DIPONEGORO MEDICAL JOURNAL
(Jurnal Kedokteran Diponegoro)
Online : http://ejournal3.undip.ac.id/index.php/medico
E-ISSN : 2540-8844
Volume 10, Number 6, November 2021

THE EFFECT OF RADIOTHERAPY ON BLOOD COMPONENTS OF CERVICAL CANCER PATIENTS

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ABSTRACT

Background: Radiotherapy exposure is known to have a lethal effect on blood cells because hematopoietic cells are very sensitive to radiation exposure even at low doses. Cervical cancer with radiotherapy can have the effect of reducing blood cells. Blood cells that may experience the effects of radiotherapy include haemoglobin, leukocytes and platelets. **Objective:** To know the effects of radiotherapy towards blood components of cervical cancer patients. **Methods:** This study was an observational pre and post test design. Secondary data were collected from medical records in the Radiotherapy Unit of Dr. Kariadi Semarang in 2019-2020 with a total of 128 cervical cancer patients undergoing 3D radiotherapy. The statistical test used Saphiro Wilk data normality test and the result data analysis used the paired t-test and Wilcoxon test. **Results:** Hypothesis testing for Hb levels using the paired t-test showed an insignificant value of p=0.749 and p=0.141. Hypothesis test for the number of leukocytes and platelets using the Wilcoxon test. Leukocytes showed a significant value of p=0.000 and insignificant p=0.957. Platelets received a significant value of p=0.000 and p=0.000. Hb value decreased by -0.44, leukocytes by -3.5, and platelets by -84.34. **Conclusion:** There was an insignificant decrease in haemoglobin levels yet significant decrease in leukocyte and platelet counts in cervical cancer patients undergoing radiotherapy where the platelets experienced the most decrease compared to haemoglobin and leukocytes.
Keywords: *3D radiotherapy, cervical cancer, haemoglobin, leukocyte, thrombocyte.*

INTRODUCTION

Cervical cancer is the fourth most malignant disease in the world. About 90% of cases of death from cervical cancer occurred in developing countries. Based on data from Global Burden Cancer (Globocan) in 2018, the incidence of cervical cancer in Indonesia is in second place of 10.7% and the mortality rate is in third place with 10.3%.[1,2]

Radiotherapy is a therapeutic modality for cancer alongside the surgery and chemotherapy. About 50% of cancer patients receive radiotherapy during the course of their disease,[3] with an estimate that radiation therapy contributes about 40% to curative treatment.[4] Radiation used to destroy cancer cells is called ionizing radiation because it forms ions and deposits energy in the tissue cells through it. The energy deposited can kill cancer cells or cause genetic changes that lead to cancer cell death. High energy radiation can damage the genetic material of cells, such as DNA, and thus prevent the cells' ability to further divide and proliferate. Radiation can damage both normal and cancer cells, but the main goal of radiotherapy is to maximize the radiation dose to abnormal cancer cells while minimizing exposure to normal cells around cancer cells or in the irradiated area.[5]

Exposure to ionizing radiation is known to have lethal effect to blood cells because haematopoietic cells are sensitive to radiation exposure even in low doses. Cervical cancer and radiotherapy may kill blood cells, and the blood components counts will decrease.[6] Blood cells that may be influenced by radiotherapy are haemoglobin, leukocytes, and platelet cells.

The decrease of leukocytes is associated with a decrease in body immunity system that plays an important role to fight infections. If the immunity falls, the body will be prone to infections.[7] Thrombocytes have the role in coagulation. The decrease in thrombocytes is called thrombocytopenia. At the thrombocyte level of <10.000/µL, spontaneous bleeding increases. At the thrombocyte level of <50.000/µL, surgical procedures are often complicated by bleeding. At the thrombocyte level of <100.000/µL, chemotherapy and radiotherapy are given more carefully because they might worsen the thrombocytopenia and higher the risk of bleeding. Things explained above are what makes therapy in cancer in optimal.[8]

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Erythrocyte cells contain haemoglobin which has an important function of delivering oxygen from the lungs to all tissues in the body.[9] Anaemia is a state of decreasing haemoglobin to <12g /dL[10] and is one of the factors that can cause tumour cells to experience hypoxia and is considered as a tumour response to radiotherapy by reducing oxygenation to the tumour and then causing the cells to become radioresistant or the level of ionizing radiation that the organism can withstand.[11] Tumour hypoxia itself can be a contributing factor to radiotherapy unresponsiveness. Also, hypoxic tumours can cause a tendency to become more progressive and metastasize.[12]

A study on the decrease in the number of erythrocytes, leukocytes and platelets in cervical cancer patients after radiotherapy from Tutut in 2012 proved that there was a decrease in the number of erythrocyte cells, leukocytes and platelets in patients after radiotherapy. The subjects of this study were all cervical cancer patients who received radiation therapy at the Radiotherapy Unit of Dr. Moewardi Hospital period May-October 2011. In this study, external radiotherapy using Cobalt-60 was used.[13]

Nisa Azarina in her 2014 study regarding the Effects of Radiotherapy on Blood Cell Production in Patients with Ca Mammae and Ca Cervix found that platelet and leukocyte cells experienced significant changes after exposure to radiation, while erythrocyte and haemoglobin cells did not show any significant response.[14]

Retianingsing in 2017 also observed the Study of Standardization of Cobalt-60 Radiotherapy Against Blood Cell Quantity in Cervical Cancer in Sanglah Hospital, Denpasar. The results of this study showed that erythrocytes did not show a decrease, while leukocytes showed a decrease that was not very sharp or very low, Hb was constant, and neutrophils at the beginning showed an increase which then decreased.[15] This research is different from previous studies, the previous study used a Cobalt 60 radiation source and the radiation technique was not explained, while this study explained the radiation technique used was a 3-Dimensional technique which lessens the exposure to normal tissue.

METHODS

This research is an observational analytic study with the type of study before and after design. This research was conducted at Dr. Kariadi Hospital Semarang in the period of April-September 2020. The sample of the study was cervical cancer patients who had completed 3-Dimensional (3D) external radiation therapy from 2019 to September 2020. The inclusion criteria for this study were patients aged ≤ 80 years, cervical cancer patients stage 1 to 4A or no metastases occurred during the study period, and patients who had undergone 3-Dimensional external radiation technique at a dose of 50 Gray. The exclusion criteria included recidive patients, cancer in other organs, and patients with blood disorders.

The sampling method was consecutive sampling in which all subjects who meet the sample criteria will be taken until the sample size is met. The independent variable in this study was cervical cancer radiotherapy and the dependent variables in this study were Hb levels, leukocyte counts, and platelet counts. Before testing the hypothesis, the data normality test was performed using Saphiro Wilk. Normally distributed data were tested using the Paired-T Test, otherwise, data with abnormal distribution was tested using the Wilcoxon test.

Table 1. Characteristics of the research sample

	n	%
Age		
≤30	1	0.8
30-40	24	18.8
41-50	37	28.9
51-60	45	35.2
61-70	18	14.1
>70	3	2.3
Transfusion		
Yes	54	42.2
No	74	57.8
Stage		
IB	4	3.1
IIA	4	3.1
IIB	35	27.3
IIIA	4	3.1
IIIB	66	51.6
IVA	1	0.8
No details	14	10.9

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RESULTS

This research was conducted in April - September 2020 at Dr. Kariadi Hospital Semarang. The sample used had met the research requirements, the inclusion criteria and the exclusion criteria. The sample data were obtained from medical records selected by consecutive sampling, where 249 cervical cancer patients underwent external radiation therapy in 2019-2020 and only 128 respondents who met the inclusion criteria. The characteristics of the research sample are presented in Table 1.

Based on the history of transfusion, it was found that patients who had a transfusion in the middle of the radiation therapy treatment to improve the general condition of the patient. So in statistical calculations, the 54 blood component levels of the patient who received blood transfusion were only calculated from before radiation until the 10th radiation. Therefore, the total of data calculated from before radiation until the 10th radiation was 128, while the total of data calculated from the 10th radiation to the 25th radiation was 74.

Normality test for the number of leukocytes and platelets shown in Table 2. The Saphiro Wilk test on the data before, 10th, and 25th radiation, had shown abnormal distribution ($p<0.05$), so to test the hypothesis we used the Wilcoxon test. Hb level normality test showed the data was distributed normally, so to test the hypothesis we used the Paired T Test.

Table 3 showed the results of the hypothesis test of the effect of radiation on the number of leukocytes using the Wilcoxon test, it is known that there was an effect of radiotherapy on the number of leukocytes in cervical cancer patients before radiation to the 25th radiation which can be seen from a significant value of 0.000 ($p <0.05$). However, in the 10th to 25th radiation process the leukocyte count was not found any significant effect of more than 0.05.

Table 2. Result of Shapiro Wilk normality test

	Before radiation (n=128)		**10th radiation (n=128)**		**25th radiation (n=128)**	
	Mean±SD (Min – Max)	**p**	**Mean±SD (Min – Max)**	**p**	**Mean±SD (Min – Max)**	**p**
Hb	12.2±1.6 (6.9 – 15.6)	0.010*	12±1.3 (8.6 – 15.4)	0.914	11.8±1.1 (9.1 – 15.8)	0.174
Leukocyte	9.3±3.1 (1.9 – 24.2)	0.000*	5.8±2.4 (2.6 – 19.9)	0.000*	5.8±2.1 (2.5 – 14.1)	0.002*
Thrombocyte	374.7±118.2 (194 – 873)	0.000*	258.4±78.4 (105 – 494)	0.017*	290.4±73.2 (140 – 516)	0.189

*Significant ($p<0.05$)

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Table 3. Result of Wilcoxon Test in Leukocytes and Platelets Counts

		Negative Ranks		Positive Ranks		Z	p
		Mean rank	Sum of Rank	Mean Rank	Sum of Ranks		
Before radiation - 10th radiation (n=128)	Leukocyte	64.81	8037	30.33	91	-9.56	0.000*
	Thrombocyte	67.38	7816.5	28.32	311.5	-9.029	0.000*
10th radiation - 25th radiation (n=128)	Leukocyte	36.78	1397.5	38.26	1377.5	-0.054	0.957
	Thrombocyte	33	561	38.21	2140	-4.341	0.000*

*Significant (p<0.05)

The results of the hypothesis test of the effect of radiation on the platelets counts were known by using the Wilcoxon test. We found that there was an effect of radiotherapy on the platelet count in cervical cancer patients which could be seen from a significant value of 0.000, where the value is less than 0.05 (p <0.05) in before radiation up to the 25th radiation.

Based on the results of the Hb level hypothesis test using the Paired T Test in Table 4, there was no effect of radiotherapy on Hb levels in cervical cancer patients because it obtained insignificant values of 0.749 and 0.141, where the value is greater than 0.05 (p> 0.05) in the process before radiation to the 25th radiation.

To find out whether there was a decrease in haemoglobin levels, leukocyte counts, and platelet counts in cervical cancer patients underwent radiotherapy, a negative rank value was used in the Wilcoxon test, which indicates whether there was a decrease in value after conducting the research test.

From Table 5, we could know that each blood level had a decrease in value from before radiation to the 25th radiotherapy. It is also known that the platelet count had decreased the most in cervical cancer patients who underwent external radiotherapy. The total impairment loss is presented in Table 6.

Table 4. Result of Paired T Test on Hb level

	Mean±SD	p	95% Confidence Interval	
			Mean Rank	Sum of Ranks
Hb before radiation - 10th radiation (n=128)	0,046±1,626	0,749	-0,238	0,33
Hb 10th radiation - 25th radiation (n=74)	0,201±1,165	0.141	-0.069	0.471

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Table 5. Negative ranks value of Wilcoxon Test

	N before - 10th	Mean before - 10th	N 10th - 25th	Mean 10th - 25th
Hb	84	57.86	44	35.35
Leukocytes	124	64.81	38	36.78
Platelets	116	67.38	17	33

In the results of the calculation of the decrease in blood component counts in Table 6, each blood level had decreased from before radiotherapy to the 25th radiotherapy meanwhile the leukocyte and platelet counts had the value increased on the 25th radiotherapy. The largest decrease after radiotherapy in cervical cancer patients occurred in platelet levels.

Table 6. Total Decrease of Blood Components Counts

	Mean before	Mean 10th	Mean 25th	Total value of decrease
Hb	12.23	12	11.79	-0.44
Leukocytes	9.3	5.76	5.8	-3.5
Platelets	374.69	258.42	290.35	-84.34

DISCUSSION

Radiation therapy for cervical cancer involves exposure of significant volume of bone marrow to high-energy photons. The patient's ability to tolerate the therapy is determined by haematological factors that reflect the potential for stem cells in the bone marrow to repair damage and to reproduce bone marrow components.[16] Bone marrow is a radiosensitive tissue and has a strong relationship between irradiated dose and volume and the risk of hematologic toxicity. The decrease in bone marrow hematopoietic cells is associated with increased adipocyte levels and inhibition of chronic hematopoiesis,[17] as confirmed by experimental studies.[18]

Based on the hypothesis test in this study, decreased haemoglobin levels in cervical cancer patients were found to be statistically insignificant, which means that there was no effect of radiotherapy on haemoglobin levels in cervical cancer patients. The choice of therapeutic modality, such as Intensity Modulated Radiotherapy (IMRT) technique, allowing the occurrence of haematological toxicity to be minimal. This may have influenced the results of this study. In a study by Mell et al., the external contours of all pelvic bones were described in planning CT scans for all patients with cervical cancer. They were able to show that leukopenia and neutropenia ≥ grade 2 were significantly reduced in patients receiving 10 Gy for less than 90% of bone marrow (11.1 and 5.6%) compared with patients receiving 10 Gy for more than 90% of bone marrow (73.7 and 31.6%).[19]

Brixey et al. analysed hematological toxicity in patients underwent conventional radiotherapy or IMRT for gynaecological cancer. Patients receiving conventional radiotherapy developed ≥ grade 2 leukopenia compared to patients receiving IMRT.[20] This benefit was achieved without marking the bone marrow as an organ at risk during treatment

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planning, but only because of the highly conformal properties of IMRT.[21] Therefore, previous studies proved that the IMRT technique caused less hematological toxicity than conventional radiotherapy techniques. The contour of the radiotherapy planning of patients in this study was not investigated further.

Although the hypothesis was rejected, the Wilcoxon test results with negative ranks showed significant results indicating a decrease in haemoglobin levels. The results of this study are consistent with the research by Majeed et al. They found that 78% of patients had a statistically significant decrease in haemoglobin levels from before radiotherapy to mid-radiotherapy. [16] Results of the study by Serkies et al. also showed that there was a decrease in haemoglobin levels during and at the end of radiotherapy treatment.[22]

Barkati et al. hypothesized that low haemoglobin levels during treatment reflect low bone marrow reserves. Patients with low bone marrow reserve may suffer from tumours that grow under hypoxic conditions leading to infiltrative phenotypes such as uterine corpus invasion and lymph node metastases. Therefore, low haemoglobin levels, or anaemia, during treatment are a substitute for hypoxemia subclinical nature in patients leading to more invasive tumours. This hypothesis is consistent with their study which showing no improvement in disease-free survival (the interval from the date of diagnosis to the first known evidence of relapse or death) or overall survival (death due to any cause) in anaemic patients who received blood transfusions during treatment.[23] Haemoglobin levels before and during treatment have been reported to be associated with other adverse prognostic factors related with other tumours, such as tumour progression and "bulky" disease.[24]

In contrast to haemoglobin, this study found a statistically significant decrease in the number of leukocytes and platelets in cervical cancer patients, which means that there is an effect of radiotherapy on the number of leukocytes and platelets of cervical cancer patients. It was also proven statistically that there was a decrease in haemoglobin levels, leukocyte, and platelet counts in cervical cancer patients underwent radiotherapy where the platelet happened to be the most affected than the other. It has been discussed that ionizing radiation causes depression of the hematopoietic system. Several clinical studies have shown a drastic reduction in the number of leukocytes, erythrocytes, and platelets during radiotherapy.[25] It has also been proposed that radiotherapy may have immunosuppressive effects and this may increase the risk of tumour development as has been shown in various solid tumors.[26,27]

CONCLUSION

In summary, we found that there was an insignificant decrease in haemoglobin levels but a significant decrease in the number of leukocytes and platelets in cervical cancer patients underwent radiotherapy where the platelets counts dropping lower than haemoglobin and leukocytes.

Referring to the limitations of this study, it is necessary to read the medical records more carefully in order to obtain more complete data. It is also necessary to carry out further research by analysing multivariately to consider other factors that may affect the decrease in blood component levels, such as cancer stage, nutritional status, comparison of IMRT therapy modalities with conventional radiotherapy, histopathology, age, presence of metastases, comorbid diseases, as well as the possible prognosis of the patients.

Ethical Approval

Ethical Clearance statement from the Health Research Ethics Committee, Faculty of Medicine, Diponegoro University and Dr. Kariadi Semarang for this research was published on May 18, 2020. The Ethical Clearance number is 62/EC/KEPK/FK-UNDIP/V/2020.

Conflicts of Interest

All authors have no conflicts of interest to disclose.

Funding

No specific funding was provided for this article.

Author Contributions

Writing-original draft preparation, Afina Yuliani Putri; writing-review and editing, Dr. dr. Yan Wisnu Prajoko, Sp.B(K)Onk, M.Kes., dr. Julian Dewantiningrum, Sp.OG(K), M.Si.Med., and Dr. dr. Ch. H. Nawangsih P., SpRad(K)Onk.Rad.

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Acknowledgments

We thank Director of RSUP Dr. Kariadi who had given permission so that the research could be conducted and we thank Faculty of Medicine of Diponegoro University for providing advice and infrastructure.

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