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RESEARCH ARTICLE

Relationship Between Necrosis, Neovascularization, and Lymphocyte Reaction in Histopathological Types of Cervical Cancer

Qurratu Kasturi Jamilah[1*], Humairah Medina Liza Lubis [2]

[1*] Undergraduate Medical Study Program, Faculty of Medicine, Universitas Muhammadiyah Sumatera Utara, Jalan Gedung Arca No 53, Kecamatan Medan Kota, Kota Medan, Sumatera Utara 20217
[2] Department of Anatomical Pathology, Faculty of Medicine, Universitas Muhammadiyah Sumatera Utara, Jalan Gedung Arca No 53, Kecamatan Medan Kota, Kota Medan, Sumatera Utara 20217

Email correspondence: qurratukasturijml@gmail.com
humairahmedina@umsu.ac.id

Abstract: Cervical cancer is a malignant tumour that grows on the cervix, more than 90% of which are caused by HPV 16 and 18. lymphocytes are one of the immune systems that play a role in immunosurveillance against cancer cells. However, cervical cancer will cause necrosis and activate Hypoxia-Inducible Factor-1 (HIF-1) which plays a role in the formation of neovascularization. Based on histopathological findings, cervical cancer types are classified into squamous cell carcinoma (SCC) and adenocarcinoma (ADC). This study aimed to determine the relationship between necrosis, neovascularization, and lymphocyte reaction in various histopathological types of cervical cancer. This research is observational analysis using medical records and histopathological slides of patients diagnosed with cervical cancer. There were 26 cases of cervical cancer consisting of 16 types of SCC and 12 types of ADC. Based on the highest percentage, more necrosis was found in ADC 81.8% (p-value 0.014), neovascularization in SCC 73.3% (p-value 0.014), and lymphocyte reaction in SCC 86.7% (p-value 0.973). This means that there was a significant relationship between necrosis and lymphocyte reaction in various histopathological types of cervical cancer, however, there is no significant relationship between neovascularization in various histopathological types of cervical cancer.

Keywords: Histopathological type of cervical cancer, necrosis, neovascularization

INTRODUCTION

Based on the 2018 Global Cancer Observatory (GLOBOCAN), globally cervical cancer is ranked as the fourth most common cause of cancer incidence and death in women throughout the world. Cervical cancer is the main cause of cancer-related deaths in women in eastern, central, southern and western Africa.[1] In Indonesia, cervical cancer ranks second after breast cancer with

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an incidence of 23.4 per 100 thousand population with a mortality rate of 13.9 per 100 thousand population. It is estimated that in 2030, deaths from cervical cancer will continue to increase with an estimate of more than 13.1 million.[2] Cervical cancer cases at the Haji Adam Malik Hospital in Medan, the number of cervical cancer sufferers who were hospitalized in 2016 was 197 people and most were found in those aged 41-52 years, namely 87 people (44.2%).[3]

The course of cervical carcinoma is a model of carcinogenesis that goes through stages or multisteps, starting from initial carcinogenesis to morphological changes until it becomes an invasive cancer. The E6 and E7 proteins play an important role in carcinogenesis, where they can block the work of the tumour suppressor proteins p53 and pRb so that cells become immortal and cell division becomes uncontrolled.[4] Epidemiological studies show that more than 90% of cervical cancer is associated with this type. Human Papilloma Virus (HPV). Where more than 130 types of HPV are known, HPV 16 and 18 are the HPV most often found in invasive cervical cancer. Population-based HPV prevalence studies show that the prevalence of HPV 16 and 18 is more likely to occur in the young adult period or under 25 years of age.[5]

Based on the 2014 World Health Organization (WHO) classification, cervical cancer can be classified based on histopathological findings into squamous cell tumours and precursors, glandular tumours and precursors, and adenocarcinoma, other epithelial tumours, mixed epithelial and mesenchymal tumours, and germ cell tumours.[6] Where squamous cell carcinoma (SCC) is the most common type of cervical cancer, however, adenocarcinoma (ADC) has a worse prognosis, this is because ADC metastases are more progressive to the ovaries and have a higher recurrence rate than SCC and adenosquamous carcinoma.[7] Because cervical cancer causes cell changes towards malignancy, the body will stimulate the immune system as the body's defence system. Lymphocytes are one of the immune systems that play a role in immunosurveillance against cancer cells. So with the activation of the immune system, the patient's prognosis will be better, this suggests that the presence of lymphocyte infiltration can inhibit tumor progression or the development of areas of malignancy.[8]

However, cervical cancer can cause cell death such as necrosis.[9] The more extensive the necrotic lesion in the tissue, the worse the patient's prognosis. Necrosis in cervical cancer occurs due to morphological changes due to the progressive degradative action of enzymes that indicate cell death. Tumor Necrosis Factor (TNF) was initially described as a factor that causes hemorrhagic tumour necrosis. Necrosis can also be caused by tissue hypoxia which will trigger Hypoxia-Inducible Factor-1 (HIF-1). HIF-1 plays a role in controlling the transcription of Vascular Endothelial Growth Factor

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(VEGF) which then triggers the formation of neovascularization.[10]

Neovascularization has a double effect on the course of cervical cancer, including stimulating the growth of surrounding tumour cells by releasing various polypeptides.[11] Tumor-associated macrophages (TAM) can also increase angiogenesis by inducing pro-inflammatory mediators such as IL-1 and IL-6 which will increase the production of pro-angiogenic factors. The more tumour cells that experience dedifferentiation and form angiogenesis, the greater the ability of tumour cells to develop and metastasize. This can worsen the prognosis in patients.[12]

Based on the description above, it is known that with the presence of a lymphocyte reaction the patient's prognosis will be better and the presence of extensive necrosis and the ability to metastasize can worsen the patient's prognosis. ADC has a worse prognosis compared to other types of cervical cancer. This makes researchers interested in finding out more about whether there is a relationship between necrosis, neovascularization and lymphocyte reactions in various histopathological types of cervical cancer by looking at the findings of necrosis, neovascularization and lymphocyte reactions in histopathological images of cervical cancer.

METHOD

The design of this research is non-experimental in the form of observational analytics with a cross-sectional approach. This research was conducted in August-December 2022 at the Laboratory of the Faculty of Medicine, Muhammadiyah University, North Sumatra.

Previously, researchers will collect data obtained from primary data carried out by examining cervical cancer histopathology slides with Hematoxylin Eosin (HE) smear preparations and secondary data taken from patient medical records obtained from hospital X in 2017-2022. The data obtained includes findings of necrosis, neovascularization, and lymphocyte reactions in various histopathological types of cervical cancer.

The data that has been collected will be analyzed statistically using the Statistical Product and Service Solution (SPSS) program. Next, the data was analyzed bivariately using Chi-Square or Fisher's Exact which was then presented in tabular form to determine the relationship between necrosis, neovascularization and lymphocyte reactions in various histopathological types of cervical cancer.

RESULT

1. Histopathological Distribution of Cervical Cancer

Table 1. Distribution Histopathological of Cervical Cancer

Histopathological of Cervical Cancer	n	%
Squamous Cell Carcinoma (SCC)	15	57,7

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Adenocarcinoma (ADC)	11	42,3
Total	26	100

Based on table 1, shows that from 26 samples cervical cancer was found with SCC type in 15 samples (57.7%) and ADC in 11 samples (42.3%). Figures 1 and 2 are the results of microscopic examination of histopathology slides for cervical cancer.

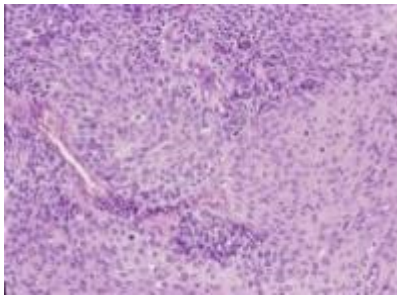

Figure 1. Squamous Cell Carcinoma in Cervical Cancer

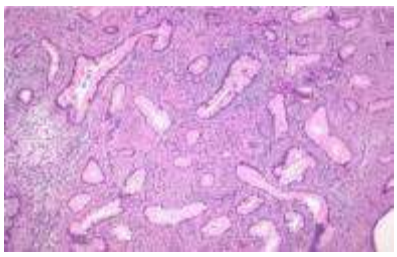

Figure 2. Adenocarcinoma in Cervical Cancer

2. Histopathological Distribution of Necrosis

Table 2. Histopathological Distribution of Necrosis

	Necrosis	n	%
Histopathological of Necrosis	+	14	53,8
	-	12	46,2
Total		26	100

Based on table 2, shows that histopathological necrosis was found in 14 samples (53.8%) and the other 12 samples (46.2%) no histopathological necrosis was found.

3. Histopathological Distribution of Neovascularization

Table 3. Histopathological Distribution of Neovascularization

	Neovaskularization	n	%
Histopathological of Neovascularization	+	19	73%
	-	7	27%
Total		26	100

Based on table 3, shows that histopathological neovascularization was found in 19 samples (73%) and the other 7 samples (27%) no histopathological neovascularization was found.

4. Histopathological Distribution of Lymphocyte Reaction

Table 4. Histopathological Distribution of Lymphocyte Reaction

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	Lymphocyte Reaction	n	%
Histopathological of Lymphocyte Reaction	+	17	65,4
	-	9	34,6
Total		26	100

Based on table 4, shows that the histopathological of lymphocyte reactions was found in 17 samples (65.4%) and in the other 9 samples (34.6%) no histopathological of lymphocyte reactions was found.

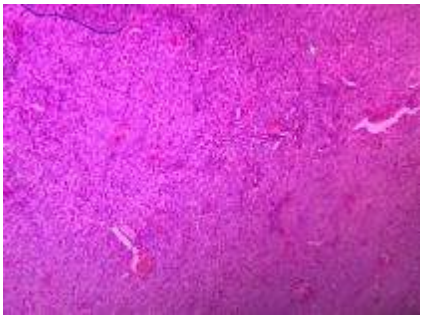

Figure 3. Necrosis

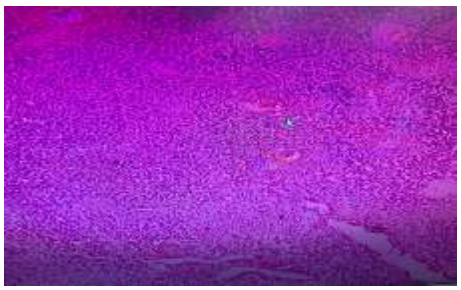

Figure 4. Neovascularization

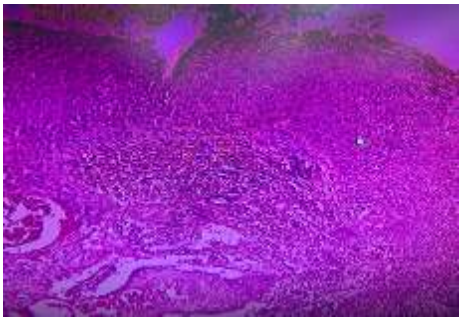

Figure 5. Lymphocyte Reaction

Figures 3,4 and 5 are the results of microscopic examination of histopathology slides for necrosis, neovascularization, and lymphocyte reactions.

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5. Chi-Square Test for the Relationship between Necrosis and Various Histopathological Types of Cervical Cancer

Table 5. Chi-Square Test for the Relationship between Necrosis and Histopathological Types of Cervical Cancer

		Histopathological Types of Cervical Cancer				Total		*p-value*
		SCC		ADC				
		N	%	N	%	N	%	
Necrosis	+	5	33,3	9	81,8	14	53,8	0,014
	-	10	66,7	2	18,2	12	46,2	
Total		15	100	11	100	26	100	

6. Chi-Square Test for The Relationship Between Neovascularization and Various Histopathological Types of Cervical Cancer

Table 6. Chi-Square Test for The Relationship of Neovascularization and Histopathological Types of Cervical Cancer

		Histopathological Types of Cervical Cancer				Total		*p-value*
		SCC		ADC				
		N	%	N	%	N	%	
Neovascularization	+	11	73,3	8	72,7	12	46,2	0,973
	-	4	26,7	3	27,3	14	53,8	
Total		15	100	11	100	26	100	

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7. Fisher Exact Test for The Relationship of Lymphocyte Reactions and Various Types of Histopathology Cervical Cancer

Table 7. Fisher Exact Test for The Relationship of Lymphocyte Reactions and Types of Histopathology Cervical Cancer

		Histopathological Types of Cervical Cancer				Total		*p-value*
		SCC		ADC				
		N	%	N	%	N	%	
Lymphocyte Reaction	+	13	86,7	4	36,4	17	65,4	0,014
	-	2	13,3	7	63,6	9	34,6	
Total		15	100	11	100	26	100	

In Tables 5 and 6 using the Chi-square test, the results of Asymptotic significance (2-sided) are 0.014 (p-value <0.05) and 0.973 (p-value> 0.05) which means that there is a significant relationship between necrosis and the type of histopathology of cervical cancer and there is no significant relationship between neovascularization and the type of histopathology of cervical cancer. And in Table 7 with the Fisher exact test, the results of Exact sig (2-sided) are 0.014 (p-value <0.05) which means that there is a significant relationship between lymphocyte reactions and the type of histopathology of cervical cancer.

DISCUSSION

Table 1 shows that of the 26 samples found, the SCC type was the most common type of cervical cancer, namely 15 samples (57.6%) and the least was ADC, namely 11 samples (42.3%). Based on theory, it is known that the incidence of ADC-type cervical cancer is the rarest type of malignancy with an incidence rate of less than 6/100,000 patients diagnosed with cervical cancer, where the SCC type is the most frequently found type of malignancy with a percentage above 90%.[13]

Cervical cancer has a survival rate of 40-50% if treated with surgery, but a local recurrence rate of 84-75% within 3-5 years.[14] The Oretically, it is known that necrosis, neovascularization, and lymphocyte reactions play a role in the aggressiveness of cancer cells. This has also been explained by the National Cancer Institute that apart from the factors of age, speed of diagnosis and treatment, stage of

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cancer, and immunocompromised, the type of cervical cancer is also one of the factors for determining prognosis.[15] In cervical cancer patients who receive post-surgical treatment the expression of TNF-α and SIL-2R will increase and gradually become normal. Therefore, examining the expression of TNF-α and SIL-2R is one of the tests recommended for evaluation when undergoing cervical cancer treatment.[16]

ADC itself has a worse prognosis than SCC, this is because ADC metastases are more progressive and have a higher recurrence rate than SCC. In this study, necrosis findings were more common in ADC and neovascularization was more common in SCC, especially poor type SCC. Differentiated and undifferentiated. This is related to the results of Aijan, M et al's research by evaluating CD34 expression as a marker of angiogenesis in cervical cancer and it was found that angiogenesis was more commonly found in SCC grading Undifferentiated carcinomas cervical cancer.[17]

However, if you look at the number of neovascularization findings on each slide unit, it is more common in the ADC type. However, this study was only limited to assessing the presence or absence of neovascularization findings without assessing how many neovascularization findings were found. As is known, neovascularization can also be caused by necrosis by activating VEGF. So with necrosis, neovascularization will be more common. This is related to the results of Jannati et al's research, which found a P-value of 0.03, which means there is a significant relationship between necrosis and neovascularization.[18] Neovascularization itself has the potential for aggressive development of cancer cells, the more neovascularization is found, the more neovascularization is found. The worse the prognosis.

On the other hand, in this study, lymphocyte reactions were more commonly found in SSC-type cervical cancer. In theory, lymphocyte infiltration can inhibit the progression of malignant cells.[19] So it can be related that with the presence of lymphocyte reactions, the immune system will be more active in fighting cancer cells so that the patient's prognosis will be better. According to Merino, JM et al the immune response has an important role in eliminating cancer cells and suggests using immunotherapy as a treatment candidate. This is because the absence of a good immune system can increase the speed of development of a malignancy.[20]

In Tables 5 and 6, based on statistical results, using the Chi-square test, the Asymptotic significance (2-sided) results were obtained, namely 0.014 (p-value <0.05) and 0.973 (p-value >0.05) which means there is a relationship there is a significant relationship between necrosis and various histopathological types of cervical cancer and there is no significant relationship between neovascularization and various histopathological types of cervical cancer. Based on Table 7, because the

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expected count was more than 20%, an alternative Chi-square test was carried out with the Fisher exact test and the Exact sig (2-sided) result was 0.014 (p-value <0.05), which means there is a significant relationship between the reactions. Lymphocytes with histopathological features of cervical cancer.

CONCLUSION

SSC-type cervical cancer is more common than ADC, based on the findings of an examination of medical records and histopathology slides of cervical cancer, it was found that necrosis was more common in ADC-type cervical cancer and the findings of neovascularization and lymphocyte reactions were more common in SCC type. Necrosis and neovascularization have a role in increasing the progression of cancer cells, while lymphocyte reactions have a role in immunosurveillance to fight cancer cells. With the findings of necrosis and neovascularization the patient's prognosis will be worse, whereas with the findings of a lymphocyte reaction, the prognosis will be better.

ACKNOWLEDGMENTS

Because this research is only limited to assessing the presence or absence of findings of necrosis, neovascularization, and lymphocyte reactions in the histopathology of cervical cancer, it is recommended to assess the extent of necrosis, neovascularization, and lymphocyte reactions objectively using formulas or other standardized methods.

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