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Radiotherapy Response in Advanced Stage of Cervical Cancer Types of Histopathology Squamos Cell Carcinoma and Adenocarcinoma

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Abstract

Background: Cervical cancer is a malignancy that occurs on the cervix, and it is the most common cancer in the world. According by GLOBOCAN in 2020, cervical cancer ranks seventh globally. The main management of advanced cervical cancer is using radiotherapy. The problem that occurs is the need for radiation for advanced cervical cancer patients while there is still a lack of availability of radiotherapy equipment, causing under treatment management.

Objective: To prove that the response to radiotherapy in patients with advanced cervical cancer types of histopathology squamous cell carcinoma is better than adenocarcinoma in Ulin General Hospital, Banjarmasin

Methods: The study used an analytic observational design with a cross-sectional approach. The sample was taken over the time span during the study from January 2021 to December 2022 and was taken by total sampling.

Results: The total sample was 128 cervical cancer patients with 91 squamous cell carcinoma samples and 37 adenocarcinoma samples. After conducting a chi-square analysis between several variables and response to therapy, a significant relationship was found between histopathology and response to therapy, which concluded that cervical cancer with histopathology of squamous cell carcinoma is more radiosensitive than adenocarcinoma. This is due to the relationship between VEGF and radiation.

Conclusion: The response of radiotherapy is more sensitive in type of histopathology squamous cell carcinoma than in cervical cancer with type of histopathology adenocarcinoma.

Keywords: Radiotherapy, Cervical Cancer, Adenocarcinoma, Squamous Cell Carcinoma

Introduction

Cervical cancer is a malignancy that occours on cervix. This cancer is the most common in the world and is a major global health challenge.1 According to data released by GLOBOCAN in 2020, cervical cancer ranks seventh globally in terms of incidence rates and ranks ninth as a cause of death.[1,2]

The incidence rate of cervical cancer in South Kalimantan ranks tenth in Indonesia with a total of 1,930 sufferers according to research data from the South Kalimantan provincial health office for 2019.[3,4] The data obtained at Ulin Banjarmasin Hospital illustrates that there has been an increase in new cases of cervical cancer every year. In 2018, the number of cases of cervical cancer reached 1,447 cases.[5–7]

The impact of cervical cancer on women is very serious, such as losing the ability to have sexual intercourse. This is a fear felt by women who have cervical cancer, causing a decrease in their quality of life. [6,8,9]

The main management of advanced cervical cancer is using radiotherapy, chemotherapy, or chemoradiation therapy, namely a combination of chemotherapy and radiotherapy.[10,11] Ulin General Hospital Banjarmasin is one of the referral hospitals in South Kalimantan for handling cervical cancer cases. The problem that occurs is the limited availability of radiotherapy facilities which causes patients to have to wait a long time so that their treatment uses more chemotherapy which causes under treatment therapy.

One of the problems that occurs is the need for radiotherapy as a therapy for patients with advanced cervical cancer, while the lack of availability of radiotherapy equipment is still very limited, causing under treatment management. Until now, there has been no study that has analyzed the response to radiotherapy in advanced cervical cancer, especially at Ulin Hospital,

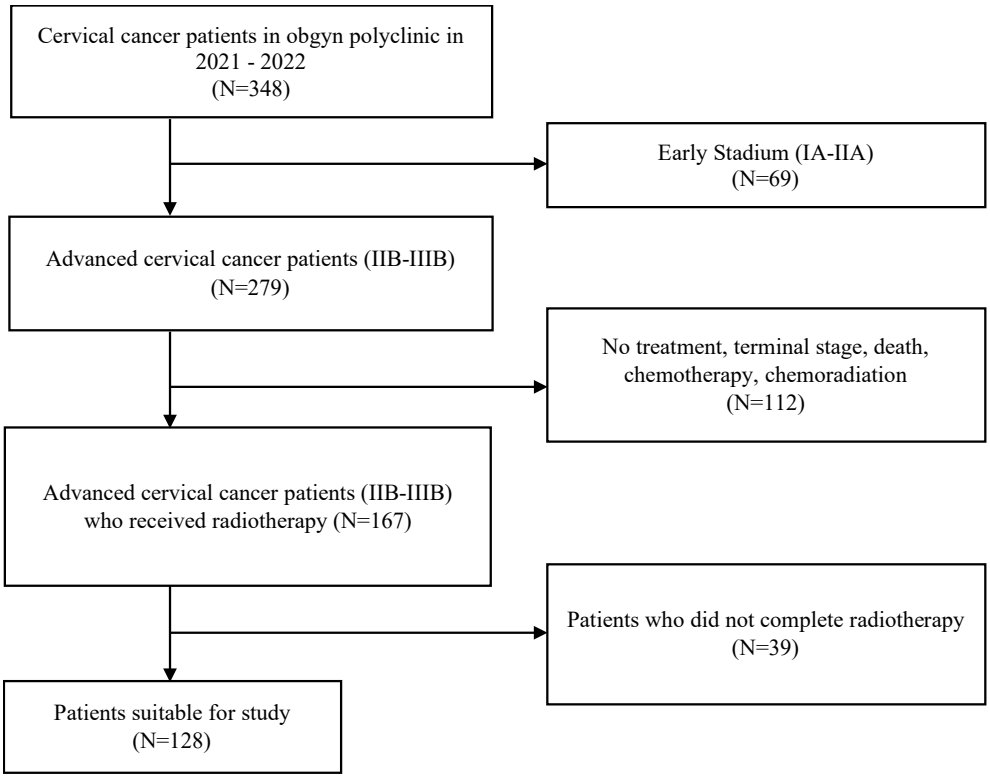

Figure 1. Flow chart showing the selection of study samples.

Banjarmasin, so researchers are interested in conducting this research with the aim of knowing the response to radiotherapy in advanced cervical cancer types of histopathology squamous cell carcinoma and adenocarcinoma and to see the factors that most influence the response to radiotherapy

Method

This study used an analytic observational design with a cross-sectional approach. The sample was taken during the study period from January 2021 until December 2022 and the data was taken by total sampling, which was divided into 2 groups, namely advanced stage cervical cancer patients with types of histopathology squamous cell carcinoma and adenocarcinoma. Analysis of the results of the study used a 2x2 chi-square test for each category with a 95% confidence interval (95% CI) with an alpha value of 0.05 (p=0.05). If the chi-square test requirements are not met (expected count <5), then the analysis will use the fisher-exact test. The analysis was then followed by multivariate analysis using the logistic regression test if a p<0.25 value was obtained in a category.

Result

In this study, a total of 128 samples of advanced cervical cancer patients with types of histopathology squamous cell carcinoma and adenocarcinoma were obtained who underwent radiotherapy at Ulin General Hospital, Banjarmasin for the period January 2021-December 2022.

Based on medical records, it was found that the number of study subjects was 128 with the characteristics of research subjects in this study seen by age, cervical cancer stage, types of histopathology, tumor size, and radiation response.

In table 1, it can be seen some of the characteristics of the subjects of this study. Most age characteristics were > 35 years with a total of 121 patients with a percentage of 94.53%. The most common stage of cervical cancer was stage IIIB, namely 77 patients or around 60.1%. In this study squamous cell carcinoma cancer were found to be more than adenocarcinoma, namely 91 patients with a percentage of 71.09%. The size of the tumor that is more than 4cm2 is higher than under 4cm2, namely 79 patients or 60.94%. In the characteristics of the radiation response in this study, there were more complete responses compared to incomplete responses, namely 69 patients or 53.9%.

Table 2 shows the characteristics of cervical cancer patients in response to therapy. Age less than 35 years had almost the same radiation response, namely 3 patients or 42.86% complete response and 4 patients or 57.14% incomplete response while those over 35 years showed more complete responses than incomplete, namely 66 patients with a percentage of 54.54%. Stage characteristics of the radiation response showed that stages IIB and IIIA had more complete responses than incomplete responses, namely 29 patients (60.41%) and 3 patients (100%), while stage IIIB had more incomplete responses than complete responses, namely

Table 1. Characteristics of Advanced Stage Cervical Cancer Patients at Ulin Hospital, Banjarmasin in January 2021 to December 2022.

Variable	Category	Total (N)	Percentage (%)
Age	< 35 years	7	5,47
	≥ 35 years	121	94,53
Stage	II B	48	37,5
	III A	3	2,34
	III B	77	60,1
Types of Histopathology	Squamous Cell Carcinoma	91	71,09
	Adenocarcinoma	37	28,91
Tumor size	< 4 cm^2	49	39,06
	≥ 4 cm^2	79	60,94
Radiation response	Complete	69	53,9
	Incomplete	59	46,1

Table 2. Characteristics of Advanced Stage Cervical Cancer Patients Against Radiation Response.

Variable	Category	Radiation Response	
		Complete (%)	Incomplete (%)
Age	< 35 years	3 (42.86)	4 (57.14)
	≥ 35 years	66 (54.54)	55 (45.45)
Stage	II B	29 (60.41)	19 (39.59)
	III A	3 (100)	0 (0)
	III B	37 (48.05)	40 (51.95)
Types of Histopathology	Squamous Cell Carcinoma	57 (62.64)	34 (37.36)
	Adenocarcinoma	12 (32.43)	25 (67.57)
Tumor size	< 4 cm^2	29 (59.18)	20 (40.82)
	≥ 4 cm^2	40 (50.63)	39 (49.37)

Table 3. Correlation between Age with Radiation Response.

Age	Radiation Response		Total (N)	*p-value* (*CI* 95%)	PR
	Complete	Incomplete			
< 35 years	3	4	7	0.413 (0.134-2.913)	0.625
≥ 35 years	66	55	121		

Table 4. Correlation between Stage of Cervical Cancer with Radiation Response.

Stage	Radiation Response		Total (N)	*p-value* (*CI* 95%)	PR
	Complete	Incomplete			
II	29	19	48	0.168 (0.739-3.154)	1.526
III	40	40	80		

Table 5. Correlation between Types of Histopathology with Radiation Response

Types of Histopathology	Radiation Response		Total (N)	*p-value* (*CI* 95%)	PR
	Complete	Incomplete			
Squamous Cell Carcinoma	57	34	91	0.002 (1.556-7.842)	3.493
Adenocarcinoma	12	25	37		

Table 6. Correlation between Tumor size with Radiation Response.

Tumor size	Radiation Response		Total (N)	*p-value* (*CI* 95%)	PR
	Complete	Incomplete			
< 4 cm^2	29	20	49	0.224 (0.688-2.906)	1.414
≥ 4 cm^2	40	39	79		

Table 7. Correlation between Types of Histopathology and Tumor size with Radiation Response in Stage II Cervical Cancer.

Stage II	Radiation Response		Total (N)	*p-value* (*CI* 95%)	PR
	Complete	Incomplete			
Types of Histopathology					
Squamous Cell Carcinoma	22	11	33	0.160 (0.657-7.947)	2.286
Adenocarcinoma	7	8	15		
Tumor Size					
< 4 cm^2	18	11	29	0.503 (0.366-3.872)	1.190
≥ 4 cm^2	11	8	19		

Table 8. Correlation between Types of Histopathology and Tumor Size with Radiation Response in Stage III Cervical Cancer.

Stage III	Radiation Response		Total (N)	*p-value* (*CI* 95%)	PR
	Complete	Incomplete			
Types of Histopathology					
Squamous Cell carcinoma	35	23	58	0.000 (2.764-24.432)	8.217
Adenocarcinoma	5	27	32		
Tumor Size					
< 4 cm^2	11	9	20	0.205 (0.635-4.702)	1.728
≥ 4 cm^2	29	41	70		

Table 9. Multivariate Analysis of Cervical Cancer Patients with Radiation Response.

Variable	Coef.	PR	SE	*p-value* (*CI* 95%)
Stage	0.4000	1.492	0.413	0.333 (0.664-3.356)
Types of Histopathology	1.317	3.731	0.421	0.002 (1.634-8.518)
Tumor Size	0.342	1.383	0.412	0.431 (0.617-3.103)
Constant	-0.990			

40 patients with a percentage of 51.95%. In the type of histopathology, it was found that squamous cell carcinoma had more complete responses than incomplete responses, namely 57 patients with a percentage of 62.64%, while the types of histopathology adenocarcinoma had more incomplete responses than complete responses, namely 25 or 67.57%. Characteristics of tumor size less than 4 and more than equal to 4 have a complete response to radiation which is more than the incomplete response, namely 29 or 59.18% and 40 or 50.63%.

The correlation between age and radiation response is shown in table 3. The table shows that there is no correlation between age characteristics and radiation response as evidenced by the value of p=0.413 (p>0.05) which indicates that the correlation between age and radiation response is not significantly related. This means that the age of patients who are less than 35 years and more than equal to 35 years does not differ significantly in response to radiation.

Table 4 shows the correlation between cervical cancer stage and radiation response. In statistical analysis, the value of p=0.168 (P>0.05) was obtained which indicated that there was no significant correlation between stage II and III cervical cancer to radiation response. This shows that there is no difference between stage II and III cervical cancer in response to radiation.

Table 5 shows the correlation between types of histopathology and response therapy. Table 5 shows that the types of histopathology have a correlation with the response to therapy. This is indicated by the value of p=0.002 (p<0.05) which indicates that there are significant results. This can be interpreted that the types of histopathology squamous cell carcinoma has a more significant complete radiation response compared to adenocarcinoma.

Table 6 shows that there is no correlation between tumor size and radiation response. This is proven by the value of p=0.224 (P>0.05). This shows that the size of the tumor which is less than 4 cm and more than 4 cm makes no difference to the radiation response.

Table 7 shows the correlation in the stage II cervical cancer types of histopathology squamous cell carcinoma and tumor size to radiation response. The table above shows that there is no significant correlation both in types of histopathology and tumor size in stage II cervical cancer to radiation response. This is indicated by the value of p=0.160 (p>0.05) for types of histopathology and p=0.503 (p>0.05) for tumor size which means that squamous cell carcinoma and adenocarcinoma and tumor size less than and more than equal to 4 do not have significant difference to the radiation response.

The correlation between stage III cervical cancer on types of histopathology and tumor size on radiation response is shown in table 8. There is a significant correlation between the types of histopathology stage III cervical cancer on radiation response as indicated by the value of p=0.000 (p<0.05), which means that the types of histopathology squamous cell carcinoma have a better (complete) radiation response compared to adenocarcinoma. There was no significant correlation between tumor size in the stage III cervical cancer and response to therapy with a value of p=0.205 (p>0.05), which means that tumor sizes less than and greater than 4 do not have a significant difference in radiation response.

Multivariate analysis is shown in table 9. Several categories with p <0.25 on bivariate analysis could be included in multivariate analysis, namely stage characteristics, types of histopathology, and tumor size. In multivariate analysis, it was found that the most influential factor on the radiation response of the three categories was the type of histopathology as indicated by the value of p=0.002 (p<0.05). This shows that the type of histopathology will affect the radiation response.

Discussion

In this study, a significant correlation was found between types of histopathology and radiation response as indicated by the value of p=0.002 (p<0.05). In the stage III cervical cancer, there was also a significant correlation between types of histopathology and radiation response as indicated by the value of p=0.000 (p<0.05). This explains that the type of histopathology squamous cell carcinoma has a better radiation response compared to adenocarcinoma. The types of histopathology squamous cell carcinoma also gave a radiation response three times better than adenocarcinoma with a PR value of 3,493. The type of histopathology squamous cell carcinoma also showed a radiation response that was 8 times better than adenocarcinoma in the stage III cervical cancer as indicated by a PR value of 8.217. Katanyoo et al, conducted a study comparing radiotherapy responses to squamous cell carcinoma and adenocarcinoma with the results that squamous cell carcinoma gave a better response compared to adenocarcinoma.[12] Pringgo et al, also conducted a study comparing all types of histopathology with radiation response with the result that the type of squamous cell carcinoma gave the best response to radiation compared to other types of histopathology.[13]

The response to radiotherapy in cervical cancer is determined by various factors. The factors that play the most role in the radiation response are Vascular Endothelial Growth Factor (VEGF) and Microvessel Density (MVD). VEGF can induce radiotherapy resistance. VEGF has a major role in the process of angiogenesis. VEGF will be activated under hypoxic conditions which will then activate the PI3K/AKT pathway which can reduce apoptosis. The decrease in apoptosis will lead to an increase in tumor cell survival. MVD is a measuring tool used to see the vascularity of tumors that show angiogenesis activity so that there is a correlation between VEGF and MVD.[10,11]

Types of histopathology squamous cell carcinoma cervical cancer has much lower VEGF expression than adenocarcinoma. This lower VEGF expression will lead to lower MVD in cervical cancer types of histopathology squamous cell carcinoma compared to adenocarcinoma. This causes squamous cell carcinoma to be more sensitive to radiotherapy than adenocarcinoma.[14] A study conducted by Tokumo et al, stated that types of histopathology adenocarcinoma cervical cancer has higher VEGF expression than squamous cell carcinoma.[14] Saijo et al, also conducted a study and obtained research results that squamous cell carcinoma type cervical cancer has lower VEGF expression than adenocarcinoma.[15] A meta-analysis study conducted by Xiaoli Hu et al, also stated that MVD affects therapy response and survival rate of patients with cervical cancer. MVD was found to be higher in types of histopathology adenocarcinoma cervical cancer compared to squamous cell carcinoma.[16]

The response to radiotherapy in this study resulted in several progressive responses. This progressive response is found more in the types of histopathology adenocarcinoma than squamous cell carcinoma. Types of histopathology adenocarcinoma cervical cancer has higher VEGF expression compared to squamous cell carcinoma. This VEGF expression causes activation of MVD so that MVD is also higher in adenocarcinoma than squamous cell carcinoma. VEGF and MVD also have a major role as angiogenesis so that when the expression of VEGF and MVD is high it will lead to an increase in tumor cell survival. High expression of VEGF and MVD will also cause resistance to therapy, causing the radiation response to become insensitive and causing a progressive response. In this study, the progressive response was included in the incomplete response.[10,11,15]

Conclusion

Radiotherapy is one of the best gold standard treatments for advanced cervical cancer. In this study it was found that type of histopathology was the only characteristic that was significantly related to radiation response while age, stage, and tumor size were not significantly related to radiation response. After multivariate analysis, the most influential factor on the response to therapy was the types of histopathology of cervical cancer.

The type of histopathology squamous cell carcinoma is more sensitive to radiation when compared to adenocarcinoma, because the type of histopathology squamous cell carcinoma has much lower VEGF expression so that the MVD in squamous cell carcinoma histopathology will be lower, which will reduce the survival of the tumor, so that Tumors are more sensitive to radiation. This occurred both overall and in the cervical cancer stage III group.

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