

Analysis of Skin Radiation Injury after External Curative and Palliative Radiotherapy of Cervix Cancer with Linac

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Abstract

Radiotherapy is a powerful tool for tumor control and treatment for various types of cancer. Despite the technological advances, cancer patients are still experiencing skin radiation injury. It is because there is energy transference. This energy generates free ion radicals, combined with normal body chemicals and causing intracellular and molecular damage. This study analyzed the probability of the skin radiation injury experienced by cervical cancer patients after external curative and palliative radiotherapy. This research was conducted at the Hasanuddin University Teaching Hospital in the Radiology section. The instrument used LINAC 6 MV external radiotherapy with the Varian brand. The state of the cancer of the samples was stage 2 B, and 3 B. Stage 2 B indicates that cancer cells had spread to the cervical tissue, uterus, and tissues adjacent to the cervix or parametria, and stage 3 B, where cancer cells had spread to the pelvic wall and caused blockage of one of them or both ureters. Because cancer has spread, removing cancer tissue or hysterectomy cannot be done. That is why the application of the dose rate for the two stages in curative therapy did not differ, such as 6.06 Gy/min to 8.26 Gy/min. On the contrary, palliative therapy uses a dose rate of 11.06 Gy/min to 13.47 Gy/min. This dose rate is higher than the curative dose rate because this therapy aims to reduce the size of cancer that has obstructed the ureteral tract

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1. INTRODUCTION

Cancer is the uncontrolled growth of body cells and spreads to all body parts. Cancer can attack anyone, and until now there has been no clear cause for this disease, nor the right treatment. However, cancer patients are increasing day by day, and are the number 6 (six) cause of death globally and continue to increase, especially lung cancer [1]. Data from GLOBOCAN 2020 shows that worldwide in 2020, there were 19.3 million new cancer cases, and nearly 10 million cancer patients die. The highest number of cancer patients (11.4%) in new cases was breast cancer, while the smallest number of patients was gastric cancer (5.6%) [2]. In Indonesia, the incidence of cancer (136.2/100,000 population) is 8th in Southeast Asia, while in Asia it is 23rd. The highest incidence rate in Indonesia for men is lung cancer, 19.4 per 100,000 population, with an average death rate of 10.9 per 100,000 population, followed by liver cancer at 12.4 per 100,000 population with an average death rate of 7.6 per 100,000 population. For women, the highest incidence rate is breast cancer, which is 42.1 per 100,000 population, with an average death of 17 per 100,000 population, followed by cervical cancer at 23.4 per 100,000 population with an average death rate of 13.9 per 100,000 population. According to Basic Health Research data from The Ministry of Health of The Republic of Indonesia, the

prevalence of tumors/cancers in Indonesia showed an increase from 1.4 per 1000 population in 2013 to 1.79 per 1000 population in 2018. The highest cancer prevalence is in DI Yogyakarta province 4.86 per 1000 population, followed by West Sumatra 2.47 per 1000 population and Gorontalo 2.44 per 1000 population [3]. With the continued increase in the number of the cancer cases, it will also be followed by increased treatment for these diseases.

A symptom of cancer in the human body is abnormal cell growth. The growth of cells that are not in their place causes several disorders that cause discomfort to the patients, such as interfering with movement, beauty, breathing, pain, because of the encouragement of cancer cells in organs, and so on. For this reason, the medical field tries to minimize the discomfort of cancer patients through therapy, namely chemotherapy and radiotherapy.

Chemotherapy is a way of treating cancer by using chemicals that are introduced into the bloodstream, either orally or intravenously. These chemicals will circulate throughout the body to destroy metastatic cancer cells. Due to the use of chemicals in chemotherapy, metabolism and organ function of cancer sufferers will be disturbed, such as hair loss, nausea, no appetite, fever, diarrhea, etc. [4,5] In contrast to radiotherapy, radiotherapy uses ionic radiation which is directly exposed to cancer cells in a very short time. As a



result, ionic radiation in therapy has become the choice if the location and size of cancer cells are known.

Radiotherapy itself can be divided into two types, namely curative radiotherapy, which aims to kill cancer cells, and palliative radiotherapy, which is used to treat discomfort for cancer sufferers, such as difficulty breathing because cancer cells have compressed the lungs, difficulty urinating, cancer cells pressing on the urinary tract, etc. [6]. Because the goals of the two types of therapy are different, the radiation dose used is also different. Curative radiotherapy uses a higher total dose and is given over a long period of several weeks. On the other hand, palliative radiotherapy uses a smaller total dose and a shorter time, because palliative therapy aims to reduce patient discomfort. As a result, the dose of radiation exposure at each therapy time will be greater in palliative radiotherapy than in curative therapy.

Therapy using ionic radiation can be done using radiation exposure from outside, and radiation exposure from inside the body, namely radioactive material placed near cancer cells for some time [7]. When external radiation therapy is used for cancer located inside the body, the first tissue exposed is the skin. According to P. Galle and R. Paulin, exposure to a single dose of 10 Gy or more was observed to cause sunburn, and the recovery time depended on the dose [8]. The appearance of ulcers, radionecrosis, and infection were also observed. Radiation exposure for single dose greater than 5 Gy and lower than 10 Gy induces skin erythema which will heal within a single-days. When radiation exposure repeatedly occurs as in radiotherapy, the skin is observed atrophy, dryness, and changes in skin color or increased pigmentation. This skin condition is known as skin injury. The effects of skin injury can occur in both types of radiotherapy. However, from a theoretical point of view, the degree of skin injury damage depends on the dose, location of radiation exposure, fractionation time, radiation exposure time, and the angle of radiation exposure [9]. Although what affects the degree of skin injury is the radiation dose. In this study, we will analyze and compare the side effects experienced by skin tissue due to exposure to ionizing radiation on curative and palliative therapy for cervical cancer cells with external therapy using LINAC.

2. EXPERIMENTAL

The research was conducted at the Hasanuddin University Teaching Hospital in the Radiology section. The instrument used was LINAC 6 MV external radiotherapy with Varian brand. The number of samples used was 55 divided into 51 people doing curative radiotherapy and 4 people doing palliative radiotherapy. All samples were cervical cancer patients with different stages ranging from stages 2B to 3B. All samples were exposed in supine position (Figure 1).

In this study, the dose received on the skin surface (D_{max}) was calculated using equation 1 (see Figure 2 for illustration mechanism).

$$\frac{\text{Dose at cancer surface}}{\text{PDD at cancer surface}} = \frac{\text{Dose at } D_{max}}{\text{PDD at } D_{max}} \quad (1)$$

PDD is Percentage Depth Dose. For the abdomen, skin thickness reaches 28.05 mm for men and 27.40 mm for women [10]. By assuming skin thickness as the radiation depth to be traveled, it can be seen that the PDD value at that depth is 95.1

% (according to the PDD table for 90 cm SSD, field size 17 cm x 20 cm, and 6 MV electrons) [11].



Figure 1 The external radiotherapy

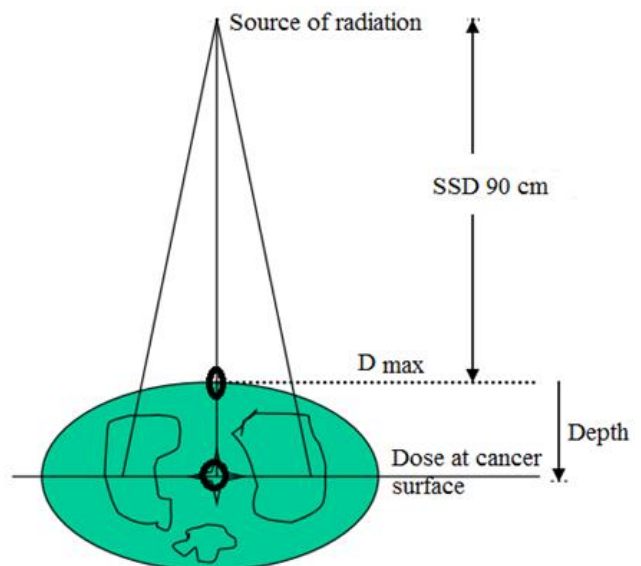


Figure 2 Illustration mechanism of the relation between radiation sources, the dose at the surface of the body patient, and the dose at the cancer target

3. RESULTS AND DISCUSSION

The average age of the sample is 51 years, the youngest is 29 years old and the oldest is 73 years old, with the highest frequency in the ages of 51 to 60 years is 45%. The frequency of young patients in the age of 29 years to 40 years is 16%, and for the elderly (61 years to 73 years) is 18%.

Stage II is the condition of the most cervical cancer patients, there are 63%, and the remaining 37% are stage III B. It is because at stage 1, the cancer cells are small and can only be seen through a microscope, even though these cancer cells have grown from the surface of the cervix to the deeper cervical tissue, so that it does not cause interference. Furthermore, the type of cancer cells of adenocarcinoma is challenging to detect at stage I [cancer council]. Cancer cells have grown outside the cervix and uterus in stage II, but have not spread to the pelvic wall or lower part of the vagina. It may cause discomfort, such as more extended periods, more

frequent occurrences, vaginal odor, or bleeding during or after sexual intercourse [12]. These are the reasons, stage II patients perform palliative therapy.

The dose used for palliative therapy is 30 Gy with 10 fractions given for 2 to 3 weeks or 20 Gy with 5 fractionations for 1 week. Fractionation is meant to give healthy tissues exposed to radiation exposure experience minimal side effects. On the contrary, the side effects on cancer cells will be maximized. For some special cases, the dose for palliative therapy is given up to 8 Gy for 1 fractionation, to shorten the treatment time. In this research, two doses were used for curative treatment; there are: 50 Gy with 25 fractionations and 70 Gy with 35 fractionations. The difference in the total dose used was due to differences in the size of the cancer, the age of the patient, and the patient's health condition. The dose given in curative therapy is higher than palliative therapy, and is given over a longer period, for example for 4 to 8 weeks or for 5 days per week.

For cervical cancer, different doses are given for curative therapy, such as for high sensitive lymphoma and germ cell tumors, a dose of 35-40 Gy is used with 15-20 fractions for 3-4 weeks, and for all types of squamous cell carcinoma a dose of 50 Gy is used with 15 fractionations for 3 weeks or 65 – 70 Gy with 30 – 35 fractionations for 6 – 7 weeks [13]. In this study, the type of cancer was adenocarcinoma, with a 50-70 Gy treatment dose with 25-35 fractionations for 5-7 weeks. Adenocarcinoma is a less common type of cervical cancer or only about 25% of total cases, and is difficult to detect because it is located in the upper part of the cervix [12].

Cervical cancer is located inside the body, so the tissue that exposed first is the skin tissue when using external radiotherapy. The skin is the body's outermost protector from heat, and regulates body heat, impact, and chemicals. The skin consists of 3 layers, the outermost layer is called the waterproof epidermis, which is the body's first protective layer and biosensor to the external environment, which consists of a layer keratinocytes. The second layer is the dermis which is just below the epidermis. This layer is a skin-strengthening layer, which is in the form of connective tissue from fibroblasts, which houses hair follicles and sweat tissue, and the deepest layer is a connective tissue composed of fat [14,15]. The skin is a tissue that is very sensitive to external disturbances, especially radiation, because the skin is easily damaged, so cells always repair tissue quickly, and also quickly mature.

In this study, the dose used in palliative therapy is 3Gy per fractionation, so the dose received by the skin surface (D_{max}) is 3.16 Gy or 0.16 Gy which is higher than the dose per fractionation in cancer cells. As well as for curative therapy, the dose used is 2Gy per fractionation, so the skin dose (D_{max}) is 2.10 Gy or 0.10 Gy higher than the fractionated dose in cancer cells. Exposure to ionic radiation in the skin, with high doses (≥ 2.0 Gy) as in radiotherapy, will cause skin tissue damage, such as inflammation. Brooks A.L. et.al. in a report on their research in the International Journal of Radiation Biology reported was written that the occurrence of tissue inflammation in the skin indicates a chromosomal aberration, due to changes in the expression of genes and proteins [16]. The same results obtained by Paulin in lymphocyte cells exposed to X-rays showed that exposure to a dose of 2 Gy made in approximately 20% of chromosomes experiencing dyscentric aberrations o/*r joining 2 chromosome [17]. These results strengthen the statement about the existence of side

effects in radiotherapy. In the long term, the effect of radiotherapy on the skin becomes dry, hyper-pigmented, peeled, thinned, atrophic, and can cause skin cancer [18, 19]. According to Salvo et al, it was observed that about 95% of radiotherapy patients had skin injury [20].

Skin injury is an injury to the skin caused by radiation exposure. There are 4 levels of skin injury, the first level is erythema, the second level is partial peeling of the skin so the skin becomes thinner, the 3rd level is the detachment of the skin, and the 4th level is the complete detachment of the skin tissue.

Exposure of ionizing radiation causes immediate damage to basal keratinocytes and hair follicle stem cells, followed by irreversible double-stranded breaks in nuclear and mitochondrial DNA and inflammation [15]. Keratinocytes are the type of cell that dominates the epidermal layer, in other words nearly 90% of the epidermal layer is keratinocyte cells. These cells originate from the deepest layer of the epidermis, that is the stratum basal that moves to the surface of the skin or the stratum corneum. The main protein present in keratinocytes is keratin. Keratin helps keratinocyte cells differentiate and move toward the stratum corneum. On the surface of the skin or stratum corneum, keratinocytes become squamous cells that are dead and do not multiply. Once the keratinocytes reach the stratum corneum, they undergo keratinization or cornification, which creates a tough outer layer of skin. Therefore, it can be concluded that keratinocyte cells play an important role in skin repair [21].

The epidermal layer damage is characterized by the presence of erythema, edema, changes in pigmentation, and peeling, thickening of the stratum corneum, loss of skin fluid, and even the loss of all layers of the epidermis [22]. Especially for cancer patients who experience exfoliation of epidermal cells, there can be a risk of infection. Repeated exposures do not give enough time for epidermal cells to make complete repair, although the remaining basal keratinocytes are stimulated to proliferate, but they are continually destroyed with each fractionated radiation treatment. Therefore, cancer patients undergoing radiotherapy will feel discomfort on the skin besides other radiotherapy effects (nausea, fever, etc.) [15]. Mendelsohn F.A. et.al. found that the immediate effects of radiation on the skin surface are ulcers due to inflammation of the tissue in the epidermal layer for the total radiation dose of radiotherapy not exceeding or approaching 30 Gy [23]. After four or five weeks, skin erythema is observed to be followed by the appearance of dry boils, characterized by itching, and melamine pigmentation in the basal layer. After two months, the inflammatory exudate and edema had subsided, leaving areas of brown pigmentation [23].

A study conducted by Ingela Turesson et. al. observed a decrease in the stratum corneum layer and an accelerated process of formation of a new one on breast cancer patients who experience radiotherapy. With a dose of 2 Gy per fraction per day for 2 weeks or a total dose of 20 Gy, it was observed that there were double-stranded breaks in the DNA of keratinocyte cells, cessation of cell growth, and apoptosis, which occurred more rapidly towards the end of therapy [24]. This condition can cause the detachment of the epidermis layer, and lead to easy infection.

Besides the epidermis, the dermis can also be affected. The dermis layer is dominated by connective tissue to support the epidermis layer, which houses hair follicles and sweat pockets, and there are also capillary blood vessels. Exposure to ionic

radiation that reaches the hair follicles will damage the hair roots and cause the hair roots to pull out, and sweat pockets which cause hair loss and dry skin, while the blood vessels will affect blood cells. [15]. In this study, a total dose of 30 Gy was given for palliative therapy. For curative therapy, the total dose given is 50 Gy and 70 Gy, and according to Mendelshon, the total radiation dose is equal to or more than 40 Gy, there will be erythema followed by wet, uncomfortable ulcers observed in the fourth week [23].

In order to reduce skin tissue damage due to exposure of ionic radiation, we use low doses, but it cannot be applied to radiotherapy. So, we use the dose rate parameter. The assumption is that at low dose rates, the biological effects of radiation exposure for normal tissues will be minimized. Although for high doses at low dose rates can cause cells to die, and cell turnover will lead to mutations, which can also cause new cancers. This is because cells have a certain cell cycle, so cells that have a short cell cycle (such as skin), will get a large number of photons (for a high dose rate), or a small number of photons (for a low dose rate). On the other hand, in cells that have longer turnover times like the liver, each cell could receive a large number of photons (for low dose rates), due to fractionation or repeated exposure. Therefore, cells may have the opportunity to repair, when low dose rates are used. In this study, the state of the cancer was stage 2 B, where cancer cells had spread to the cervical tissue, uterus, and tissues adjacent to the cervix or parametria, and stage 3 B, where cancer cells had spread to the pelvic wall, and caused blockage of one of them or both ureters. Because the cancer has spread, the removal of cancer tissue or hysterectomy cannot be done. That is why, the application of the dose rate for the two stages did not differ, such as 6.06 Gy/min to 8.26 Gy/min.

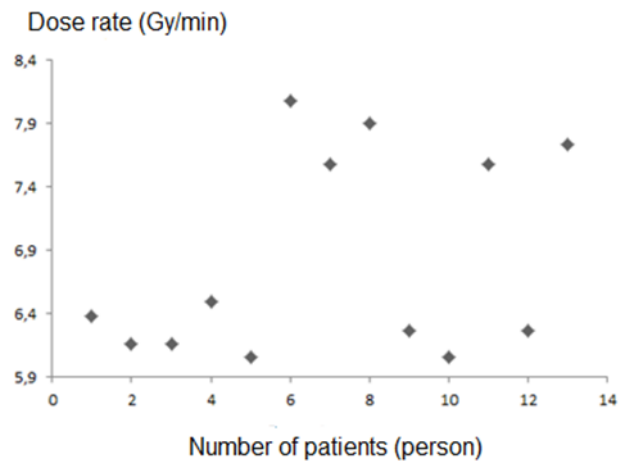
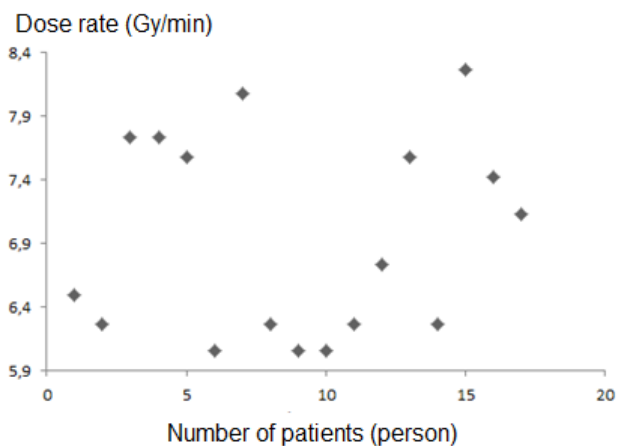


Figure 3. Dose rate for stage 2B (a) and stage 3 B (b)

On the contrary, palliative therapy uses dose rate of 11.06 Gy/min to 13.47 Gy/min. This dose rate is higher than the curative dose rate, because the aim of this therapy is to reduce the size of the cancer that has obstructed the ureteral tract. This is consistent with what was obtained by CC Ling and Steel G.G., who found that increasing the dose rate from 1 Gy/min to 10 Gy/min resulted in decreased cell survival to 0.1% and a lethal effect on cells for dose rates from 2 Gy/min [25-26].

Based on the description above, radiotherapy to treat cancer of the internal organs such as cervical cancer, will make morphologic and functional changes in the surface tissues (skin injury) as a direct result of ionizing radiation. Therefore, the therapy should not be done only by external radiotherapy, but by combining it with chemotherapy or internal radiotherapy. It is due to minimize the negative effects of radiation exposure on other healthy tissues, such as the skin, and to reduce the discomfort of cancer patients after radiotherapy. However, the preferred therapy is external radiotherapy [27-31].

4. CONCLUSION

The use of radiation in the medical field of radiotherapy has excellent benefits, especially for cancer patients. Besides killing cancer and preventing metastases, it can also relieve pain, and impair the function of other organs due to cell enlargement through palliative therapy. However, the use of large doses of radiation in a short period can cause other problems, such as skin irritation when directly exposed to radiation, such as itching, ulcers, sensitive skin, or changes in skin color. Therefore, treatment for cancer patients does not only use one type, such as external radiotherapy, but is should be combined with other therapies, such as chemotherapy and internal radiotherapy.

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