ORIGINAL RESEARCH

Incidence of radiation proctitis in cervical cancer receiving radiation therapy at Dr. Kariadi Hospital, Semarang, Indonesia

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ABSTRACT

Objective: To determine the incidence of radiation proctitis in cervical cancer patients after radiation at Dr. Kariadi Hospital, Semarang, Indonesia.
Materials and Methods: A descriptive analytic study on 356 cervical cancer patients who received radiation therapy at Dr. Kariadi Hospital Semarang from January 2017 to December 2018 who met the inclusion criteria. Factors assessed included age, BMI, hematologic, stage, histopathology, history of radical hysterectomy surgery and duration of radiation. Cervical cancer staging was assessed using FIGO 2018. Statistical analysis was performed using Mann Whitney with a significant value of $p < 0.05$.
Results: From the Chi-square analysis, the relationship between radiation period (less than 56 days and more than 56 days) ($p=0.164$), the relationship between age ≥45 and the incidence of proctitis ($p=0.208$), BMI ≥25 and the incidence of proctitis ($p=0.838$), Hb <10 with the incidence of proctitis ($p=0.492$), parity ≤1 with the incidence of proctitis ($p=0.137$), the relationship between the histopathological examination results with the incidence of proctitis ($p=0.253$), and stage level with the incidence of proctitis ($p=0.226$) were not significant. The highest incidence of proctitis occurred in stage 3B of the cervical cancer patients (14.5%).
Conclusion: The prevalence of proctitis in cervical cancer patients for the period 2017-2018 was 15.4%. Age, histopathological appearance, stage, history of anemia, history of radical surgery and appearance of symptoms after surgery with symptoms of proctitis did not show a significant relationship.

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Highlights:

1. Radiation proctitis is a post-radiotherapy concern, urging research to reduce its occurrence and improve the well-being of patients.
2. Radiotherapy is the primary treatment for advanced cervical cancer, offering hope and preserving quality of life for patients.

INTRODUCTION

Cervical cancer is an important problem for women, especially in developing countries. Cervical cancer is known as the number one killer disease for women in Indonesia. In Indonesia, in 2020, there were 213,546 new cancer cases out of 135 million women. Data from Globocan 2020 explains that the mortality rate for cervical cancer in Indonesia reaches 21,003 (9%) of the entire population.[1]

The etiology of cervical cancer is infection with oncogenic HPV subtypes (subtypes 16 and 18). Several factors that can increase the risk of cervical cancer include sexual activity at a young age, sexual activity with multiple partners, smoking, multiparity, sexually transmitted diseases, and immunosuppressant states.[2]

Cervical cancer treatment involves surgery (e.g., cervical conization or radical hysterectomy) and non-operative approaches like chemotherapy and radiation. Selection of treatment depends on the International Federation of Gynecology and Obstetrics (FIGO) stage. Patients in stage IA1 typically undergoes cervical conization, while those in IB1, IB2, IIA1, and IIA2 receive radical hysterectomy with pelvic lymphadenectomy, occasionally followed by postoperative radiation or chemoradiation. Patients in stages IIB-IIIB generally undergo chemoradiation or radiation, while those in stages IVA-IVB may receive palliative chemoradiation or palliative radiation based on individual circumstances.[3-6]

However, radiation therapy can cause several complications, including radiation proctitis. Radiation with a dose of more than 20 Gy can cause a decrease in ovarian follicular volume and activity so that it can lead to permanent infertility and ovarian dysfunction, ovarian stenosis, and cystitis. Previous studies have shown that the most common complications of radiotherapy for cervical cancer are rectal complications. This was possible because almost all patients were treated with Cobalt-60, with opposing AP/PA planes and subsequent low-dose brachytherapy involving the risk of underpacking (especially the posterior vagina) and displacement of the applicator due to the long treatment time.[7-9] There are several factors that influence the occurrence of radiation proctitis after radiotherapy in cervical cancer, including high doses radiation that can cause damage to cancer cells and one of the most commonly affected is the rectum and the most common is radiation proctitis.[8,10] The objective of this study was to determine the incidence of radiation proctitis in cervical cancer patients after radiation at Dr. Kariadi Hospital, Semarang, Indonesia.

MATERIALS AND METHODS

This was a descriptive analytic study with analytical work on 356 cervical cancer patients who received radiation therapy at Dr. Kariadi Hospital Semarang from January 2017 - December 2018 who met the inclusion criteria. The inclusion criteria included being diagnosed with cervical cancer based on histopathological examination and internal examination, having been diagnosed as a patient with cervical cancer based on vaginal touch examination, having completed 25 times external rays and three times inner rays or according to the full radiation dose (after complete radiation) and there were no complaints of blood stools (haematochezia) after complete radiation which had been confirmed by colonoscopy examination. The exclusion criteria were cervical cancer patients who did not receive radiation therapy, cervical cancer patients who received radiation therapy but not complete, patients who were not examined at the time of definitive therapy, patients who died, and patients with incomplete data.

Factors assessed included age, BMI, hematologic, stage, histopathology, history of radical hysterectomy surgery and duration of radiation. Cervical cancer staging was assessed using FIGO 2018.

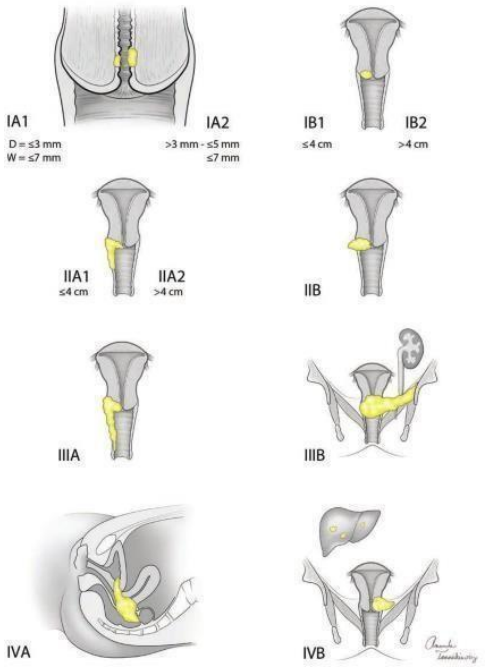

Figure 1. Cervical cancer staging based on FIGO 2018.[5]

Univariate analysis was carried out to see the characteristics. Bivariate analysis was performed to see the relationship between characteristic factors and the incidence of radiation proctitis. Data processing and analysis used SPSS program for computer. The value was considered significant if $p < 0.05$.

RESULTS AND DISCUSSION

From the data collection of cervical cancer patients who searched for treatment at Dr. Kariadi Hospital Semarang

in 2017 and 2018, there were a total of 1274 patients. From these 1274 patients, only 356 patients met the inclusion and exclusion criteria in this study. The characteristics and results of the research data analysis are shown in Table 1.

Bivariate test between mean age, histopathological appearance, stage, history of anemia, history of radical surgery and appearance of symptoms after surgery with symptoms of proctitis did not show a significant relationship (p >0.05).

From the Chi-square analysis, the relationship between radiation period of less than 56 days and more than 56 days showed p=0.164, the relationship between age 45 and the incidence of proctitis (p=0.208), BMI 25 and the incidence of proctitis (p=0.838), Hb <10 with the incidence of proctitis (p=0.492), parity ≤1 with the incidence of proctitis (p=0.137) and the relationship between the results of histopathological examination and proctitis incidence (p=0.253) all were not significant.

From these results, none of the 7 patients in the small cell and clear cell groups had proctitis. Results of Chi-square test of operated cervical cancer patients revealed p=0.799, while stage level with incidence of proctitis had p=0.226. Of the 356 patients included in this study, the highest incidence of proctitis occurred in stage 3B cervical cancer patients, comprising 39 patients (14.5%).

Table 1. Characteristics and results of research data analysis

No	Variables	n (%)	Mean ±SD	p
1	Patients' age	356 (100%)	53.73±0.5	
2	Histopathological type			0.827
	Epidermoid Ca	166 (46.6%)		
	Cervical Adeno Ca	44 (12.4%)		
	Cervical Adeno Squamous Cell Ca	139 (39%)		
	Small Cell Cervical Ca	3 (0,8%)		
	Clear Cell Cervical Ca	4 (1.1%)		
3	Stages			0.356
	Stage 1 B	7 (2%)		
	Stage 2 A	4 (1.1%)		
	Stage 2 B	63 (17.7%)		
	Stage 3 A	2 (6%)		
	Stage 3 B	269 (75.6%)		
	Stage 4 A	3 (0,8%)		
	Stage 4 B	8 (2.2%)		
4	History of Anemia			0.632
	Anemia	55 (15.44%)		
	No Anemia	301 (84.55%		
5	Average parity			0.682
	0	10 (2.8%)		
	1	28 (7.9%)		
	2	115 (32.3%)		
	3	102 (28.7%)		
	4	56 (15.7%)		
	5	26 (7.3%)		
	6	10 (2.8%)		
	7	4 (1.1%)		
	8	5 (1.4%)		
6	Previous radical operation			0.226
	Yes	11 (15.4%)		
	No	345 (84.6%)		
7	Proctitis			
	Yes	55 (15.4%)		
	No	301 (84.6%)		
8	Duration of radiation			0.699
	56 days	61 (17.13%)		
	>56 days	295 (82.8%)		
9	Body mass index	356 (100%)	22.29 ± (4.53)	0.24

Table 2. The relationship of independent variables with the incidence of proctitis

Independent variables		Dependent variables (Proctitis)		Significance (X2)
		Yes	No	
Duration of Therapy (days)	<56	8	53	0.164
	>56	47	248	
Age	≥45	50	254	0.208
	<45	5	47	
BMI	≥25	12	62	0.838
	<25	43	239	
Hb	<10	25	152	0.492
	≥10	30	149	
Parity	≤1	9	29	0.137
	>1	46	272	
Histopathology	Epidermoids and cervical adeno ca	47	294	0.253
	Small cell and clear cell	0	7	
Operation	Yes	2	9	0.799
	No	53	292	
Stages	Stage 1B	0	7	0.226
	Stage 2A	2	2	
	Stage 2B	12	51	
	Stage 3A	1	1	
	Stage 3B	39	230	
	Stage 4A	0	3	
	Stage 4B	1	7	

In this study, 918 (72%) data could not be included in the study because the data were incomplete. The analysis was made only to 28% of all existing patients. Besides, in daily life not all patients who came with complaints of haematochezia and melena underwent colonoscopy.

In patients with early-stage cervical cancer, surgery is performed and then the radicality of the operation and the results of anatomic pathology are assessed or adjuvant therapy is given in the form of radiation or a combination of chemoradiation if necessary. Meanwhile, for advanced cervical cancer, chemo-radiation is performed, the external radiation and intracavitary radiation/brachytherapy. The dose of external radiation or External Beam Radiotherapy (EBRT) is given in the range of 40-60 Gy, with fractional administration at a dose of 1.8 – 2 Gy per day. For the administration of brachytherapy, 7 Gy per administration was used.[11,12]

At Dr. Kariadi Hospital, Semarang, Indonesia, brachy-therapy is given 3 times with a dose of 7 Gy each with an interval of 1 week. While external radiation was given 2 Gy every day for 5 times every week. Several devices are used for radiation therapy. The advantages of 3D and IMRT are that targets and organs at risk can be determined more precisely, because radiation planning is done with a CT simulator. Whereas, if we use 2D tool, the simulator uses bone landmarks, so that targets and risk organs are determined from existing imaging results or determined from general anatomical locations.

From the results of this study, the minimum age was 30 years, and the highest age was 98 years. In a study by Soebagyo (1992), it was found that the 41-45 year-age group mostly underwent radiation therapy, where 32.1% received external radiation and 23.2% received radium. In a study by Widaya and Mirza (2012), the average age of patients with stage IIB - IIIB was 48 years, while the average age of cervical cancer patients who experienced recurrency was 51.49.[10] From this study, it can be seen that there was a shift in the average age, where in 1992 the average age of cervical cancer was 40.5 and the average age in 2021 was found to increase to 48 years and in this study it was 53 years. This can be used as an evaluation that the age shift is increasing, and it is assumed that there is an increase in life expectancy and problems with early detection.

According to Juergen et al. (2003), Hb level during radiotherapy is the strongest prognostic factor to describe local control and life expectancy.[13,14] Meanwhile, according to Pablo et al. (2016), anemia and examination of IHC, Growth-1 and HK-II will describe the response to therapy and are associated with low life expectancy.[15]

In this study, the mean Hb level was 10.13 (SD 4.20). At Dr. Kariadi Hospital, the Hb standard used was 10. This study only observed the effect of radiation on the incidence of anaemia, instead of the success of therapy and the survival of the cervical cancer patients. In previous research in 1992, most clinical stages were in stage IIB, where the external radiation group was 55.4% and the radium group was 44.8%, while those in stage IB was quite a lot, as much as 16.1% and 25.6%. Those in stage IIA were as much as 5.35% and 12.8%. For stage III the percentages were 17.9% and 16.8%. For stage IV, it was 5.35% and 0% ($p < 0.01$).[15]

Meanwhile, in a study at Dr. Kariadi Hospital (2012), there was a shift in the number of cervical cancer patients where most of the patients (76.2%) was in stage IIIB. In this study, the most stages were in stage IIIB, as many as 269 patients (75.6%). Interestingly, the study in 1992 found many patients in stage IB (16.1%), while this study obtained those in stage IB as much as 2% (7 cases).[15]

In this study, the most common histopathological type was squamous type, which was found in 166 cases (46.6%), not much different from adenosquamous type of 139 cases (39%). There was no significant relationship between the type of histopathology with the incidence of radiation proctitis.

In general, this type of histopathology is associated with the success rate of therapy. At Dr. Kariadi Hospital in 2012 there were 61.4% of resident cases with normal BMI status.[13] In this study, the mean BMI of 22.29 was still classified as normal. If we observed the body mass index only, there would be no shift for 3 decades in cervical cancer patients managed at Dr. Kariadi Hospital. In a study at the hospital in 2012 it was found that there was a significant relationship between radiation duration and anemia, where anemia increased the incidence of recurrent uterine cervical cancer. From this study, there was no significant relationship between the incidence of proctitis and BMI.[13]

A study showed that the recommended duration of radiotherapy is in a maximum of 55 days,[15] while other studies found no significant difference in life expectancy for total radiation less than 8 weeks and more than 8 weeks, and the lengthening of the total duration of radiation is a prognostic factor for poor outcomes in cervical cancer patients, where the ideal duration limit is less than 56 days.[16,17]

In this research, only 17.13% (61 patients) received radiotherapy for less than 56 days. When examining the association, the duration of radiation showed a statistically non-significant correlation with the occurrence of radiation proctitis. Further investigation is needed to explore the relationship between radiation duration and proctitis incidence in this study, while the proctitis rate was 15.4% when the radiation period exceeded 56 days.

Radiation proctitis is a condition in the gastrointestinal tract caused by the radiation process in the management of cervical cancer, characterized by the presence of haematochezia and or melena. Colonoscopy examination is required to determine the presence of proctitis, indicated by hyperaemic and telangiectatic surfaces of the digestive tract found.[18,19]

The radiation tolerance dose from the gastrointestinal tract, large intestine and rectum is 60-80 Gy. The pathogenesis of radiation proctitis is not known with certainty. Initially there will be mucosal injury accompanied by slow growth and tissue remodelling and then ischemia occurs. Intestinal crypt damage cannot be replaced by surface epithelial cells which are expected to produce involution crypts, resulting in mucosal injury and in the lamina propria of the intestine, an inflammatory reaction occurs which will involve T lymphocytes, macrophages, and neutrophils. Furthermore, there will be degradation of the sub-mucosa, so that there will be interference with the formation of enzymes and reactive oxygen metabolites. After the radiation is complete, regeneration will occur so that the mucosa is filled again.[20,21]

This study had several limitations, where the data collection system was obtained from incomplete and inconsistent medical records. In addition, there were patients whose management of radiation proctitis due to cervical cancer was not one-way. Data on the type of equipment used for radiation was not included, so that this study only observed the prevalence. Finally, there was no standard management of radiation proctitis cases, with the result that not all patients with complaints of melena or hematoschizia were confirmed with colonoscopy or endoscopy.

CONCLUSION

The prevalence of proctitis in cervical cancer patients for the period 2017-2018 was 15.4%. Patients' age, histopathological appearance, stage, history of anemia, history of radical surgery and symptoms of proctitis did not show a significant relationship. The continuation of this research would improve cervical cancer management services and can better understand the effects of radiation on healthy organs, especially the gastrointestinal tract. Many cases of radiation proctitis cases marked by the presence of hematoschizia by colonoscopy examination will become a problem in the management of post-radiation cervical cancer. The onset of hematoschizia is only the beginning of the occurrence of radiation proctitis which will subsequently become more severe to illeus and even rectovaginal fistula. The clinical occurrence of this radiation proctitis must be able to be diagnosed in the early stages and the causative factors should have been recognized inherent from the source of the output of radiotherapy devices. The presence of complaints of abdominal pain, diarrhea, haematochezia, and melena should be followed up with a colonoscopy or endoscopy, so that the side effects of radiation, the radiation proctitis, can be identified.

DISCLOSURES

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Conflict of interest

The authors declare that they have no competing interests. that may be perceived as inappropriately influencing the representation or interpretation of reported research results.

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Author contribution

All authors have contributed to all processes in this research, including preparation, data gathering and analysis, drafting and approval for publication of this manuscript.

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