

The effect of volume target on quality of radiotherapy using 3DCRT and IMRT: dosimetry and radiobiological evaluation

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Abstract: The main goal of radiotherapy is to deliver the maximum possible dose to the target volume and the minimum possible to the surrounding healthy tissue. In this study, planning was carried out on the TPS Eclipse Varian Medical System using 3DCRT and IMRT techniques for 14 cancer patients. 6 cases of lung cancer with PTV were in the range of 175.1 cc - 875.5 cc, and eight brain cancer patients with a PTV range of 148.5 cc - 841.2 cc. This study aims to determine the effect of target volume on the quality of radiation therapy planning using the 3DCRT and IMRT techniques. The evaluation was carried out using dosimetry and radiobiology analysis. Dosimetry assessment analyzes the average dose, D98, D50, D2, CI, and HI on PTV and the average dose on OAR. Radiobiological evaluation by calculating the value of TCP, NTCP, and UTCP. The results showed that based on dosimetry and radiobiology evaluation, the IMRT technique provides better planning quality for radiation therapy by increasing the probability of cancer cells dying at PTV and reducing the risk of OAR compared to planning using the 3DCRT technique. The effect of PTV on planning quality using statistical regression tests showed that PTV did not significantly impact the quality of radiation therapy planning results either using the 3DCRT technique or the IMRT technique.

Keywords: radhiotherapy, 3DRT, IMRT, dosimetry, radiobiogy

1. Introduction

Radiotherapy is a cancer healing method that uses ionizing radiation to damage cancerous tissue. Ionizing radiation is radiation of electromagnetic waves or charged particles whose energy can ionize the medium through which they pass. The main goal of radiotherapy is to provide the maximum radiation dose to the cancer cells and the minimum possible radiation to the surrounding healthy tissue. Planning is needed before radiotherapy is carried out, which is called the Treatment Planning System (TPS). TPS is a process that involves oncologists, therapists, and medical physicists to plan the most suitable radiation therapy technique for cancer patients.

Since 2002 several large hospitals in Indonesia have used 3-Dimensional Conformal Radiotherapy (3DCRT) and Intensity Modulated Radiotherapy (IMRT) techniques in radiotherapy planning for the treatment of various cancer cases. Even though many studies prove that IMRT can provide a better cure rate with a much lower risk of side effects than 3DCRT (Bakui, 2013), In some instances, radiotherapy planners still choose to use the 3DCRT technique because the treatment time is relatively shorter. At Santosa Kopo Hospital, Bandung, the handling of cancer cases with a large target volume prioritizes the use of the 3DCRT technique over the IMRT technique. Based on the experience of therapy planners for cancer cases with large tumor volumes, commonly found in cancer cases in Indonesia due to delays in diagnosis, the use of IMRT is more complex. It does not give better results than 3DCRT. Meanwhile, the 3DCRT and the IMRT techniques have no limit on the target volume size that can be treated.

Stanley conducted research on the effect of target volume on the results of radiotherapy planning in 2011. In his research, Stanley examined the effect of volume on the conformity index (CI) value in 105 patients. The results of Stanley's research stated that the target volume did not affect CI. Similar results were also obtained by Collin (2006) in his study of 82 brain cancer patients.

This study will examine the effect of target volume on the quality of the results of radiation therapy planning using the 3DCRT and IMRT techniques. The planning quality from the two techniques was obtained from dosimetry and radiobiology analysis. In addition to examining the effect of volume, the 3DCRT and IMRT techniques will be compared to determine which technique provides better planning quality.

2. Research Method

This study was conducted on 14 cancer patients with dosimetry and radiobiology evaluation using 3DCRT and IMRT techniques. This study consists of 4 main steps starting with selecting compatible lung and brain cancer patients for therapy using the 3DCRT and IMRT techniques with the same number and direction of radiation beams. The second step is making a radiation therapy plan. The results of the 3DCRT technique planning are taken from the plans made by the hospital previously. In contrast, the IMRT technique is simulated using the TPS Eclipse Varian Medical System Software using the same radiation beam settings and doses as the 3DCRT technique. Furthermore, the planning results will be evaluated by dosimetry and radiobiology analysis. Then the t-test statistic will determine the significance of the difference between the two techniques, and the F-test regression statistic will determine the effect of the target volume on planning quality.

2.1. Patients Selection

This study selected 14 cancer patients, six lung cancer patients, and eight brain cancer patients who could be treated with the same dose and radiation beam settings using the 3DCRT and IMRT techniques. The selected patients each have a different target volume. Six lung cancer patients at Santosa Kopo Hospital Bandung received radiation therapy using the 3DCRT and IMRT techniques. These six patients have PTV target volumes

ranging from 175.1 cc – 880.9 cc. The dose prescribed was 50 Gy with 2 Gy per fraction for all patients. Eight brain cancer patients received radiation therapy using the 3DCRT and IMRT techniques with PTV target volumes ranging from 148.5 cc – 841.2 cc. The dose prescribed was 2 Gy per fraction for 30 fractions for a total dose of 60 Gy for all patients.

2.2. 3DCRT Planning

The 3DCRT technique is a cancer treatment that forms a radiation beam according to the tumor's shape with the help of a multi-leaf collimator (MLC) to adjust the shape of the beam. The 3DCRT radiation therapy plan is called forward planning, where optimization is done manually. In the 3DCRT technique, required parameters are selected, such as the number of radiation beams, the beam's angle, and the beam's shape. The parameter is entered into the TPS so that the computer can calculate the results of the dose distribution. The results of the dose distribution then become the basis for radiation therapy planners to iterate over the various parameters needed to produce an optimal dose distribution.

In this study, the results of planning using the 3DCRT technique were taken from plans made at Santosa Kopo Hospital, Bandung, for 14 selected patients. Planning was made using the TPS Eclipse Varian Medical System Software available at the hospital. The patient's dicom file of the CT scanning results is inputted into the TPS Eclipse software, where the oncologist then defines the target volume by contouring the PTV and OAR.

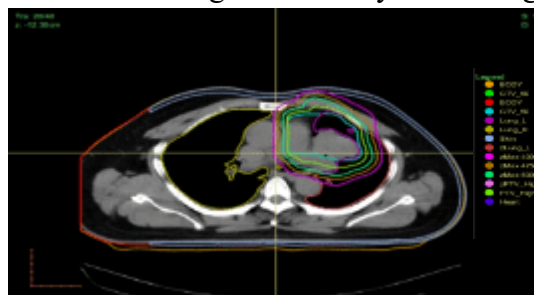


Figure 1. Volume Contours of Lung Cancer Patient

Figure 1 shows the dicom file after being contoured by an oncologist. Then the 3DCRT technique was chosen for planning. The first thing to do was to determine the user origin and isocenter and determine the number and direction of the radiation beams. It then matches MLC to the target volume structure. The dose was determined according to the prescribed's dose by the oncologist, and then a reference point around the target volume was selected. TPS will carry out calculations and normalization. If the PTV and OAR tolerance dose have met the ICRU standard, the process is continued with DVH evaluation.

Beam and dose settings in planning using the 3DCRT technique carried out by the Hospital are guidelines for planning simulations using the IMRT technique.

2.3. IMRT Planning

The IMRT technique is an extension of the 3DCRT technique in which a beam of light is divided into smaller beams to achieve accurate light intensity at each point in the tumour tissue. Unlike the 3DCRT technique, IMRT applies inverse planning. In the IMRT technique, the prescribed dose distribution is determined. Then the computer system will calculate and determine the intensity of the radiation beam to be generated according to the desired dose distribution. The planner determines the dose distribution by giving maximum and minimum dose limits for all structures, such as PTV and OAR.

The dicom file from the planning using the 3DCRT technique is used to create a simulation of the IMRT planning. The first step is to provide a dose value for PTV according to the oncologist's prescription and dose tolerance for OAR based on the Quantitative Analysis of Normal Tissue Effects in the Clinic (QUANTEC) guidelines in table 1. The OAR reviewed in this study were healthy lungs and heart for lung cancer cases as predictors of pneumonia and heart failure risk. Brainstem for brain cancer cases as predictors of the risk of cranial nerve disorders after radiotherapy.

Table 1. Normal tissue tolerance limits for standard fractionation based on QUANTEC (Emami, 2013)

OAR	Tolerance	Risk
Healthy lungs	$D_{\text{mean}} < 27 \text{ Gy}$ $V_{20} < 40 \%$	Pneumonia
Heart	$D_{\text{mean}} < 26 \text{ Gy}$ $V_{30} < 46 \%$	Heart Failure
Brainstem	$D_{\text{max}} < 54 \text{ Gy}$	Cranial Nerve Disorders

The next step is to adjust the amount and direction of the radiation beam in the same way as the 3DCRT technique that was previously planned. IMRT optimization and calculation of dose distribution. The calculation results are then evaluated if the dose distribution has been met, which has been determined previously, then the plan is approved; if not, re-optimization is carried out.

The results of planning using the 3DCRT and IMRT techniques in lung and brain cancer patients were then analyzed by dosimetry and radiobiology evaluation. Analyzed used to compare the results of radiation therapy planning using the 3DCRT and IMRT techniques, as well as investigate the effect of target volume on the planning quality of both techniques.

2.4. Dosimetry Evaluation

In this study, the data evaluated were the results of radiotherapy planning using the 3DCRT and IMRT techniques using the TPS Eclipse Varian Medical System software. Evaluation is carried out by applying the principles of radiotherapy to provide the maximum possible dose for PTV and the minimum possible dose for OAR. This study produced a plan in the form of a DVH and isodose curve, which describes the distribution of doses on the target volume and OAR. DVH analysis was performed to compare

planning results using the 3DCRT and IMRT techniques. Figure 2 shows an example of DVH, which will be analyzed in this study.

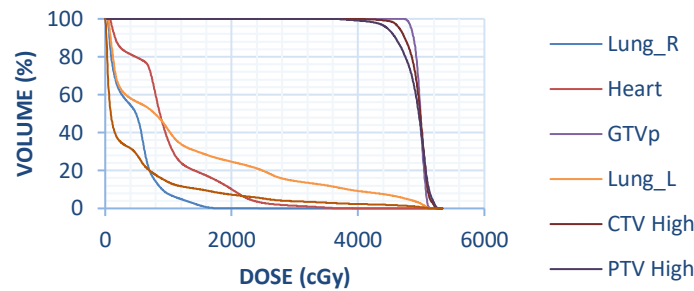


Figure 2. DVH of lung cancer results of planning using the 3DCRT technique

Based on ICRU Report 50 of 1993, the uniformity of dose distribution is expressed in the minimum and maximum doses at PTV. The maximum dose of PTV should not exceed 107% of the prescribed dose to avoid radiotherapy effects, and the minimum dose should not be less than 95%. ICRU Report 50 is a report published in the 3DCRT era. In 2010 the latest ICRU report for IMRT and complex 3DCRT planning was published. In this ICRU Report 83, near minimum (D98) and near maximum (D2) doses are introduced to replace the maximum and minimum doses for evaluating the distribution of doses in PTV. D98 and D2 represent 98%, and 2% received doses of PTV. There are no recommendation limits D98 and D2 in this report. The planner is responsible for approving the plan if it is deemed to have met the desired standards. The average dose, Dmean and D50 will also be analyzed to see if the dose distribution at 50% of the PTV is approaching the prescribed dose.

DVH can also show the distribution of doses from radiation therapy plans that have been made. However, the large number of data, curves and lines in the DVH make the analysis of radiation therapy planning complex, so an index is needed that can describe the volume of PTV covered by radiation at a specific dose and the homogeneity of the dose distribution. Two analytical tools used to evaluate radiation therapy planning are the conformity index (CI) and the homogeneity index (HI).

2.4.1. Conformity Index (CI)

To review the effects of the target volume and normal tissue irradiated in an index, Van't riet (2007) introduces a new conformity index called the conformation number (CN). The following equation calculates this CI value,

$$CI = \frac{TV_{95}}{TV} \times \frac{TV_{95}}{V_{95}} \quad (1)$$

The first part of equation (1) defines the coverage quality of the target volume, and the second part shows the normal tissue volume that received a dose greater than or equal to 95% of the prescribed dose. This CI is in the range of 0 to 1. An index value of 1 indicates an excellent CI value.

2.4.2. Homogeneity Index (HI)

Another index used for evaluation in this study is the Homogeneity Index (Yoon, 2007) which shows the homogeneity of the distribution of doses in the PTV with a mathematical formulation,

$$HI = \frac{(D_1 - D_{99})}{D_{mean}} \quad (2)$$

D99 and D1 are the doses at 99%, and 1% of PTV, and Dmean is the average dose at PTV. HI, values are in the range of 0 to 1, with values closer to zero indicating a higher degree of homogeneity.

2.5. Radiobiology Evaluation

Currently, the results of radiation therapy planning are only evaluated by dosimetric analysis. Hospitals have not used radiobiological models that describe tumour response and OAR to evaluate planning results (Deb, 2009). In this study, DVH data from the 3DCRT and IMRT techniques will also be evaluated using a radiobiological model that reviews biological effects. Calculating the Tumor Control Probability (TCP), which shows the probability of cancer cells dying after radiotherapy, Normal Tissue Complication Probability (NTCP) shows the probability of complications in OAR after radiotherapy, and therapeutic gain or Uncomplicated Tumor Control Probability (UTCP). The goal of radiation therapy is achieved when the TCP value reaches a maximum value of 100% and minimizes the NTCP value to 0%. The maximum TCP and minimum NTCP values will produce the maximum UTCP values, indicating a high probability of cancer cells dying and a low probability of normal tissue complications.

The TCP calculation is carried out by reviewing the repopulation effect using the Zaider-Minerbo model, also known as the death-birth ratio model (Zaider & Minerbo, 2000). This model is widely used in evaluating radiotherapies, such as brachytherapy and teletherapy. Zaider and Minerbo derive the TCP formula as a function of time as follows.

$$TCP = \prod_i \left[1 - \frac{P_s(T_n)e^{(b-d)T_n}}{1 - (p_s(T_n)e^{(b-d)T_n} \sum_{j=1}^n \frac{1}{p_s(T_j)} [e^{(b-d)t(T_{j+1})} - e^{(b-d)t(T_j)}])} \right]^N \quad (3)$$

With b, d is the rate of cells born and the rate of dead cells fulfilling the relationship $b - d = \gamma$, γ is a parameter indicating the doubling time of tumour cells, $N = \rho V$ is the number of cells starting from the tumour. This equation is then modified for fractionation with time interval variations for each fraction and heterogeneous dose distribution (Chang, 2016).

$$TCP = \prod_i TCP(D_i, v_i) \quad (4)$$

$$TCP = \prod_i \left[1 - \frac{P_s(T_n)e^{\gamma T_n}}{1 - (p_s(T_n)e^{\gamma T_n} \sum_{j=1}^{n-1} \frac{1}{p_s(T_j)} [e^{-\gamma t(T_{j+1})} - e^{-\gamma t(T_j)}])} \right]^{\rho v_i} \quad (5)$$

with,

$$p_s(T_j) = \exp \left[-\alpha \left(\frac{j}{n} D_i \right) - \frac{\beta \left(\frac{j}{n} D_i \right)^2}{j} \right] \quad (6)$$

and

$$t(T_j) = \frac{T_j - T_k + |T_j - T_k|}{2} \quad (7)$$

D_i is the total dose given to the sub-volume v_i , n is the fractionated amount, $p_s(T_j)$ is the survival factor of cells after the j -th fraction predicted by a linear quadratic model where α and β are radiosensitivity parameters, γ is the speed of cell repopulation, T_j is the time between the first fraction to the j -fraction, T_k is the kick-off time, and $t(T_j)$ is the number days of therapy. The Zaider Minerbo TCP model parameters used in this study are shown in table 2.

Table 2. Zaider Minerbo TCP parameter values Lung and brain cancer cases

Parameters	Value	
	Lung Cancer (Valdes, 2013)	Brain Cancer (Jones, 2007)
α	0,43	0,4 (Robinson,2015)
β	0,02	0,008
γ	0,01	0,017
ρ	10^6	10^7
T_k	14 days	28 days
T_p	67,5 days	39,46 days

In addition to calculating TCP by reviewing the target PTV volume, the probability of healthy tissue complications will also be reviewed by calculating the NTCP value. The OAR reviewed in this study were healthy lungs and heart for lung cancer cases and brainstem for brain cancer cases whose complication probabilities were calculated using the Lyman-Kutcher-Burman (LKB) NTCP model.

The Lyman model is designed to describe a uniform complication probability for all or part of an organ volume (Lyman, 1985). The rarity of normal tissue receiving uniform radiation has created several DVH reduction algorithms to change the heterogeneous to uniform dose distribution to produce the same NTCP. The effective volume method (Kutcher & Burman, 1989) is the most frequently used, accompanying Lyman's NTCP model. The combination of these formulas is known as the Lyman-Kutcher-Burman (LKB) model. The LKB formula, which is mathematical but more conceptual, was first initiated by Mohan (1992). The equation calculates NTCP based on this model,

$$NTCP = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^t e^{-\frac{t^2}{2}} dx \quad (8)$$

with,

$$t = \frac{D_{eff} - TD_{50}}{mTD_{50}} \quad (9)$$

and

$$D_{eff} = \left(\sum_i v_i D_i^{1/n} \right)^n \tag{10}$$

The NTCP of the LKB model in this study was calculated using the Radbiomod program in visual basic Microsoft Excel 2013 with the available parameters (Chang, 2016). The OAR reviewed for lung cancer cases is healthy lungs and heart. As for the case of brain cancer, OAR that is reviewed is the brainstem. There were 2 OARs reviewed for lung cancer cases, so the total NTCP of all complicated organs was calculated by the following equation (11),

$$NTCP \text{ Total} = 1 - \prod_i (1 - NTCP_i), \tag{11}$$

Where $NTCP_i$ is the NTCP value of each complicated organ.

The TCP and NTCP values are then used to determine the therapeutic gain (TG). TG is generated from the results of calculating the probability of uncomplicated tumour control or UTCP, which is generated by the equation,

$$UTCP = TCP \times \prod_i (1 - NTCP_i), \tag{12}$$

where i represents each critical organ reviewed in lung and brain cancer in this study. A high UTCP value indicates that therapy planning results in a biologically higher TG and can be considered a better therapy plan.

3. Results and Discussion

The results of this study are planning using the 3DCRT and IMRT techniques. The planning quality was determined by dosimetric and radiobiological analysis in both techniques. A comparison of PTV dosimetry evaluation results is shown in table 1.

	Lung Cancer			Brain Cancer		
	3DCRT	IMRT	P	3DCRT	IMRT	P
Dmean	50,36±1,09	50,82±0,78	0,57	60,76±1,38	61,76±0,56	0,12
D98	44,73±1,67	45,77±3,99	0,64	57,15±1,54	58,76±1,46	0,02
D50	50,78±0,98	51,05±0,79	0,72	60,86±1,40	61,94±0,67	0,11
D2	53,62±1,67	53,13±4,30	0,22	63,06±1,62	63,41±0,23	0,55
CI	0,87±0,07	0,96±0,05	0,09	0,97±0,44	0,99±0,02	0,09
HI	0,20±0,05	0,20±0,12	0,99	0,11±0,05	0,07±0,02	0,15

Table 3. Comparison of PTV dosimetry of planning results using the 3DCRT and IMRT techniques with the t-test

Table 3 shows that the IMRT technique gives higher Dmean, D98, D50, and D2 values for brain cases than the 3DCRT technique. The same was shown for lung cancer cases, except for D2, where the 3DCRT technique gave a higher score because 2 out of 6 patients had D2 above the maximum tolerated dose of 107%. The recommended ICRU Report No. 50 of 1993. These results show that the IMRT technique provides more significant cancer DNA damage than the 3DCRT technique. In addition to dose statistics that can be analyzed from DVH, PTV dosimetry evaluation is also carried out by calculating CI and HI index. Regarding CI and HI, the IMRT technique provides better PTV coverage and

homogeneity of dose distribution than the 3DCRT technique for lung and brain cancer cases.

In addition to PTV dosimetry analysis, radiotherapy evaluation also needs to be done on normal organs at risk around PTV (OAR). The OAR reviewed is healthy lungs and heart for lung cancer and brainstem for cases of brain cancer.

Table 4. Comparison of Dmean OAR planning results using the 3DCRT and IMRT techniques with the t-test

	D _{mean}		P-value
	3DCRT	IMRT	
Healthy Lung	5,27±1,43	5,20±1,70	0,84
Heart	11,75±7,33	7,37±4,85	0,03
Brainstem	13,15±13,30	12,73±7,75	0,90

Table 4 shows that the IMRT technique gave lower Dmeans for the three OARs than the 3DCRT technique, with a significant difference in Dmeans of heart. This result shows that the IMRT technique can reduce the risk of pneumonia and heart failure much better than the 3DCRT technique for lung cancer cases. Meanwhile, the IMRT technique can reduce the risk of cranial nerve disorders due to excessive doses on the brainstem for cases of brain cancer.

Determining the quality of the results of radiation therapy planning using the 3DCRT and IMRT techniques with radiobiological evaluation can be seen from the probability value of UTCP uncomplicated tumour control obtained from the TCP target volume and NTCP OAR values.

Table 5. Radiobiological comparison of planning results using the 3DCRT and IMRT techniques with the t-test

	Lung Cancer			Brain Cancer		
	3DCRT	IMRT	P	3DCRT	IMRT	P
TCP	98,56±0,88	98,94±0,97	0,45	96,43±1,7	98,02±1,0	0,01
NTCP	1,53±0,77	1,53±0,77	0,96	0,07±0,17	0,00±0,00	0,34
UTCP	97,04±0,38	97,43±1,24	0,42	96,37±1,7	98,02±1,7	0,01

Table 5 shows the results of the radiobiological analysis of lung and brain cancer cases in this study. The TCP values for these two techniques show that the IMRT technique gives a higher probability of cancer cell death than the 3DCRT technique. The average value of total NTCP for lung cancer cases using the 3DCRT technique is the same as the IMRT technique, 1,53 ± 0.77. This result means that both techniques provide the same total probability of healthy lung and heart OAR complications while protecting both organs from the risks of pneumonia and heart failure. Whereas for cases of brain cancer, the IMRT technique gives a lower NTCP value in the brainstem. This value means that

the IMRT technique can reduce the risk of cranial nerve disorder that can cause visual disturbances after radiotherapy.

UTCP is the probability of uncomplicated tumour control, indicating the quality of a radiation therapy plan by reviewing the biological effects of PTV and OAR cells. The UTCP values for lung and brain cancer cases obtained in this study showed that, based on radiobiological evaluation, the IMRT technique resulted in a better quality of radiation therapy planning than the 3DCRT technique.

Analysis of the effect of target volume on the results of radiation therapy planning using the 3DCRT technique and IMRT technique for lung and brain cancer cases using regression analysis and F-test. In this study, regression analysis was performed for lung and brain cancer cases using Dmean PTV, CI, HI, and UTCP as dependent variables and target volume as independent variables. Tables 6 and 7 display the regression equations and the significance F value of the quality of radiation therapy for lung and brain cancer cases.

	3DCRT		IMRT	
	Regression	F	Regression	F
D_{mean} PTV	$48,68 + 0,0031 x VT$	0,18	$51,69 + 0,0017 x VT$	0,16
CI	$0,79 + 0,00014 x VT$	0,17	$0,99 + 0,00008 x VT$	0,34
HI	$0,19 - 0,000008 x VT$	0,92	$0,13 + 0,00013 x VT$	0,52
UTCP	$97,64 + 0,0011 x VT$	0,52	$98,11 + 0,0013 x VT$	0,54

Table 6. Results of statistical regression tests on the results of planning radiation therapy using the 3DCRT and IMRT techniques for lung cancer cases

	3DCRT		IMRT	
	Regression	F	Regression	F
D_{mean} PTV	$60,70 + 0,00016 x VT$	0,95	$62,14 + 0,0012 x VT$	0,23
CI	$0,96 + 0,000037x VT$	0,65	$0,99 + 0,000003 x VT$	0,94
HI	$0,067 + 0,00012 x VT$	0,18	$0,086 + 0,000047 x VT$	0,29
UTCP	$100,00 + 0,013 x VT$	0,09	$97,75 + 0,0013 x VT$	0,90

Table 7. Results of statistical regression tests on the results of planning radiation therapy using the 3DCRT and IMRT techniques for brain cancer cases

Tables 6 and 7 show the regression equation for all evaluation results with a significance value of $F > 0.05$. The results of the PTV, CI, HI, and UTCP Dmean regression tests showed that for all parameters, the radiation therapy quality had a significance F value higher than 0.05. This value means that the target volume does not significantly affect the quality of radiation therapy using either the 3DCRT technique or the IMRT technique for lung and brain cancer cases.

4. Conclusion

Few conclusions were obtained based on a study conducted on 14 cancer patients using 3DCRT and IMRT techniques with dosimetry and radiobiology evaluation. The IMRT technique provides a higher dose and probability of cancer cell death, with better conformity and homogeneity in the PTV. IMRT technique also better reduces the risk of heart failure for lung cancer cases and the risk of cranial nerve disorders for brain cancer cases compared to the 3DCRT technique. There is a significant difference between the 3DCRT and IMRT techniques in Dmean of Heart, with the IMRT technique giving a lower value. This result indicates that in cases of lung cancer, the IMRT technique is more recommended to reduce the risk of heart failure after radiotherapy. There is a significant difference between the 3DCRT and IMRT techniques in UTCP and D98 PTV brains, with the IMRT technique giving a higher score. This difference means that the IMRT technique is more recommended for brain cancer cases because it gives a higher probability of cancer cells dying than the 3DCRT technique.

The results of the PTV, CI, HI, and UTCP Dmean regression tests showed that for all parameters, the radiation therapy quality had a significance F value higher than 0.05. This value means that the target volume does not significantly affect the quality of radiation therapy using either the 3DCRT technique or the IMRT technique for lung and brain cancer cases.

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