Survival and Clinicopathological Features of Cervical Carcinoma Patients with Radiation Therapy

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Abstract: Cervical cancer has a high incidence with a low survival rate. The clinicopathological profile and risk factors cause this. Most cervical cancer sufferers are late in realizing this, contributing to the severity suffered. Radiation has a very important role because it is a therapy that can be done in cervical cancer patients who have experienced an advanced level of severity. This study aims to determine the survival and influence of the clinicopathological and risk factors of radiation patients as a consideration in selecting effective therapy to increase the survival rate of cervical cancer patients. The benefit of this research is to help evaluate cervical cancer management procedures with radiation therapy applied in many hospitals in Indonesia to increase the success of therapy for cervical cancer. An analytical observational study with a retrospective cohort type using medical record data with samples of all patients diagnosed with cervical cancer who received radiation therapy from January to December 2017. Samples in this study were 111 patients. This study revealed that the five-year survival rate of cervical cancer patients was only 53.1%. There was an influence on the clinicopathological stage ($p<0.000$), histopathology ($p<0.000$), lymph node status ($p<0.000$), degree of differentiation ($p<0.001$), and risk factors for age ($p<0.038$), parity ($p<0.001$), education (0.022), marital status (0.001), contraceptive use ($p<0.000$), and BMI ($p<0.000$) which resulted in a log-rank p-value <0.05, so it was concluded that there was an effect between these variables on cervical carcinoma survival rate. Multivariate, it was found that radiation, histopathology, lymph node status, contraception, and BMI had a significant effect ($p<0.005$) on the survival rate of cervical cancer patients. The results of this study indicate that the survival rate of cervical cancer patients is still low, and there is a clinicopathological and risk factors that influence the survival rate of cervical cancer patients.
Keywords: Survival rate; cervical carcinoma; radiation therapy

INTRODUCTION

About 200,000 deaths from cervical cancer occur in developing countries. The number of new patients with cervical cancer ranges from 90-100 cases per 100,000 population, with 40,000 cases of cervical cancer each year. (Andrijono et al., 2013). The estimated number of cervical cancer in Indonesia is very high, with a range of 98,692 cases in 2013 with an incidence of 17 per 100,000 women in Indonesia (Pusat Data dan Informasi, 2015). Data on suspected cervical cancer in Indonesia based on the results of early detection in 2020 were 5,847 (Pusat Data dan Informasi, 2020).

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The survival rate for cervical cancer patients in Indonesia is still very low. This is caused by various factors, the most important of which is the Clinicopathological Profile. Cervical cancer greatly affects the patient's survival rate, that is, cervical cancer stage, histopathology, degree of tissue differentiation, cervical cancer cell metastases, and clinical response to cervical cancer therapy (Yang et al., 2019). The early-stage survival rate is 31.5%, while the advanced-stage survival rate is only 4.1% (Telaumbanua, 2019). Squamous cell carcinoma is the most common type of histopathology in cervical cancer, with a range of 80-85% in cervical cancer patients, thus affecting the survival rate of patients, and some types have a poor response to radiation therapy (Lubis, 2016). Patients with grade poorly differentiation greatly affect cervical cancer survival rates (Telaumbanua, 2019). Positive lymph node status has a 5-year survival rate of only about 20% (Sinaga, 2020). Patients with LVSI involvement increase the risk of cervical cancer recurrence three times which will affect the survival rate of cervical cancer patients (Balaya et al., 2020). Complications caused by the outcome of the cancer course and side effects of treatment also affect the survival and quality of life of cervical cancer patients and their survival rate (National Health Service, 2015). Cervical cancer risk factors such as age, parity, and so on contribute to the incidence of cervical cancer and can affect the survival rate of cervical cancer patients. Risk factors for cervical cancer include sexual activity, lifestyle, multiparity, sexually transmitted diseases, impaired immunity, and hormonal contraception (Andrijono et al., 2013).

Radiation therapy aims to destroy malignant cells in the cervix and kill the parametrial and lymph nodes in the pelvis. Radiation therapy can be performed in patients with stage II B, III, and IV cervical cancer. Treatment therapy is adjusted to be curative to kill cancer cells that spread and metastasize in the surrounding tissue or as palliative therapy, which is therapy at an advanced stage that cannot be cured to increase the survival rate of cervical cancer patients (Cohen et al., 2019).

Research that has been conducted in the Netherlands previously found that the 5-year survival rate of cervical cancer patients in this study increased from 68% to 74%. However, in this study, it was found that radiation therapy as primary therapy could significantly reduce the 5-year survival rate of cervical cancer patients (p<0.001). In contrast, brachytherapy as primary therapy increased significantly (p<0.001) over time (Wenzel et al., 2021) when compared with research on survival rates in Indonesia, research conducted in Malang in 2014 previously found the one-year survival rate for patients with locally advanced cervical cancer who received radiation therapy without intracavitary brachytherapy at dr. Saiful Anwar Malang general hospital by 72% (Sherly, 2014).

Related to this, previous research conducted in Malang City using only a one-year survival rate regarding cervical cancer needs to be redeveloped by conducting the latest research, including a 5-year survival rate based on the high number of cervical cancer cases that have increased with novelty, including all predictor factors for survival rate from clinicopathological profile and risk factors for cervical cancer patients. The clinicopathological profile and risk factors for cervical cancer patients that have been described previously can be a novelty and reference for research to get the right initial treatment so that it can reduce patient mortality, especially in the late stages of cervical cancer patients receiving radiation therapy. This will increase the survival rate and can be a consideration in the selection of therapy and the duration of effective therapy in cervical cancer patients. This study aims to determine the survival and influence of the clinicopathological and risk factors of radiation patients

as a consideration in selecting effective therapy to increase the survival rate of cervical cancer patients.

MATERIALS AND METHODS

This study uses an analytic observational research design with a retrospective cohort type using medical record data; in this study, the researchers tried to find the effect between variables by analyzing the data collected in April 2022. The sample population was all women who have cervical cancer in the oncology department of the Department of Obstetrics and Gynecology dr. Saiful Anwar Malang general hospital. The research sample was taken by retrospective cohort study, collecting data from medical records of cervical cancer patients from January to December 2017 who received radiation therapy. Based on the medical record data obtained, there were 136 patients suffering from cervical cancer with radiation therapy but based on the inclusion criteria where all patients had finished receiving radiation therapy management and had complete radiation therapy and exclusion which included these criteria were patients who only received operative therapy and chemotherapy without radiation therapy and have other malignancies, then in this study obtained 111 samples. Then fill in the data collection sheet containing the required patient medical records related to clinicopathological profile data; these are stage, histopathology, lymph nodes, degree of differentiation, lymphovascular invasion, complaints/complications, and risk factors; these are age, parity, education, occupation, contraceptive use, menstrual history, marital status, body mass index and area of residence.

In this study, data analysis techniques were used to analyze the 5-year survival of cervical cancer patients who received radiation therapy using the Kaplan Meier test survival analysis using spss version 25 so that it will bring up the survival characteristics of cervical cancer patients followed by the log-rank test which aims to determine the level of significance of each independent variable, the clinicopathological profile and risk factors on the probability of survival so that at the end of the results will bring up factors that significantly affect the survival rate five years of cervical cancer patients based on clinicopathological profile and risk factors.

Using the spss version 25 application, univariate analysis was carried out to find the characteristics of each variable. In survival analysis, to find the effect of each variable on the survival of cervical carcinoma patients, the log-rank test was used as a bivariate analysis in the survival test in this study. In this study, the assumption of PH was tested to determine the next analysis with two criteria. It is said that survival meets the assumption of PH if the lines on the Kaplan Meier curve do not intersect, then the analysis is time-independent. If it is not, then the analysis used is the cox regression full model or cox regression, full reduced model. After testing the PH assumption, it can be determined whether or not bivariate analysis can be carried out. If the PH assumption is not met, then bivariate analysis with Cox regression cannot be performed. In multivariate analysis, if the variable meets the PH assumption, the multivariate analysis uses time-independent cox regression. However, if it is not and based on the theory that each variable is important, multivariate analysis can be performed using the full cox regression analysis or the reduced model. The choice between these two models is based on clinical importance and statistics. The statistical model selection is carried out using the likelihood ratio test to see the significant difference in the degree of freedom that corresponds to the conclusion. It is said that HO is rejected if the value of LR/df > 3.8, which means that the reduced model cannot be accepted so that the full model is a better model and vice versa.

This study found that all variables did not meet the PH assumption where the graphic lines contained in the Kaplan Meier curve intersect, so there is no need for comprehensive bivariate analysis. Only the log-rank test was used to prove each variable's effect on the cervical carcinoma survival rate. All of the clinicopathological profile variables and risk factors in this study are very important and are suspected of affecting the survival of cervical cancer patients so that multivariate analysis can be carried out according to the criteria (p < 0.25) using cox regression reduced model analysis based on the results of model selection statistic obtained LR/df = 0.199, smaller than 3.8 (ΔLR/df < 3.8) then the reduced model is the best multivariate analysis model in this study, the clinicopathological profile variables and risk factors that meet the criteria are included in the analysis based on their stratification to see the size the small influence of these variables multivariate on the survival of cervical carcinoma patients in dr. Saiful Anwar Malang.

The Ethics committee approved this research of general hospital dr. Saiful Anwar Malang, regarding the protection of human rights and welfare in medical research, has carefully reviewed the research protocol entitled with the number of registration 400/007/K.3/302/2022.

RESULTS AND DISCUSSION

Based on data from January to December 2017, 136 cervical cancer patients received radiation therapy. After all medical records were searched, based on the inclusion and exclusion criteria, 111 samples were obtained. After a follow-up was conducted to determine the survival status of cervical cancer patients, there were 52 people with dead status and 59 people with living status, so the 5-year survival rate of cervical cancer patients who received radiation therapy at dr. Saiful Anwar Malang general hospital only 53.1%. The characteristics of this research sample can be seen in Tables 1 and 2.

Subject Characteristics

Based on the clinicopathological characteristics of the research sample, it was shown that there was a significant effect of radiation characteristics (p<0.05). Of the 52 people with death status, 31 (59.6%) had definitive curative radiation, and 21 (40.4%) had palliative radiation. Meanwhile, of the 59 people with living status, the majority were 50 (84.7%) with definitive curative radiation and only 9 (15.3%) with palliative radiation. Reviewed the characteristics of the radiation technique, it was shown that there was no significant difference (p>0.05) in the characteristics of the radiation technique in patients, both in patients with dead status and patients with living status, likewise on histopathological characteristics, lymph node status, complaints of pain, complaints of bleeding, and complaints of hydrophoresis.

Reviewed from the characteristics of completeness of therapy, all patients received complete therapy. The stage level of most patients was at stage IIIB in both dead and living patients. However, there were differences in staging characteristics (p<0.05), where the stage rate in patients with death was higher (stages IVA and IVB) than in patients with living status. Likewise, on the characteristics of the degree of differentiation, patients died more in Grade III degree of differentiation.

All cervical carcinoma patients did not have data variation in terms of lymphovascular invasion and patient complaints. No examination of lymphovascular invasion was carried out because there was no data on examination of lymphovascular invasion in dr. Saiful Anwar Malang general hospital has various complaints. Complaints of pain and bleeding in patients who died and patients who lived were relatively the same (p>0.05). Meanwhile, for CKD (Chronic Kidney Disease) and

hydrophoresis complaints, there was a significant difference (p<0.05) where positive status was more commonly found in patients with CKD (Chronic Kidney Disease) and hydrophoresis complaints.

Table 1. Clinicopathological Profile Characteristics Table

Characteristics of Clinicopathology	Survival Status		Total value	p-value
	Died	**lived**		
Radiation				
- Curative Definitive	31 (59.6%)	50 (84.7%)	81 (72.9%)	0.003*
- Palliative	21 (40.4%)	9 (15.3%)	30 (27.0%)	
Technical_Radiation				
- External Radiation	40 (76.9%)	37 (62.7%)	77 (69.3%)	0.105
- Combination Radiation	12 (23.1%)	22 (37.3%)	34 (30.6%)	
Equipment_Therapy				
- Complete	52 (100%)	59 (100%)	111 (100%)	-
Cancer Stage				
- IIB	0 (0%)	9 (15.3%)	9 (8.1%)	0.005*
- IIIA	2 (3.8%)	1 (1.7%)	3 (2.7%)	
- IIIB	36 (69.2%)	41 (69.5%)	77 (69.3)	
- IVA	6 (11.5%)	7 (11.9%)	13 (11.7%)	
- IVB	8 (15.4%)	1 (1.7%)	9 (8.1%)	
Histopathology				
- Non Keratinizing squamous cell	11 (21.2%)	13 (22%)	24 (21.6%)	0.235
- Keratinizing Squamous cell ca	35 (67.3%)	31 (52.5%)	66 (59.4%)	
- Adenokarcinoma	3 (5.8%)	5 (8.5%)	8 (7.2%)	
- Others	3 (5.8%)	10 (16.9%)	13 (11.7%)	
Lymph Node Status				
- Positive	20 (38.5%)	13 (22%)	33 (29.7%)	0.059
- Negative	32 (61.5%)	46 (78%)	78 (70.2%)	
Degree_Differentiation				
- Grade I	16 (30.8%)	29 (49.2%)	45 (40.5%)	0.012*
- Grade II	24 (46.2%)	27 (45.8%)	51 (45.9%)	
- Grade III	12 (23.1%)	3 (5.1%)	15 (13.5%)	
Lymphovascular Invasion				
- No Data	52 (100%)	59 (100%)	111 (100%)	-
COMPLAINT				
- Yes	52 (100%)	59 (100%)	111 (100%)	-
Painful				
- Positive	21 (40.4%)	30 (50.8%)	51 (45.9%)	0.270
- Negative	31 (59.6%)	29 (49.2%)	60 (54.0%)	
Bleeding				
- Positive	43 (82.7%)	45 (76.3%)	88 (79.2%)	0.405
- Negative	9 (17.3%)	14 (23.7%)	23 (20.7)	
CKD (Chronic Kidney Disease)				
- Positive	17 (32.7%)	1 (1.7%)	18 (16.2%)	0.000*
- Negative	35 (67.3%)	58 (98.3%)	93 (83.7%)	
Hidrophoresis				
- Positive	7 (13.5%)	6 (10.2%)	13 (11.7%)	0.590
- Negative	45 (86.5%)	53 (89.8%)	98 (88.2%)	

*Significantly different based on the results of the Chi-Square test at level α = 0.05

Table 2. Risk Factor Characteristics Table

Characteristics of Risk Factors	Survival Status		Total value	p-value
	Died	**lived**		
Age Group				
- 31-40 years old	1 (1.9%)	11 (18.6%)	12 (10.8%)	0.006*
- 41-50 years old	16 (30.8%)	17 (28.8%)	33 (29.7%)	
- 51-60 years old	28 (53.8%)	17 (28.8%)	45 (40.5%)	
- 61-70 years old	3 (5.8%)	10 (16.9%)	13 (11.7%)	
- 71-80 years old	4 (7.7%)	4 (6.8%)	8 (7.2%)	
Menopausal Status				
- Not menopausal	8 (15.4%)	19 (32.2%)	27 (24.3%)	0.039*
- Already Menopause	44 (84.6%)	40 (67.8%)	84 (75.6%)	
Parity				
- 1 Time (Primipara)	6 (11.5%)	19 (32.2%)	25 (22.5%)	0.009*
- ≥2 times (Multipara)	46 (88.5%)	40 (67.8%)	86 (77.4%)	
Education				
- Primary school	23 (44.2%)	23 (39%)	46 (41.4%)	0.152
- Junior high school	11 (21.2%)	5 (8.5%)	16 (14.4%)	
- Senior High School	17 (32.7%)	29 (49.2%)	46 (41.4%)	
- College	1 (1.9%)	2 (3.4%)	3 (2.7%)	
Profession				
- Have a job	26 (50%)	24 (40.7%)	50 (45.0%)	0.325
- Don't have a job	26 (50%)	35 (59.3%)	61 (54.9%)	
Type Of Work				
- Government employees	1 (1.9%)	1 (1.7%)	2 (1.8%)	0.225
- Private employees	12 (23.1%)	17 (28.8%)	29 (26.1%)	
- Self-employed	6 (11.5%)	1 (1.7%)	7 (6.3%)	
- Others	7 (13.5%)	5 (8.5%)	12 (10.8%)	
- Don't have a job	26 (50%)	35 (59.3%)	61 (54.5%)	
Marital Status				
- Married 1 time	39 (75%)	33 (55.9%)	72 (64.8%)	0.036*
- Married ≥ 2 times	13 (25%)	26 (44.1%)	39 (35.1%)	
History_Menstruation				
- There is a Disturbance	17 (32.7%)	20 (33.9%)	37 (33.3%)	0.893
- No disturbance	35 (67.3%)	39 (66.1%)	74 (66.6%)	
Contraception Use				
- Hormonal contraception	23 (44.2%)	27 (45.8%)	50 (45.0%)	0.855
- Non-hormonal	10 (19.2%)	9 (15.3%)	19 (17.1%)	
- Never used	19 (36.5%)	23 (39%)	42 (37.8%)	
Type Of Contraception				
- Combination Hormones	8 (15.4%)	4 (6.8%)	12 (10.8%)	0.015*
- Progesteron Only	16 (30.8%)	36 (61%)	52 (46.8%)	
- Non Hormonal	9 (17.3%)	7 (11.9%)	16 (14.4%)	
- Never used	19 (36.5%)	12 (20.3%)	31 (27.9%)	
BMI (Body Mass Index)				
- Underweight	21 (40.4%)	7 (11.9%)	28 (25.2%)	0.000*
- Normal	23 (44.2%)	23 (39%)	46 (41.4%)	
- Overweight	3 (5.8%)	7 (11.9%)	10 (9.0%)	
- Obesity	5 (9.6%)	22 (37.3%)	27 (24.3%)	

Residence			
- Village	23 (44.2%)	35 (59.3%)	58 (52.2%)	0.112
- City	29 (55.8%)	24 (40.7%)	53 (47.7%)	

*Significantly different based on the results of the Chi-Square test at level α = 0.05

Based on the characteristics of the risk factors for cervical carcinoma, the study sample showed that there were significant differences in age, menopausal status, parity, marital status, type of contraception, and BMI (Body Mass Index) (p<0.05). Patients with more death status were found at the age of 51-60 years, as many as 28 (53.8%). Meanwhile, patients with more living status were found at the age of 41-50 years and 51-60 years, respectively, as many as 19 (32.2%) patients. Reviewed from the characteristics of menopausal status and parity, patients with death status were more common than patients with menopause and parity ≥ 2 times (Multipara). On the characteristics of marital status and type of contraception, it was shown that the majority of patients who died were married once, 39 (75%) and 19 (36.5%) did not. In living patients, the majority of Hormonal contraception Progesterone Only, as many as 36 (61%) patients. In terms of BMI (Body Mass Index), more patients died than patients with underweight and normal BMI (Body Mass Index), which were 21 (40.4%) and 23 (44.2%).

Assumptions of Proportional Hazard Research Variables

The Proportional Hazard (PH) assumption test was conducted to determine whether there was an inter-group influence on each clinicopathological profile and the observed risk factors for cervical carcinoma on the survival rate using the Kaplan Meier method. The results of Kaplan Meier's analysis of each of the clinicopathological profiles and risk factors for cervical carcinoma can be seen in table 3.

Table 3. Kaplan Meier Analysis Table Cervical Carcinoma Survival Rate

Variable	Median Survival Time	Log Rank p-value
Radiation		
- Curative Definitive	55	0.000*
- Palliative	49	
Technical_Radiation		
- External Radiation	56	0.000*
- Combination Radiation	52	
Equipment_Therapy		
- Complete	54	-
Cancer Stage		
- IIB	57	0.000*
- IIIA	57	
- IIIB	54	
- IVA	50	
- IVB	56	
Histopathology		
- Non Keratinizing squamous cells ca	55	0.000*
- Keratinizing Squamous cells ca	53	
- Adenocarcinoma	53	
- Others	59	
Lymph Node Status		
- Positive	59	0.000*

- Negative	53	
Degree_Differentiation		
- Grade I	51	0.001*
- Grade II	55	
- Grade III	59	
Lymphovascular Invasion		
- No Data		
Age Group		
- 31-40 years old	59	0.038*
- 41-50 years old	53	
- 51-60 years old	54	
- 61-70 years old	54	
- 71-80 years old	50	
Menopausal Status		
- Not menopausal	53	0.203
- Already Menopause	55	
Parity		
- 1 Time (Primipara)	57	0.001*
- ≥2 Times (Multipara)	54	
Education		
- Primary school	53	0.022*
- Junior high school	52	
- Senior High School	55	
- College	58	
Profession		
- Have a job	53	0.351
- Do not have a job	55	
Marital Status		
- Married one time	56	0.001*
- Married ≥ two times	51	
History_Menstruation		
- There is a Disturbance	53	0.473
- No disturbance	55	
Contraception Use		
- Hormonal contraception	56	0.000*
- Non-hormonal contraception	54	
- Never used contraception	50	
BMI (Body Mass Index)		
- Underweight	53	0.000*
- Normal	56	
- Overweight	55	
- Obesity	50	
Residence		
- Village	55	0.674
- City	54	

*Significantly influential based on the results of the Log Rank test at the level of $\alpha = 0.05$

Based on the results of the Log Rank test in table 3 above, it is shown that of all variables; several variables show a significant effect on cervical carcinoma survival rate (p<0.05). These variables were radiation, radiation technique, cancer stage, histopathology, lymph node status, degree of differentiation, age, parity, education, marital status, contraception, and BMI. While the other variables obtained p>0.05, which shows no significant effect on cervical carcinoma survival rate. Further testing of the PH assumption was carried out using a survival graph. PH assumption is said to be fulfilled if there is no intersection in the survival graph. The survival graph of the clinicopathological profile variables and cervical cancer risk factors that significantly influence cervical carcinoma survival rate (p<0.05) can be seen in Figure 1.

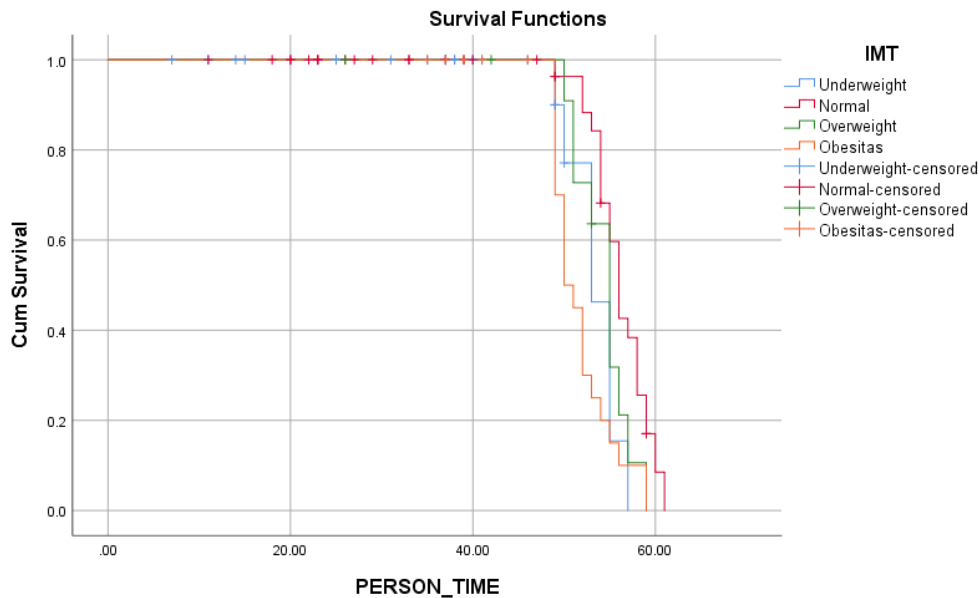Survival Functions

Survival Functions

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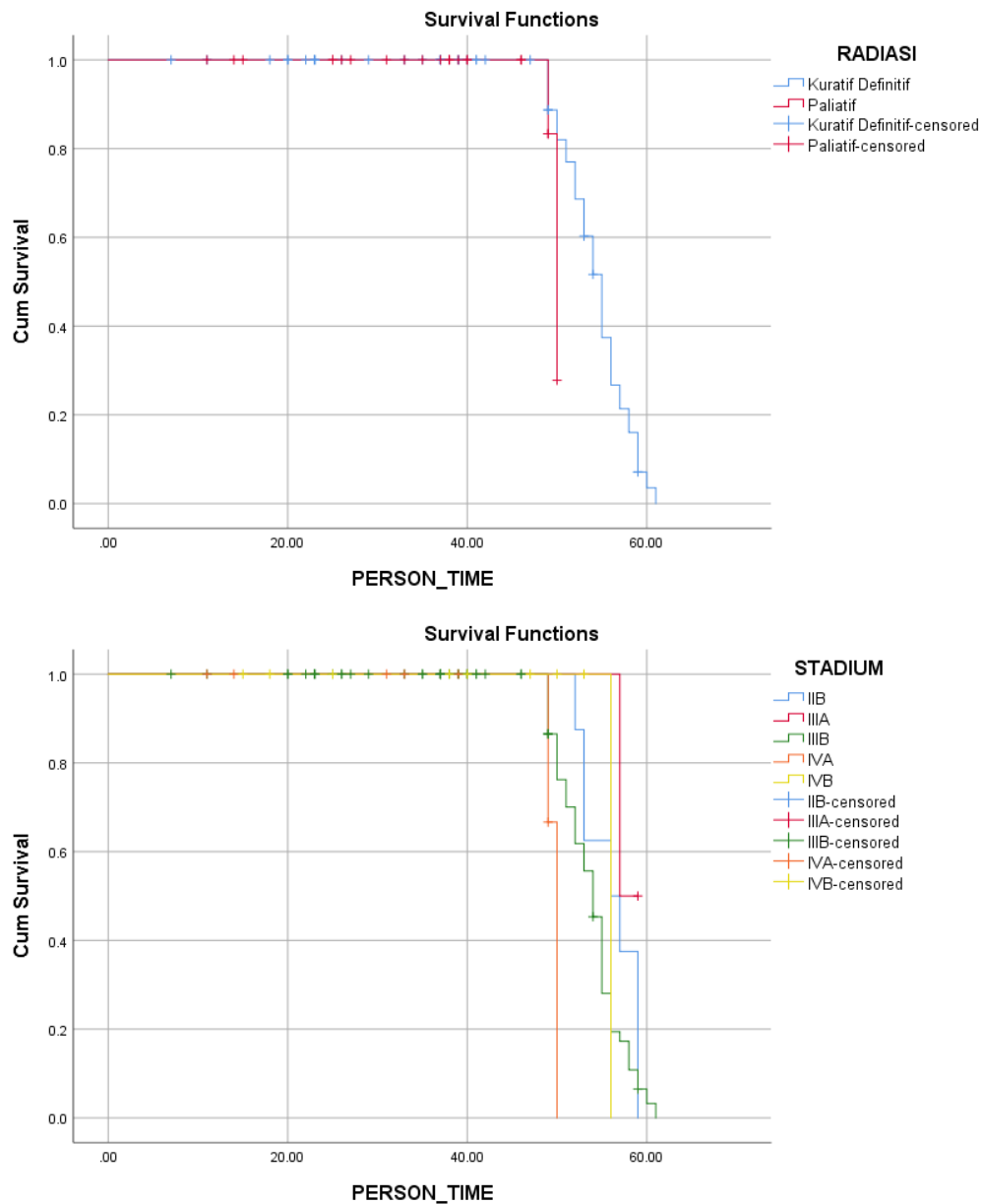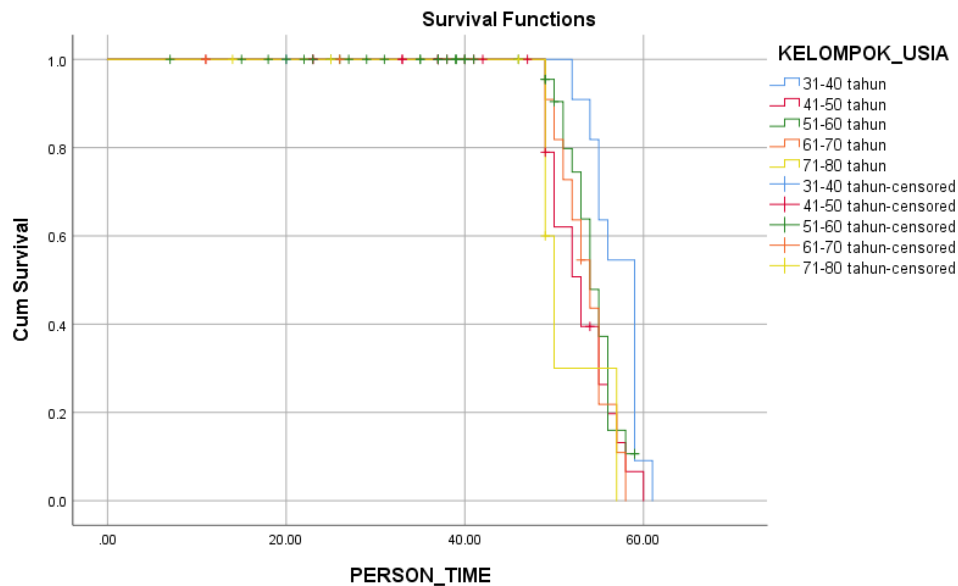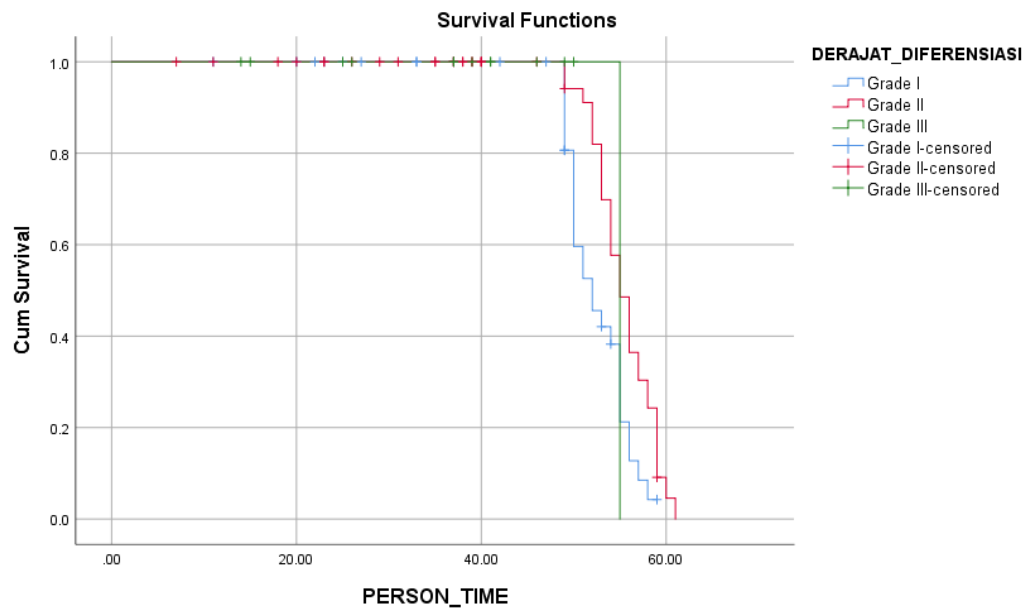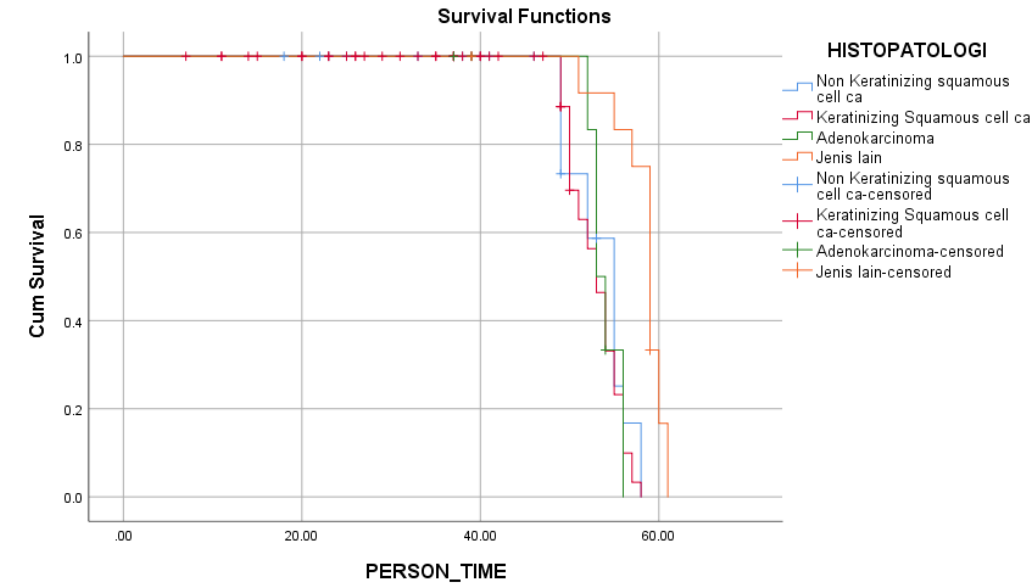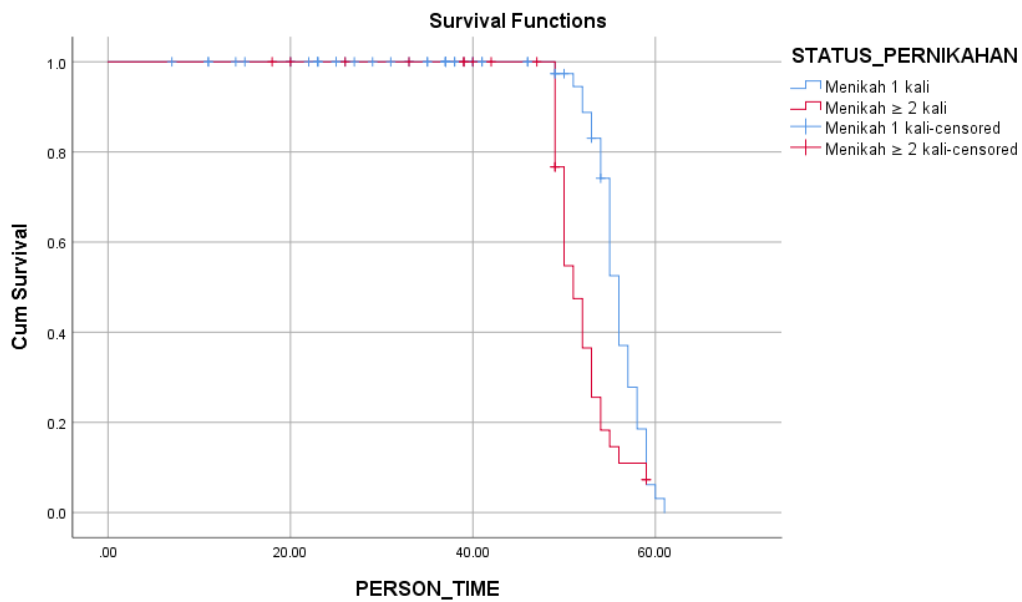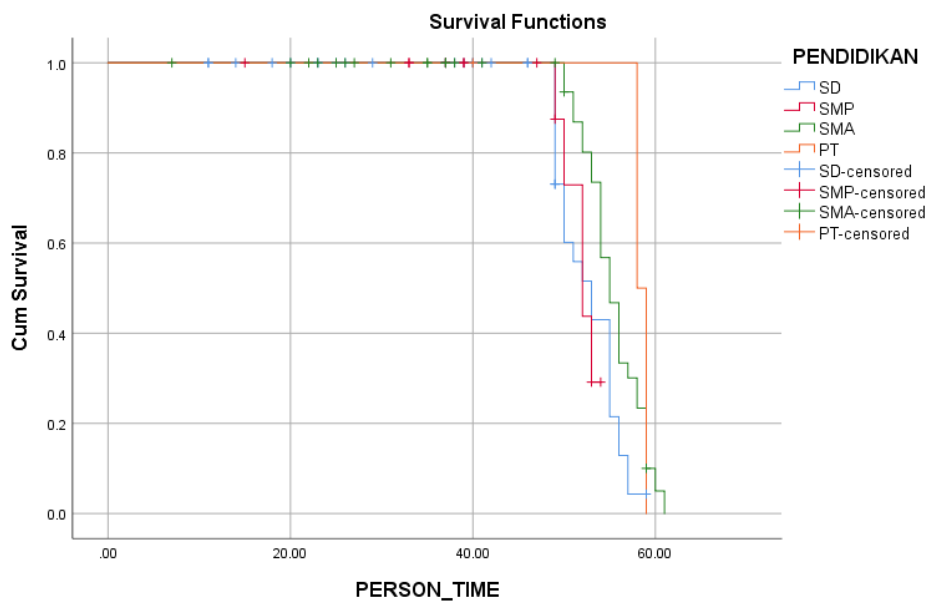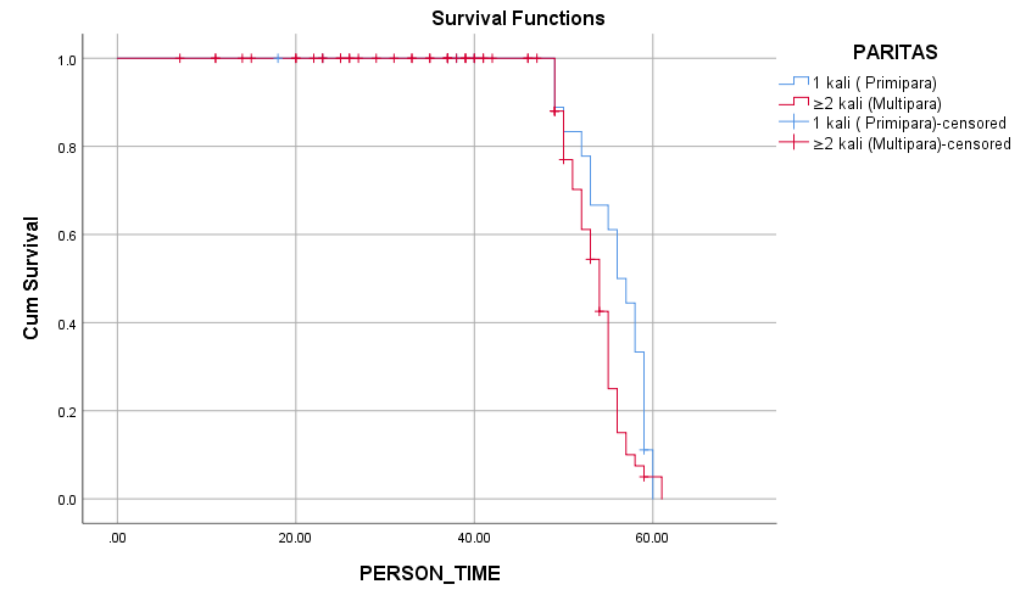
Figure 1. Survival Graph of the Effect Clinicopathological Profile and Risk Factors on Cervical Carcinoma Survival Rate

Based on Figure 1, it is shown that there is an intersection of the lines on the survival graph. This test shows that the PH assumption of the influence of the clinicopathological profile and risk factors is not met. Based on the results of the Kaplan Meier curve on the effect of radiation on cervical carcinoma survival rate, it was found that palliative radiation had a lower survival rate with a median survival time of 49 months compared to definitive curative radiation with a median survival time of 55 months. The external radiation technique has a median survival time of 56 months.

In the Clinicopathological Profile, stages IV A and IV B had lower survival rates, with median survival times at 50 and 56 months compared to other stages. Histopathology of the keratinizing squamous cell type had a lower survival rate, with the median survival time at 53 months compared to others. Lymph node status was obtained at 15,579 with a 95% CI of 3,587-67,662, which concluded that patients with lymph node-negative status had a higher survival rate of 15,579 times than patients with lymph node-positive status. The degree of differentiation obtained was 0.742 with a 95% CI of 0.419-1.313, which concluded that patients with grade I differentiation had a higher survival rate of 0.742 times than patients with other grades.

The risk factors for the age category of 71-80 years have a lower survival rate, with the median survival time being in the 50th month compared to other categories. Multiparas had a lower survival rate with a median survival time of 54 months compared to primiparas. Elementary and junior high schools have lower survival rates, with median survival times at 52 and 53 months compared to other levels. Marital status > 2 times had a lower survival rate, with the median survival time being at month 51 compared to marital status one time. The use of contraception was obtained at 1,943 with a 95% CI of 1,227-3,076, which concluded that patients using non-hormonal contraception had a higher survival rate of 1,943 times than patients using hormonal contraception. Underweight had a lower survival rate with a median survival time of 53 months compared to other BMI statuses.

Effect of Radiation on Cervical Carcinoma Patient Survival

Bivariate analysis was conducted to examine the relationship between radiation and cervical carcinoma patients' survival rate using the Hazard Ratio value obtained by cox regression analysis. The results of the HR analysis can be seen in table 4.

Table 4. Hazard Ratio Test Results Table with Cox Regression Radiation Relationship with Cervical Carcinoma Patient Survival

Variable	Hazard Ratio	p-value	95% CI
Radiation	11.226	0.000	4.003 - 31.486

Based on table 4, the HR value is 11,226 with 95% CI 4,003 - 31,486, and a p-value of 0.000 indicates a significant relationship between radiation and bivariate survival rate for cervical cancer patients. Based on the results of the HR test with cox regression of the relationship between radiation and cervical carcinoma patients' survival, it was concluded that at any time, cervical cancer patients who received radiation therapy had 11.266 times more likely to die compared to other therapies.

Effect of Clinicopathological Profile and Risk Factors on Survival of Cervical Carcinoma Patients in Multivariate

Multivariate analysis was conducted to examine the effect of clinicopathological profiles and risk factors on the survival rate of cervical carcinoma patients using Cox regression analysis. Variables for testing are variables with a p-value of less than 0.25: radiation, radiation technique, cancer stage, histopathology, lymph node status, degree of differentiation, age, parity, education, marital status, contraception use, and BMI. The results of the multivariate analysis are shown in table 5.

Table 5. Multivariate Analysis Results Table with Cox Regression

Variable	B	HR	p-value	95% CI
Radiation	0.743	2.102	0.010*	1.197 - 3.691
Technical_Radiation	0.221	1.247	0.182	0.902 - 1.726
Cancer Stage	-0.039	0.962	0.853	0.636 - 1.454
Histopathology	-0.379	0.685	0.043*	0.474 - 0.989
Lymph Node Status	2.746	15.579	0.000*	3.587 - 67.662
Degree_Differentiation	-0.299	0.742	0.306	0.419 - 1.313
Age Group	0.029	1.029	0.855	0.754 - 1.406
Parity	-0.519	0.595	0.253	0.245 - 1.448
Education	-0.089	0.915	0.644	0.626 - 1.336
Marital Status	0.172	1.187	0.618	0.605 - 2.329
Contraception Use	0.664	1.943	0.005*	1.227 - 3.076
BMI	0.373	1.453	0.033*	1.031 - 2.047

*Significantly influential based on the results of the Cox regression analysis at the level of $\alpha = 0.05$

Based on table 5, the radiation variable was obtained (p<0.010). From this test, it is proven that the radiation variable has a significant effect on the survival rate of cervical cancer patients. Similarly, histopathological variables, lymph node status, contraception use, and BMI (body mass index) had a significant multivariate effect (p<0.05) on the survival rate of cervical cancer patients.

The 5-year survival rate for cervical cancer patients, in general, is 71%. About 200,000 deaths from cervical cancer occur in developing countries (Andrijono et al., 2013). A previous study conducted in the Netherlands found that the 5-year survival

rate of cervical cancer patients in this study increased from 68% to 74%. However, in this study, it was found that radiation therapy as primary therapy could significantly reduce the 5-year survival rate of cervical cancer patients (p<0.001). In contrast, brachytherapy as primary therapy increased significantly (p<0.001) over time (Wenzel et al., 2021). In Indonesia, namely Malang City, in 2014, the results showed a one-year survival rate for patients with locally advanced cervical cancer who received radiation therapy without intracavitary brachytherapy at Dr. Saiful Anwar Malang 72% (Sherly, 2014). This study revealed the 5-year survival of cervical cancer patients who received radiation therapy at dr. Saiful Anwar Malang general hospital is only 53.1% (Table 1). The clinicopathological profile of cervical cancer patients greatly affects the survival rate (Yang et al., 2019).

The stage in this study showed a significant effect on the survival rate of cervical carcinoma who received radiation at dr—Saiful Anwar Malang general hospital (p<0.000) (Table 3). Cancer Stage rates in patients who died were higher in advanced stages, that is, stages IVA and IVB, compared to patients with living status. This is in line with other studies which state that the early-stage survival rate is 31.5% while the advanced-stage survival rate is only 4.1% (Telaumbanua, 2019). Histopathology in this study showed a significant effect (p<0.000) (Table 3), with squamous cell carcinoma being the most common characteristic compared to other histopathologies. Research states that the histopathological type of squamous cell is the type that contributes the most to the decline in the life of cervical cancer patients (Benitez-restrepo & Arias-ortiz, 2020). The degree of differentiation in this study showed a significant effect (p<0.001) (Table 3). In this study, it was found that in the degree of differentiation, the status of the patient who died was more common than in grades II and III. The degree of differentiation is one of the important prognostic factors in determining the administration of faster and more effective therapy in cervical cancer patients (Becker et al., 2017). In the results of multivariate analysis in other journals, it was proven that cervical cancer patients with poorly differentiated had 1.45 times the risk of significantly lowering the survival of cervical cancer patients (p<0.001) (Matsuo et al., 2018). Lymph node status in this study showed a significant effect (p<0.000) (Table 3). In another study, cervical cancer patients with negative lymph node metastases had a better 5-year survival rate of 85-90%, while patients with positive lymph node status only ranged from 20% (Sinaga, 2020). Lymph node status is the most independent predictive factor of the prognosis of cervical cancer that influences so that it can determine appropriate and effective therapy to improve the long-term survival of cervical cancer patients (Gai et al., 2019).

Risk factors greatly affect the survival rate of cervical cancer patients (Andrijono et al., 2013). Age in this study significantly affected the survival rate of cervical carcinoma who received radiation at dr. Saiful Anwar Malang general hospital (p<0.038) with more death status obtained at the age of 51-60 years, as many as 29 (53.8%) patients (Table 3). Based on research that was conducted in Spain, it was found that age as one of the independent variables had a significant effect (p<0.001), where the age range of 55-64 years had an 85% increased risk of death due to lack of response to good therapy in the patient's body, especially when patient receiving internal radiation therapy or brachytherapy (Amengual et al., 2020). Parity in this study showed a significant effect (p<0.001) on the survival status of death; most of the cervical carcinoma patients were multiparous, with a percentage of 88.5% (Table 3). Multiparas increase the risk of cervical cancer by 4-10 times greater than primiparas with an OR of 4.66 (2.043-10.66), so parity is one of the important risk factors for cervical cancer that can contribute to the survival of cervical cancer patients (Sharma

& Pattanshetty, 2018). Education in this study showed a significant effect (p<0.022) where most of the patients had only low and middle education (Table 3). Patients with a low level of education have three times more likely to develop cervical cancer, with an odds ratio of 3.54 (1.59-7.87) compared to those with a higher education level (Sharma & Pattanshetty, 2018). Contraception in this study showed a significant effect (p<0.000) where most of them used hormonal contraception control with a percentage of 44.2% (Table 3). Other studies also prove that users of combined hormonal contraception can experience an increased risk of cervical cancer by one time with an RR of 1.19 (95% CI 1.10-1.29) compared to progesterone-only or even non-hormonal contraceptive users (Iversen et al., 2021). Marital status in this study showed a significant effect (p<0.001) (Table 3). Women who have had a marriage partner more than once will increase the risk of cervical cancer, which contributes to the survival rate of cervical cancer and decreases the quality of life of these women (Carneiro et al., 2017). BMI (body mass index) in this study showed a significant effect (p<0.000) where there were as many as 40.4% of patients had an underweight BMI (body mass index) (Table 3). This is in line with previous studies which stated that BMI (body mass index) with a clinical response of patients where patients with underweight status only produced a clinical response of 25% and a progressive clinical response of 75%, this is because in underweight status there is an imbalance of protein and energy intake which causes metabolic changes that will have an impact bad on the results of therapy (Werestandina, 2014).

Radiation is a therapy that can be given to cervical cancer patients who have experienced advanced severity (Bhatla et al., 2018). Radiation therapy can be performed in patients with stage II B, III, and IV cervical cancer. Treatment therapy is tailored to curative or palliative therapy (Cohen et al., 2019). Regarding radiation therapy in this study, it was found that from 111 cervical cancer patients who received radiation therapy at dr. Saiful Anwar Malang general hospital obtained as many as 81 patients who received definitive curative therapy with a total death status of 31 people (38.2%) and a living status of as many as 50 people (61.7%), while those who received palliative radiation therapy were 30 patients with a total status of 30 patients, 21 patients (70%) died and only nine patients lived (30%) (Table 1). Most of the patients received definitive curative radiation, but the survival rate of patients who received palliative radiation was very low, with a lower median survival time (49 months) compared to definitive curative radiation; as many as 77 patients who received external radiation techniques where only 48% or 37 patients had live status while 40 patients (51.9%) had death status. In contrast, those who received combined radiation technique had a death status of only 35.2 % or as many as 12 patients and who had a living status of as many as 22 patients (64.7%), so it can be concluded that patients receiving combination therapy will have a better survival rate than those with external radiation therapy only. Multivariable Cox regression analysis in other journals also showed that the combined radiation technique on radiation would contribute to a better survival rate with HR 0.58 95% confidence interval 0.52-0.66; p<0.001 compared to using the external radiation technique only (Young Ae Kim, Min-Soo Yang, 2021).

The advantage of this study is that the results of the study can be used as an evaluation material in a gynecological oncology referral hospital related to the radiation therapy, especially combination radiation in cervical cancer patients, as a consideration in selecting effective therapy to increase the survival rate in order to increase the success of therapy given to patients cervical carcinoma by considering the clinicopathological profile and patient risk factors that affect the survival rate. The main limitation of this study is the retrospective design. A retrospective study tends to

have fewer potential data sources. The medical record completeness factor also affects the number of samples obtained because most of the required data does not exist.

CONCLUSION

In conclusion, the results of this study indicate a 5-year survival rate for cervical cancer patients who received radiation therapy at dr. Saiful Anwar Malang general hospital was only 53.1%. Profile of clinicopathology cancer stage ($p < 0.000$), histopathology ($p < 0.000$), lymph node status ($p < 0.000$), degree of differentiation ($p < 0.001$) and risk factors for age ($p < 0.038$), parity ($p < 0.001$), education (0.022), marital status (0.001), contraceptive use ($p < 0.000$), and BMI ($p < 0.000$) had an effect on cervical carcinoma survival rate. Where radiation, histopathology, lymph node status, type of contraception, and BMI had a significant multivariate effect ($p < 0.005$) on the survival rate of cervical cancer patients. The use of combination radiation therapy in cervical cancer patients contributes to a better survival rate compared to external radiation only. It is hoped that the use of combination radiation therapy with consideration of the clinicopathological profile and risk factors that affect the survival of cervical cancer patients can be a clinician's consideration in determining the administration of therapy in cervical cancer patients to increase cervical cancer survival rates patient.

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CONFLICT OF INTEREST

All authors state that there is no conflict or problem with any party in the writing of this journal publication.

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