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Association of HPV Genotyping with HIF1-Alpha in Advanced Cervical Cancer on Response to Radiotherapy

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Abstract

AIM: This study aims to determine the relationship between the HPV genotype in uterine cervical cancer and the expression of HIF-1α due to tissue hypoxia and its impact on radiation response.

METHODS: This study is an analytic and observational study with a cross-sectional design with the inclusion criteria in this study that was new cervical cancer Stage IIB, IIIA, IIIB, and IVA patients treated at the oncology polyclinic who had never undergone radiotherapy and would be treated with radiation.

RESULTS: Sixty patients advanced cervical cancer aged 25 to >45 years were involved patients. The majority had HPV genotype 16 infections. There was no significant relationship between treatment response and HPV genotype (HPV 16 genotype [p = 0.844], HPV 18 genotype [p = 0.161], other HPV genotypes [p = 0.108]), radiation response with HIF-1α expression (p = 0.503; OR 1.569 [0.417–5.899]), HIF1α expression with HPV genotype (HPV genotype 16 (p = 0.648; OR 1,357 [0.356–5.041]), HPV 18 genotype (p = 0.344; OR 1,458 [0.089–2.373]), and other HPV genotypes (p = 0.505; OR 1.667 [0.368–7.553]) as well as HIF-1α expression and HPV genotypes to radiation response (p > 0.05).

CONCLUSION: Cervical cancer with infection with HPV Genotype 18 tends to express HIF1α strongly and increased partial radiation response. Overall statistically, there was no significant association between infection with certain genotypes of HPV with radiation response or HIF-1α expression in tumor tissue with radiation response.

Introduction

Cervical cancer is the fourth most common malignancy in women. Every year, 500,000 new cases emerge, and 250,000 die [1]. In Indonesia, cervical cancer is the second most common cancer in women, with 23.4 cases/100,000 population and 13.9 deaths/100,000 population [2]. In 2020, at our center, there were 350 new cases of cervical cancer, with 335 at an advanced stage.

According to the WHO, 99% of cervical cancer are associated with high-risk HPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68). HPV genotypes 16 and 18 are the most common causes of cervical cancer and precancerous lesions (70%) [3], [4], [5], [6], [7]. Several studies suggest that the HPV genotype can be a prognostic indicator for cervical cancer [5]. HPV with genotype 18 has a higher risk of mortality and recurrence [6].

Hypoxia induction factor (HIF)-1α is a predictive marker in the response and prognosis of patients at an advanced stage who received radiotherapy [7]. HIF1α induces the expression of pyruvate dehydrogenase kinase (PDK), which inhibits the enzyme pyruvate dehydrogenase through phosphorylation and control critical glycolytic enzymes to generated maximum Adenosine Triphosphat [14]. Is HIF1α activation is related to specific HPV genotypes and causes tumor tissue hypoxia leading to decreased response of cervical cancer radiation therapy.

Methods

Patients and treatment

This is an analytic and observational study with a cross-sectional design, followed by a comparative analysis. From January 2022 to September 2022 new cervical cancer Stage IIB, IIIA, IIIB, and IVA patients treated at oncology polyclinic who had never undergone radiotherapy and would be treated with radiation at

Hasan Sadikin Hospital, Bandung, Indonesia, were included in the study. Radiotherapy was administered to the whole pelvic region in 25 fractions of 1.8 Gray (Gy) for a total dose of 45 Gy for 5 weeks. Follow-up of radiotherapy responses included clinical examination of patients conduct in 3 months and measured by the RECIST criteria and measured using gynecological bimanual examination and MRI or CT scan or transvaginal ultrasonography.

The exclusion criteria from this study were: Cervical cancer patients who had secondary cancer; patients with complicated diabetes mellitus, heart disease, and anemia; patients who did not complete radiation therapy; and the patient who died. Medical data extracted from computerized medical records included demographic, clinical, imaging, and clinical staging.

The study was approved by the institutional review board.

HIF1α and HPV DNA genotyping

The independent variables in this study were high-risk HPV genotypes (HPV types 16, 18, and other high-risk types [31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, and 68]) using HPV XpressMatrix™ Genotyping Kit and HIF1α expression on histopathological examination, which was then divided into weak (score <10%) and strong (score >10%).

Statistical analysis

Data processing and analysis were carried out using SPSS version 24.0 for Windows. Characteristics of research subjects were analyzed according to descriptive statistics. Before the analysis of the association between variables, the normality of the data was tested using the Shapiro–Wilk test, with the alternative Kolmogorov–Smirnov. The significance test carried out with an unpaired t-test and the Mann–Whitney test. Statistical analysis for categorical data was tested by Chi-square test with alternative Exact Fisher and Kolmogorov–Smirnov test. Bivariate analysis and binary logistic regression analysis was performed. The independent variables included in the logistic regression model were independent variables that, in bivariate analysis, had $p < 0.25$. Therefore, the results are considered significant if $p \leq 0.05$.

Results

This is the first study to investigate the association between HPV genotype and HIF-1α expression and radiation response, involved 60 women with advanced cervical cancer aged 25 to >45 years.

Characteristics of research subjects based on response to radiotherapy

Of the 60 patients, 22 gave a partial response to radiation therapy, and 38 showed a complete response. Table 1 shows the characteristics of the research subjects. In the partial response group, the majority of patients were >45 years old (n = 18 [81.8%]), and the rest were in the 35–44 year of age group (n = 4, [18.2%]). In the partial response group, the majority of patients were in stage II (n = 12, [54.5%]), followed by Stage III in 9 (40.9%) and Stage IV in 1 (4.5%). Meanwhile, based on BMI, the majority of patients with partial response were in the BMI group of 18.5–25.0 (n = 11, [50.0%]), followed by BMI 25–30 in 6 (27.3%), BMI <18.5 in 3 (13.6%), and BMI >30 as many as 2 (9.1%) people.

Table 1: Comparison of the characteristics of research subjects based on radiation response

Variables	Response to radiotheraphy		p-value
	Partial	Complete	
	N = 22	N = 38	
Age			0.371
25–34 years old	0 (0.0%)	3 (7.9%)	
35–44 years old	4 (18.2%)	5 (13.2%)	
>45 years old	18 (81.8%)	30 (78.9%)	
Stage			0.510
II	12 (54.5%)	22 (57.9%)	
III	9 (40.9%)	16 (42.1%)	
IV	1 (4.5%)	0 (0.0%)	
BMI			0.362
<18.5	3 (13.6%)	1 (2.6%)	
18.5–25.0	11 (50.0%)	23 (60.5%)	
25.0–30.0	6 (27.3%)	12 (31.6%)	
>30.0	2 (9.1%)	2 (5.3%)	

For categorical data, the p value is determined using the Chi-square test, with the Kolmogorov–Smirnov test and Fisher's exact as alternatives if the Chi-square conditions are not met. The significance level is determined by a p value of 0.05.

In the complete response group, the majority of patients were also >45 years old (n = 30, [78.9%]), followed by 3 (7.9%) in the 25–34 years old group, and 5 (13.2%) age 35–44 years. The proportion of stages in the complete response group was also similar to the partial response group; the majority of patients were in Stage II (n = 22, [57.9%]), followed by Stage III in 16 (42.1%) and Stage I in 1 (2.6%) person. Patients with BMI <18.5 were 1 (2.6%), 18.5–25.0 were 23 (60.5%), BMI 25–30 were 12 (31.6%), and BMI >30 were 2 (5.3%) person.

Analyses of categorical data, such as age, stage, and BMI in Table 1 above, were evaluated using the Chi-square test, which yielded $p > 0.05$, indicating that the differences were not statistically significant.

The association of HPV genotypes with HIF-1α expression

Of the 60 patients, 11 had xfweak HIF-1α expression, and 49 had strong HIF-1α expression (Table 2, Figure 1). In the weak HIF-1α expression group, the majority of HPV genotypes found were type 16 (n = 6 [54.5%]), followed by other types (n = 3 [27.3%]), and the last one was type 18 (n = 2 [18.2%]). In the strong HIF-1α expression group, the majority of patients had HPV genotype type 16 (n = 23 [46.9%]), followed by type 18 (n = 16 [32.7%]), other types (n = 9 [18.4%]), and the negative category (n = 1 [2.0%], Figure 2).

Table 2: Association of HPV genotypes with HIF-1α expression

Variables	HIF-1α expression		p-value
	Weak	Over expression	
	N = 11	N = 49	
HPV genotypes			0.725
Negative	0 (0.0%)	1 (2.0%)	
Type 16	6 (54.5%)	23 (46.9%)	
Type 18	2 (18.2%)	16 (32.7%)	
Other types	3 (27.3%)	9 (18.4%)	

For categorical data, the p value is calculated based on the Chi-square test with the alternative of Kolmogorov–Smirnov and Fisher's Exact tests if the Chi-square requirements are not met. The value is considered significant if the p value<0.05.

For the analysis of categorical data in the table above was not statistically significant (p > 0.05). The likelihood of patients with weak HIF1α expression with HPV genotype 16 was 1357 times compared to patients with strong HIF1α expression, with a confidence interval of (0.365–5.041) (Table 3).

Table 3: Relationship between HIF1α expression and HPV 16 genotype

Variable	Genotype		OR (CI 95%)	p value
	Type 16	Type 18, Others, Negative		
	N = 29	N = 31		
HIF1α expression			1.357	0.648
Weak	6 (20.7%)	5 (16.1%)	(0.356–5.041)	
Strong	23 (79.3%)	26 (83.9%)		

For categorical data, the p value is calculated based on the Chi-square test with the alternative of the Kolmogorov–Smirnov test and Fisher's exact if the Chi-square requirements are not met. The value of significance based on the value of p<0.05.

The likelihood of patients with weak HIF1α expression with HPV genotype 18 was 0.458 times compared to patients with strong HIF1α expression, with a confidence interval of (0.089–2.373) (Table 4).

Table 4: Relationship between HIF1α expression and HPV 18 genotype

Variable	Genotype		Genotype	p value
	Type 18	Type 16, Others, Negative		
	N = 18	N = 42		
HIF1α expression			0.458 (0.089–2.373)	0.344
Weak	2 (11.1%)	9 (21.4%)		
Strong	16 (88.9%)	33 (78.6%)		

For categorical data, the p value is calculated based on the Chi-square test with the alternative of the Kolmogorov–Smirnov test and Fisher's Exact if the Chi-square requirements are not met. The value of significance based on the value of p<0.05.

The probability of patients with weak HIF1α expression with other HPV genotypes was 1,667 times compared to patients with strong HIF1α expression, with a confidence interval of (0.368–7.553) (Table 5).

Table 5: Relationship between HIF1α expression and other HPV genotypes

Variable	Genotype		OR (CI 95%)	p value
	Other	Type 16, type 18, Negatif		
	N = 12	N = 48		
HIF1α expression			1.667	0.505
Weak	3 (25.0%)	8 (16.7%)	(0.368–7.553)	
Strong	9 (75.0%)	4 (83.3%)		

For categorical data, the p value is calculated based on the Chi-square test with the alternative of the Kolmogorov–Smirnov test and Fisher's Exact if the Chi-square requirements are not met. The value of significance based on the value of p<0.05.

The association between response to radiotheraphy and HIF-1α expression

In the weak HIF-1α expression group, the majority showed complete radiation response (n = 6 [54.5%]), while the rest showed partial radiation response (n = 5 [45.5%]). The same thing was found in the HIF-1α overexpression group, where the majority of patients showed complete radiation response (n = 32 [65.3%]), and the rest showed partial response (n = 17 [34.7%]) (Table 6).

Table 6: The association between response to radiotheraphy and HIF-1α expression

Variables	HIF1α expression		OR (CI 95%)	p-value
	Weak	Overexpression		
	N = 11	N = 49		
Response to radiotherapy			1.569	0.503
Partial	5 (45.5%)	17 (34.7%	(0.417–5.899)	
Complete	6 (54.5%)	32 (65.3%)		

For categorical data, the p value is calculated based on the Chi-square test with the alternative of the Kolmogorov–Smirnov test and Fisher's Exact if the Chi-square requirements are not met. The significance value is based on the p value<0.05.

For the analysis of the categorical data, there is no statistically significant difference in response to radiotheraphy and HIF-1α expression (p = 0.503). The odds ratio value above shows that the probability of patients with partial response to express weak HIF1α is 1,569 times compared to patients with complete response. With a confidence interval of (0.417–5.899).

The association between radiation response and HPV genotypes

In the negative HPV genotype group, only one subject was found and showed a complete response to radiation (n = 1 [100%]). In the Type 16 group, the majority gave a complete response (n = 18; [62.1%]) and the rest showed a partial response (n = 11 [37.9%]). In the type 18 group, the same proportion of radiation response was obtained. In the other type group, most patients responded completely (n = 10 [83.3%]).

The odds of patients with partial radiation response with HPV genotype 16 were 1111 times that of patients with complete radiation response, with a confidence interval of (0.389–3,177) (Table 7). The odds of patients with partial response to therapy with HPV genotype 18 were 0.231 times compared to patients with complete response to therapy, with a confidence interval of (0.719–6,920) (Table 7). The odds of patients with partial response to therapy with other HPV genotypes were 0.280 times that of patients with complete response to therapy, with a confidence interval of (0.055–1.419) (Table 7). Although in overall,

Table 7: Relationship between HPV type and radiation response

Variable	Response to radiation		OR (CI 95%)	p value
	Partial	Complete		
	N = 22	N = 38		
HPV 16			1.111 (0.389–3.177)	0.844
Type 16	11 (50.0%)	18 (47.4%)		
Type 18, other types, and negative	11 (50.0%)	20 (52.6%)		
HPV 18			2.231 (0.719–6.920)	0.161
Type 18	9 (40.9%)	9 (23.7%)		
Type 16, other types, and negative	13 (59.1%)	29 (76.3%)		
Other types			0.280 (0.055–1.419)	0.108
Other types	2 (9.1%)	10 (26.3%)		
Type 16, type 18 and, negative	20 (90.9%)	28 (73.7%)		

For categorical data, the p value is calculated based on the Chi-square test with the alternative of the Kolmogorov–Smirnov test and Fisher's Exact if the Chi-square requirements are not met. The results are significant if p<0.05.

the association between radiation response and HPV genotypes was not statistically significant (Table 8) (p = 0.257).

Table 8: The association between radiation response and HPV genotypes

Variables	HPV genotypes				p-value
	Negative	Type 16	Type 18	Other types	
	N = 1	N = 29	N = 18	N = 12	
Radiation response					0.257
Partial	0 (0.0%)	11 (37.9%)	9 (50.0%)	2 (16.7%)	
Complete	1 (100.0%)	18 (62.1%)	9 (50.0%)	10 (83.3%)	

For categorical data, the p value is calculated based on the Chi-square test with the alternative of the Kolmogorov–Smirnov test and Fisher's Exact if the Chi-square requirements are not met. The results are significant if p<0.05.

The association of HIF-1α expression and HPV genotype to radiation response

In multivariate analysis in the model were HIF1α expression and HPV genotype, showed that all variables had p>0.05. It indicates that simultaneously and overall, the expression of HIF-1α and HPV genotype did not affect the radiation response. Meanwhile, the analysis of the final model shows a more substantial but no significant relationship. Therefore, it can be concluded that statistically, no variables are related to radiation response (Table 9).

Table 9: Multivariate analysis to determine the association between HIF1 expression and HPV genotype and radiation response

Variables	B	SE	Wald	Nilai P	OR	CI 95%	
						Lower	Upper
Initial model							
HIF1α expression	0.466	0.680	0.470	0.493	1.594	0.421	6.038
HPV genotypes	0.235	0.340	0.480	0.488	1.265	0.650	2.463
Final model							
HPV genotypes	0.228	0.339	0.454	0.500	1.257	0.647	2.441

Multivariate analysis with binary logistic regression. The independent variable included in the logistic regression model is the independent variable that in the bivariate analysis has a p value<0.25.

Discussion

Decades of research have established that human papilloma virus (HPV) infection is a leading cause of cervical cancer; yet, it remains unclear and contentious how this virus modulates tumor response to radiation. A hypoxic microenvironment stimulates the expression of several genes in tumor tissue. One of these genes is HIF-1α, which indicates that cells are developing under hypoxic conditions. As a biomarker of tissue hypoxia, HIF-1α can be employed as an indicator of anaerobic metabolism in cancer cells. One of the factors that reduces the responsiveness of a tumor to radiation is hypoxic tissue [8].

In the results of data analysis, we found that HPV 18 genotypes had trend to express strong HIF1α expression (16 [32.7%] vs. 2 [11, 1%]) (OR 95% CI: 0.458 [0.089-2.373]), although in overall certain HPV genotypes did not have a significant relationship with

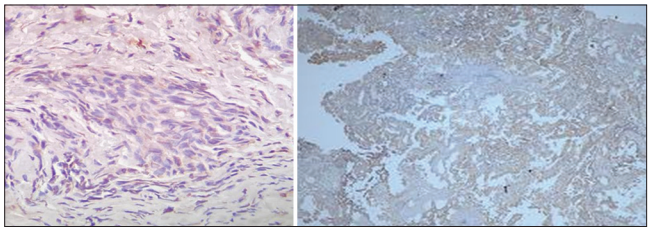

Figure 1: Negative and weak immunostaining HIF-1α, ×400. Uterine cervical cancer lesion

HIF1α expression (p > 0.05). According to Onuki *et al.*, HPV-16 infection showed better radio sensitivity than patients receiving chemo radiation [9]. A recent study also reported a favorable prognosis in Chinese patients with HPV Type 16-positive tumors [10]. However, Hall *et al.*, in an *in vitro* study, suggested that intrinsic radio sensitivity may not be related to the genotype of the infecting HPV [11]. Our results also show that the sensitivity of tumor response to radiotherapy does not differ between infections of the HPV-16, 18, and other genotypes (35, 39, 45, 51, 52, 53, 56, 59, and 68) (p = 0.257). From our study data, patients with HPV genotype 16 were 1111 times more likely to have partial radiation response compared to complete radiation response (CI 95%: 0.389–3,177), partial response patients with HPV 18 genotype was 0.231 times (CI 95%: 0.719–6,920), and in other HPV genotypes 0.280 times compared to patients with complete response to therapy, with a (CI 95%: 0.055–1.419). Controversial results show that other factors such as tumor size, histologic type, level of differentiation, lymph node involvement, and metastasis also play a major role in radioresistance [9], [10].

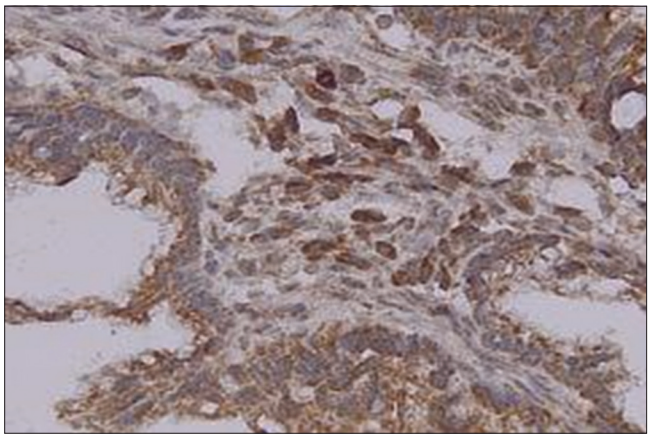

Figure 2: Strong positive immunostaining HIF-1α, ×200. Uterine cervical cancer lesion

Radiotherapy is still one of the best treatments for cervical cancer [8]. Our results showed that among the 60 patients included in the study, 38 patients showed a complete response, and 22 partial response. In addition, we also found that most patients in this study had HIF-1α solid expression (49/60). However, our statistical analysis found no association between HIF-1α expression and response to radiation therapy (p = 0.503; OR 1.569 [0.417–5.899]). Although, in our

study data, the group with partial response to weak HIF1α expression was 1569 times compared to the group with complete response.

HIF-1α is a dimeric protein complex that plays an integral role in response to low oxygen concentrations or hypoxia. It causes angiogenesis, an increase in this gene in ischemic patients may increase the proliferation of blood vessels required for oxygenation. On the other hand, it allows the survival and proliferation of cancer cells due to its angiogenic properties, HIF-1α inhibition can potentially prevent the spread of cancer [12], [13].

Han *et al.* concluded that HIF-1 expression is associated with a poorer prognosis for advanced cancer patients treated with chemotherapy, radiotherapy, or chemoradiotherapy [14]. Winata *et al.* demonstrated the relationship between pulsatility index (PI), resistance index (RI), and HIF-1α with the clinical response after external radiation in patients with cervical cancer stage IIB to IVA. The mean values of PI and HIF-1α were significantly lower in patients who showed a good response after radiation [15]. Song *et al.* found that miR-21 upregulation in radiotherapy-resistant cervical cancer was at least partly due to HIF-1α overexpression and was further enhanced via the PTEN/Akt/HIF-1α feedback loop [16]. In addition, in an *in vitro* study using mice, radioresistance in cervical cancer cells occurred due to HOTAIR overexpression through upregulation of HIF-1α expression [17]. Hypoxic conditions increase HIF-1α-dependent radiation resistance by increasing VEGF expression and inhibiting p53 expression [8]. Thus, it may contribute to resistance to radiation therapy [18].

Conclusion

Tumor cells in cervical cancer with infection with HPV genotype 18 tend to express HIF1α strongly compared to other high-risk HPV genotypes. The partial radiation response of HPV 18 genotype along in tumors expressing weak HIF1α, although statistically, there was no relationship between HIF-1α expression in tumor tissue and radiation response. Other factors such as the large size of the tumor before radiation, tumor differentiation, immune status of the patient, involvement, and metastasis of lymph nodes, and tumor vascularity are also major contributing factors to radiation response in cervical cancer.

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