accuracy of the model with experimental data can be interpreted by the value of Root Mean Square (RMSE) and Mean Absolute Precentage Error (MAPE). The smaller the RMSE (close to 0) the RMSE value, the more accurate the prediction results will be (Suprayogi., Et al. 2014). Meanwhile, the MAPE percentage shows the best model validation [22].

Validation ith RMSE and MAPE was carried out in the last part of the simulation for the evaluation of the volume model shown in tables 4.3 and 4.5 with the best RMSE and MAPE criteria in patient 12, namely 0.96 and 2.31%. Patient 5 showed the greatest criteria for MRSE and MAPE values, namely 3.34 and 25.74%. The duration of treatment in the experiment lasted 5 days each week for 30 days. The model validation adjusted the duration and dose fraction of 2.2 Gy in experimental radiotherapy, namely the initial radiotherapy, days 1, 6, 11, 16, 21 and 26.

Table 1. Simulation Constants

Constants	Information	Value	Unit	Reference
Constants	Information	Value	Unit	Reference
N	Tumor volume	Input	cm^3	Gai.,dkk, 2017
P	Growth parameters (Growth rate which refers to changes in certain variables)	7×10^{-3}	1	Geng, 2017
K	Tumor carrying capacity or available capacity	30	cm^3	Geng, 2017
α/β	Quadratic linear component (describing cell death as directly proportional to dose)	10	Gy	Joiner, 2009
d	Dosage per fraction (daily dose given during therapy)	Input	Gy	KEMENKES, 2017
T	Time	Input	Day	KEMENKES, 2017

The best model validation and experimentation are in Figures 1. The average patient had a significant volume reduction in the late stages of treatment. The difference in decrease was due to the initial volume and different α and β values in each patient. This shows the level of diversity in the cell sensitivity of each patient to the radiation dose received.

Treatment of tumors and cancer with radiotherapy has the principle of killing or reducing cancer tissue optimally and not destroying normal tissue around cancer cells. The existence of simulation and modeling is able to provide the best for planning and optimization during radiotherapy. The dosage and duration used in radiotherapy are according to the degree of susceptibility of nearby organs to the tumor tissue and the condition of the tumor tissue. In this study, the patient with the greatest volume reduction and the fastest duration was in patient 3 with the best dose fraction of 2.2 Gy and the volume at week 6 was 5.33 cm^3. Conversely, for the smallest volume reduction with a long duration, patient 12 had the best dose of 2.2 Gy and the volume at week 6 was 30.22 cm^3.

According to the Ministry of Health [23] definitive dose of curative radiotherapy without chemotherapy for high risk (primary tumor and positive lymph nodes, including possible subclinical infiltration of primary tumors and high risk lymph nodes): 66 Gy (2.2 Gy / fraction) to 70 Gy (1 , 8-2 Gy / fraction). Whereas for low to medium risk (locations where subclinical spread is suspected): 44-50 Gy (2 Gy / fraction) to 54-63 Gy (1.6-1.8 Gy / fraction). All therapy are given 5 days a week for both primary and glandular tumors for 6-7 weeks.

The dose of radiotherapy is given gradually in fractions. The greater the dose given, the tumor shrinks rapidly. However, the dose of radiotherapy is not given directly in large quantities. According to Beyzadeoglu et al. [5] single dose radiotherapy is not effective for tumor control and has serious side effects, so fractionated doses of radiotherapy are applied. This study used hypofraction, which is a fraction dose> 2 Gy with the number of fractions per day ≤ 1, the number of fractions per week ≤ 5, the number of fractions per treatment ≤ 25-35, and the total dose <45-70 Gy. The purpose of hypofraction is generally used for palliative purposes in the management of metastatic tumors.

According to Chua [24] in his study showed that the fractionation dose was superior to a single dose in

Table 2. Results of the validation of the patients model 1-7

Constants	Patients						
	1	2	3	4	5	6	7
α	0.0149	0.0187	0.0228	0.0176	0.0208	0.0215	0.0187
β	0.00149	0.00187	0.00228	0.00176	0.00208	0.00215	0.00187
RMSE	1.85	1.94	1.97	0.89	3.34	2.22	1.88
MAPE (%)	7.58	22.85	18.34	11.35	25.74	23.58	20.76

Table 3. Results of the validation of the patients model 8-13

Constants	Patients						
	8	9	10	11	12	13	14
α	0.0188	0.0198	0.0208	0.0199	0.00285	0.00498	0.0188
β	0.00188	0.00198	0.00208	0.00199	0.000285	0.000498	0.00188
RMSE	2.01	1.75	1.87	1.97	0.96	3.77	2.01
MAPE (%)	23.22	20.68	16.63	18.34	2.31	10.22	23.22

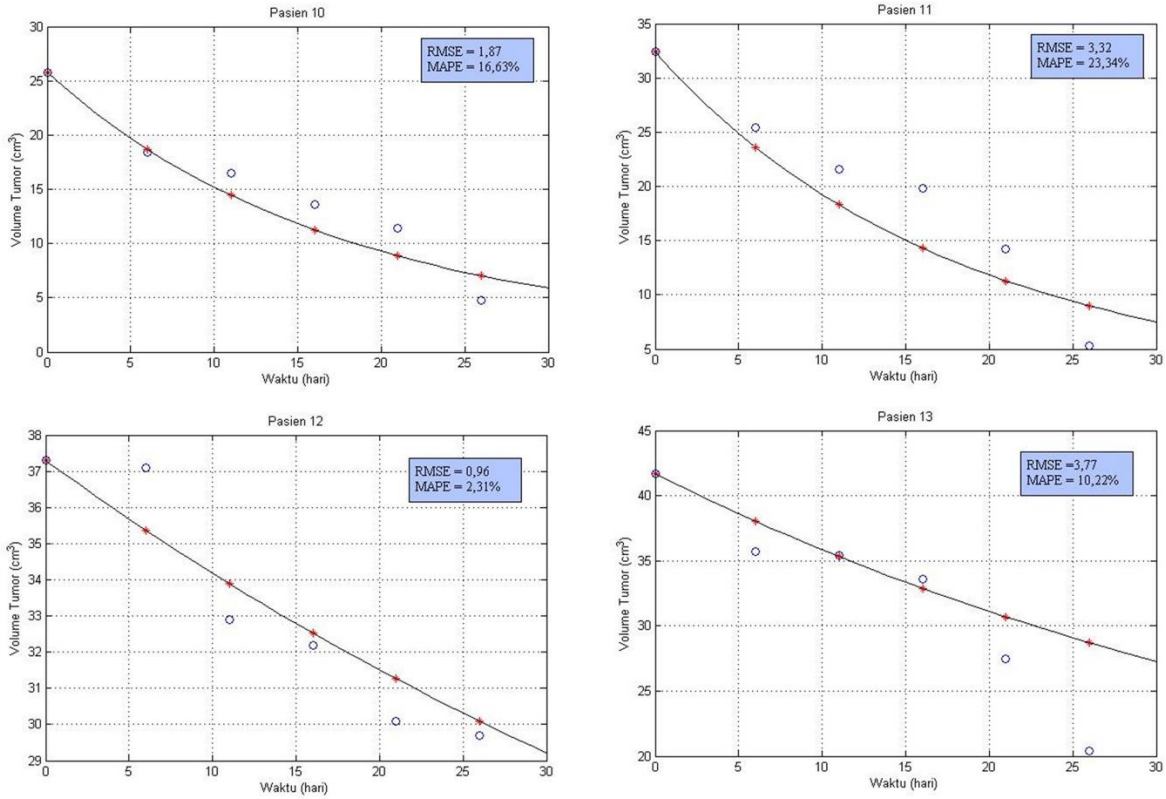

Figure 1 Simulation of Patients 10-13 Model (Solid Line) and Clinical Data (Blue Circle).

saving the local failure of nasopharyngeal carcinoma, especially in the treatment of recurrent and all-stage

disease. Records of 125 NPC patients who received median radiation dose were 12.5 Gy in single fraction and 34 Gy in 2-6 fractionation. The incidence of severe advanced complications was 33% at single dose and 21% at fractionated dose, including brain necrosis (16% and 12%) and bleeding (5% and 2%).

According to Hasan [25] radiation in biological networks is divided into three phases, namely the phases of physics, chemistry and biology. Photon ionizing radiation that hits biological tissue, initially causes a physical phase by ionization and excitation methods. Furthermore, a chemical phase occurs with the formation of free radicals. Free radicals that are formed cause biological damage by damaging DNA. Irreparable DNA damage will lead to cell death.

4. CONCLUSION

`Mathematical models of tumor growth and radiotherapy models using the Runge Kutta Order 4 method have different accuracy. The best accuracy is the best RMSE and MAPE in patient 12, namely 0.96 and 2.31%. Patient 5 showed the greatest criteria for MRSE and MAPE values, namely 3.34 and 25.74%. The duration of treatment in the experiment lasted 5 days each week for 30 days. The accuracy of all patients occupies sufficient criteria. The suitability of the model and experiment for each patient is different, this is due to various influencing factors. The biggest effect of the α and β values, the smaller the accuracy value which indicates the better the criteria for the best model.

AUTHOR CONTRIBUTION

This writing contribution is intended as an additional library to support the lecture process and the development of science and technology, especially in the fields of Medical Physics and Biophysics. Later, it can be used as a reference for tumor cell radiotherapy treatment plans.

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