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Correlations of Protein 53 (p53) Expression with the Degree of Tumor Budding in Cervical Carcinoma

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ABSTRACT

Background: Cervical carcinoma is a malignant tumor that is most often found in the female reproductive system. Persistent Human Papillomavirus (HPV) infection is the most important factor in the development of cervical carcinoma. The E6 and E7 oncoproteins in HPV inhibit the action of p53. As a result, p53 transcription and the apoptosis process are inhibited. Tumor budding has been extensively studied and established as a significant prognostic factor. This study aims to determine the relationship between p53 expression and the degree of tumor budding of cervical carcinoma.

Method: This cross-sectional study used 50 paraffin blocks and secondary data from patients diagnosed with cervical carcinoma stored at BaliMed Denpasar Hospital. Paraffin blocks were then subjected to immunohistochemical examination to evaluate p53 expression and H&E examination to evaluate the degree of tumor budding. Data analysis was performed using the Spearman test and linear regression test with the SPSS 25 software program.

Results: The results showed that thirty-two subjects had low expression of p53, and 62,5% of them had high-grade tumor budding. The p53 expression is lower in cervical cancer with high-grade tumor budding compared with low-grade tumor budding (rs = -0.33). There are significant correlations between p53 expression and the degree of tumor budding in patients with cervical carcinoma (p = 0.018). A total of 50 samples that met the inclusion and exclusion criteria were analyzed. The majority of patients were aged ≤ 50 years (58%) and had squamous cell carcinoma (90%) in the early stage (92%). Low p53 expression was found in 64% of samples. A significant negative correlation was found between p53 expression and tumor budding grade (p = 0.018; r = -0.333), which remained significant in multivariate analysis (p = 0.024; r^2 = -0.328), indicating that low p53 expression is associated with high-grade tumor budding.

Conclusion: The p53 expression was significantly downregulated in cervical carcinoma with high-grade tumor budding. These findings indicate that tumor budding can be considered as a prognostic marker, but further research that sorts HPV dependent and HPV independent cervical carcinomas is needed.

INTRODUCTION

Cervical carcinoma is the most common disease in developing countries and is in the top ten in developed countries [1]. Cervical carcinoma is the leading cancer in developing countries and among the ten most common in developed nations. Approximately 50% of deaths due to cervical carcinoma occur in developing countries. Cervical carcinoma cases in Indonesia occupy the second-highest position after breast carcinoma. There were around 32,469 (17.2%) new cases of cervical carcinoma, with a death rate of 18,279 (8.8%) cases [2].

Persistent infection of Human Papillomavirus (HPV) is the most crucial factor in the development of cervical

carcinoma. HPV 16 and 18 are the most common HPV serotypes that cause cervical carcinoma (70% of cases) [3]. The E6 and E7 oncoproteins provide oncogenic characteristics to HPV. E6 oncoprotein works by inhibiting the action of p53 through E6 ligase. Thus, the p53 transcription and the apoptosis process are disrupted [4].

Early stages of cervical cancer don't usually involve symptoms, which often causes cervical cancer to be diagnosed at a late stage and has metastasized. The lymph node pathway is the most common route for cervical carcinoma metastases [5]. The metastatic status of cervical carcinoma is beneficial for determining prognosis and therapy. However, the lymph node metastases cannot always be determined because lymphadenectomies are not routinely performed. Therefore, new parameters are needed to predict the likelihood of lymph node metastasis, enabling clinicians to assess the prognosis and appropriate therapy for patients.

Tumor budding has been studied and is associated with tumor aggressiveness. Tumor budding is defined as the presence of single tumor cells or isolated small clusters of tumor cells (up to five tumor cells) scattered in the stroma at the invasive front [6]. In colorectal carcinoma, tumor budding has been extensively studied and established as a significant prognostic factor. Tumor budding in cervical carcinoma has not been widely studied. However, recent studies indicate that high-grade tumor budding is positively correlated with the size of the primary tumor, deep stromal invasion (DSI), parametrial invasion, and lymph node metastasis. These findings suggest that high-grade tumor budding contributes to more aggressive biological behavior in patients with cervical carcinoma [7].

A recent study has shown that p53 staining is associated with tumor budding in colorectal carcinoma. The mechanism of how p53 influences the grade of tumor budding has not been well explained [8]. A study demonstrates that p53 can regulate genes involved in cell migration through Slug or Snail, transcription factors that regulate the expression of tumor suppressors such as E-cadherin. Loss of E-cadherin is associated with metastatic events in cancer [9]. E-cadherin mediates contact between cells in some tissues. In the development of cancer cells, proliferation and contact between these cells fail to be inhibited. Loss of E-cadherin expression is said to be related to the epithelial-mesenchymal transition (EMT) process. EMT is the ability of epithelial cells to transform from immobile to motile mesenchymal progenitor cells [10]. The changes in E-cadherin expression are thought to be related to the grade of tumor budding, where tumor budding is also said to be an early stage of the EMT process [11]. Thus, this study aims to investigate the correlation between protein 53 (p53) expression and the degree of tumor budding in cervical carcinoma.

METHODS

This research used a cross-sectional study design at BaliMed Denpasar Hospital on 50 patients with cervical carcinoma who met the inclusion and exclusion criteria using simple random sampling. The samples in this study were wild-type p53 paraffin blocks from patients diagnosed with cervical carcinoma that were stored at the BaliMed Denpasar Hospital from 2021 to 2022. Inclusion criteria were all wild-type p53 paraffin blocks of cervical carcinoma that had been diagnosed histopathologically. Exclusion criteria included paraffin blocks that were damaged or did not contain sufficient tumor mass, as well as paraffin blocks from patients who had received chemoradiation.

The age, type of cancer, and stage of cancer data were obtained from medical records. Meanwhile, p53 expression data were obtained from immunohistochemical (IHC) examination, and the grade of tumor budding data were obtained from hematoxylin and eosin (H&E) staining. Age is divided into two categories: > 50 years and ≤ 50 years. Types of cancer are divided into squamous cell carcinoma (SCC) and non-SCC (adenocarcinoma, adenosquamous). Cancer stages are divided into early stages (IA-IIA) and late stages (IIB-IV). Paraffin blocks of cervical carcinoma were subjected to IHC staining using anti-p53 antibodies (wild type) to evaluate p53 expression. The p53 expression obtained was wild-type p53 expression. Observations were carried out using a microscope with 400x magnification in five different fields of view by an anatomical pathologist. The percentage of cell nuclei-stained brown by the wild-type p53 antibody was then calculated, and the average rate across the five visual fields was determined. p53 expression is grouped into low expression (nuclei stained < 50%) and high expression (nuclei stained ≥ 50%) [12]. The samples were then re-cut for H&E staining to evaluate the degree of tumor budding. Observation of the degree of tumor budding was carried out using a light microscope on slides with the highest visible tumor budding at the invasive edge. Then, the tumor budding was observed with 100x magnification, and a hotspot area was selected. The tumor budding is then observed with 200x magnification, and the number of tumor buddings is calculated to determine the degree. The degree of tumor budding is categorized into low-grade (buds < 10) and high-grade (buds ≥ 10) [13].

All data were then tabulated and analyzed. Univariate analysis was carried out to obtain a frequency distribution and to obtain the characteristics of the subjects. Bivariate analysis was carried out with the Spearman Rank Test using the IBM SPSS version 25 application to determine the correlation between p53 expression and the grade of tumor budding of cervical carcinoma.

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RESULT

A total of 50 samples that met the inclusion and exclusion criteria were obtained. **Table 1** shows that most of the samples (58%) were ≤ 50 years old, while 21 samples (42%) were > 50 years old. The majority of the samples (90%) had SCC, and five samples (10%) had Non-SCC (adenocarcinoma, adenosquamous). Most of the samples (92%) were at an early stage, and four samples (8%) were at a late stage. p53 expression was dominated by the low expression p53 (64%), and the other 18 samples (36%) had high expression of p53. Meanwhile, between the low-grade tumor budding and high-grade tumor budding, the grade exhibits the same number.

The correlation between p53 expression and the degree of tumor budding was analyzed using the Spearman Rank Test with a significance value of 0.05. **Table 2** shows that p = 0.018, which indicates a significant relationship between p53 expression and the degree of tumor budding in cervical carcinoma at BaliMed Denpasar Hospital. The correlation coefficient is -0.33, meaning the strength level is weak. The correlation coefficient is negative, so the relationship between the two variables is in the opposite direction, meaning that the lower the p53 expression, the higher the grade of tumor budding. **Figure 1** illustrates the expression of p53 in cervical carcinoma.

Table 1. Research sample characteristics

Characteristics	N (%)
Age (year)	
> 50 years	21 (42)
≤ 50 years	29 (58)
Type of cancer	
SCC	45 (90)
Non-SCC	5 (10)
Cancer stage	
Early stage	46 (92)
Late stage	4 (8)
P53 expression	
Low expression	32 (64)
High expression	18 (36)
Tumor budding	
Low-grade buds	25 (50)
High-grade buds	25 (50)

SCC: squamous cell carcinoma

Table 2 Correlations between p53 expression and the degree of tumor budding in cervical carcinoma

Variable (n = 50)	Tumor budding		P	Correlation coefficient (rs)
	Low-grade buds (n = 25)	High-grade buds (n = 25)		
P53 expression				
Low expression	12 (37.50%)	20 (62.50%)	0.018*	-0.333
High expression	13 (72.20%)	5 (27.80%)		

*Spearman Rank Test: Statistically significant if the p-value is less than 0.05

Table 3. Correlations between p53 expression and the degree of tumor budding in cervical carcinoma by multivariate analysis

Variable (n = 50)	Tumor budding		Bivariate analysis		Multivariate analysis	
	Low-grade buds (n = 25)	High-grade buds (n = 25)	P	Correlation coefficient (r)	P	Correlation coefficient (r^2)
P53 expression						
Low expression	12 (37.50%)	20 (62.50%)	0.018*[a]	-0.333	0.024*[b]	-0.328
High expression	13 (72.20%)	5 (27.80%)				

*a Statistically significant by bivariate analysis
*b statistically significant by multivariate analysis

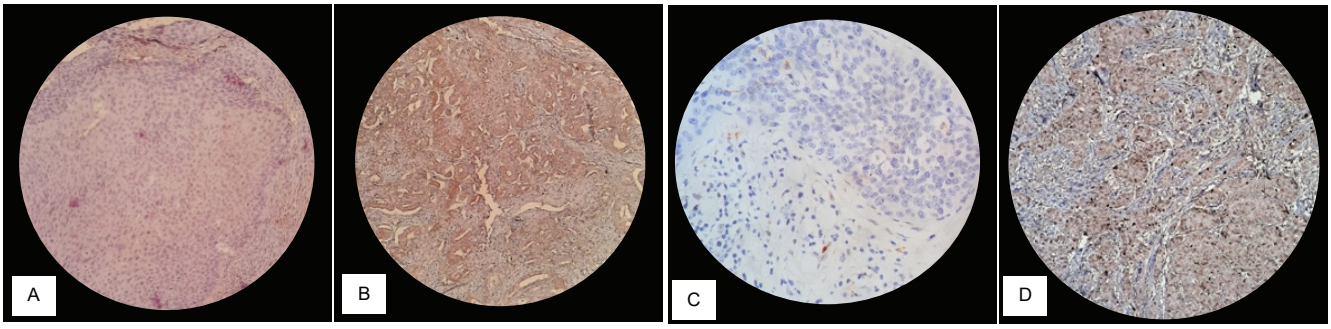

Figure 1. p53 expression, as indicated by the percentage of brown-stained cell nuclei using the wild-type p53 antibody at 200x magnification. (A) low expression p53; (B) high expression p53; (C) low expression p53 in high-grade tumor budding; (D) high expression p53 in low-grade tumor budding.

DISCUSSION

The majority of cervical carcinoma cases were in women younger than 50 years old in this study. Another study found something similar, that the majority of cervical carcinoma patients occurred in the 40–49-year-old group [14]. As someone gets older, the risk of cervical cancer will be higher. This is because, as age increases, a person's exposure time to carcinogens also increases [15].

The majority of subjects in this study had SCC (90%). This is congruent with other studies on tumor budding in cervical cancer, which states that the most common type of cervical cancer is SCC (66.9%), followed by adenocarcinoma (27.2%), and adenosquamous (5.9%) [7]. HPV 16 and 18 have a predilection for squamous cells starting from the squamocolumnar junction (SCJ) area. Initially, HPV will infect the basal cells of the cervical SCJ and form oncoproteins E6 and E7. Later on, the dysplasia will occur in the cervical cells, which then develops into invasive cancer [16]

This is aligned with another study on tumor budding in cervical cancer, which states that the most common type of cervical cancer is SCC (66.9%), followed by adenocarcinoma (27.2%), and adenosquamous (5.9%) [7]. HPV 16 and 18 have a predilection for squamous cells starting from the squamocolumnar junction (SCJ) area. Initially, HPV will infect the basal cells of the cervical SCJ and form oncoproteins E6 and E7. Later on, the dysplasia will occur in the cervical cells, which then develops into invasive cancer [16].

In this study, most subjects were in the early stages (stages I–IIA) (92%). In this study, most of the subjects were in the early stages. Another study also obtained similar results, that most cervical cancer was detected at stage I (46.2%), followed by stage III (21.3%) [17]. This happens because routine screening is carried out, so the cases can be detected earlier. Other studies have found different results. The study stated that most of the subjects were found in the late stage (IIIB). This happens because the early stages of cervical cancer are asymptomatic, so the patient feels nothing wrong with their body. Thus, patients didn't get themself checked and led to late diagnosis [5].

The majority of subjects in this study have low expression of p53. There are more subjects with low p53 expression than high p53 expression in this study. This is congruent with a study by Arsyad et al. [18]. The types of HPV that have a high risk of causing cervical cancer are HPV 16 and 18. In cervical cancer carcinogenesis, HPV 16 and 18 will produce oncoproteins E6 and E7. E6 will inactivate the p53 gene through a binding mechanism, the ubiquitin-dependent proteolytic pathway (E6AP). If p53 expression decreases in cells, then the normal function of p53 as a cell growth regulator will not occur. The E7 oncoprotein works by taking over normal cell cycle regulation [19].

In this study, the grade of tumor budding was categorized into two: low-grade and high-grade [13]. The use of a two-tiered or three-tiered tumor budding system provides valid results. In cervical cancer, a two-tiered system is more often used [20]. The comparison of subjects with low and high grades of tumor budding in this study was equal. Another congruent study by Jesinghaus et al. [21] also reported that the comparison of subjects with low- and high-grade tumor budding yielded nearly identical results. Although the mechanism of tumor budding formation in cervical cancer has not been thoroughly explained, there are indications that the molecular events that cause tumor budding formation are also related to tumor invasion and metastasis [11].

Expression of E6 and E7 by HPV causes chromosomal instability, integration of foreign DNA, and other mutational events in cells. Oncoprotein E6 induces the degradation of p53, which is an essential process in the oncogenesis of HPV-induced cervical carcinoma. At the beginning of carcinogenesis, wild-type p53 will be downregulated [22]. Other studies suggest that p53 dysfunction in malignant tumors is mainly caused by inactivation of p53 by binding protein mechanism or TP53 mutation. Murine double minute 2 (MDM2) is a

protein that acts as a negative regulator of p53. MDM2 acts as an E3 ubiquitin ligase, attaching ubiquitin chains to p53 and marking it for degradation by the proteasome. Thus, the p53 expression in cells is decreased [23].

Other research explains that the decrease of wild-type p53 (WTp53) often occurs in the context of increased p53 mutations. Non-functional p53 mutants tend to accumulate in cells, where they then interact with WTp53 and affect its stability and normal function. Several studies have shown that p53 mutants can form a complex with WTp53, inhibit its activity, or even direct WTp53 to the protein degradation pathway [24].

Furthermore, p53 can also influence the expression of other genes involved in regulating the cellular phenotype. p53 influences E-Cadherin expression and is involved in the EMT process. EMT is a process where epithelial cells lose their polarity and adhesion. This process increases the ability of these cells to migrate and increases their invasiveness, leading to tumor invasion and metastasis. p53 can inhibit transcription factors such as Snail, Slug, or ZEB, which normally suppress E-Cadherin expression. Moreover, p53 can also influence signaling pathways related to EMT, such as the transforming growth factor beta (TGF-β) pathway. Activation of p53 can interfere with the TGF-β pathway that triggers EMT [25].

Decreased E-cadherin expression has been associated with tumor budding formation in colorectal cancer. E-Cadherin also plays a role in cell motility by regulating intracellular signals related to the cell cytoskeleton and migration. A decrease in E-Cadherin expression can increase the ability of cancer cells to spread to their surrounding tissue. This increases the chance of tumor budding, where cancer cells spread beyond the primary tumor. Decrease of E-Cadherin expression may trigger cellular phenotypic changes that support the EMT process. Cancer cells that experience EMT tend to break away from the primary tumor and form tumor budding [26].

Other studies have demonstrated that microRNAs are involved in the EMT process. In cervical carcinoma, miR-21 is classified as an oncogene miR because it stimulates cell proliferation and migration. In a recent study, it was found that upregulation of miR-21 in cervical carcinoma tissues modulates EMT activation that induces lymphatic metastasis. The expression of miR-21 is significantly overexpressed in cervical carcinoma with lymph node metastases compared to cervical carcinoma without lymph node metastases [27].

Several studies have reported that p53 expression is significantly related to the degree of tumor budding. High-grade tumor budding is also stated to be a risk predictor for lymph node metastasis (LNM) and correlates with tumor metastasis, recurrence, and poor survival [8]. Studies with similar results suggest that high-grade tumor budding is associated with p53 mutation status. Tumor budding is expressed as histomorphological epithelial-mesenchymal transition (EMT), which is associated with the metastatic process in various epithelial tumors [20].

High-grade tumor budding is positively correlated with primary tumor size, deep stromal invasion (DSI), DSI parametrium invasion, and lymph node metastasis. These findings suggest that high-grade tumor budding contributes to more aggressive biological behavior in cervical carcinoma patients [7]. Similar studies indicate that the number of buds correlates significantly with poorer tumor differentiation, higher FIGO stage, larger primary tumor, and DSI. These findings suggest that tumor budding is an early event of cervical carcinoma invasion and is associated with the development of cervical carcinoma. This study also supports the statement that tumor budding has a worse impact on the clinical outcome of carcinoma cervix and can be considered as an adjuvant therapy plan for patients [28].

CONCLUSIONS

The p53 expression was significantly downregulated in cervical carcinoma with high-grade tumor budding. These findings suggest that high tumor budding contributes to more aggressive biological behavior in cervical carcinoma. These findings indicate that tumor budding can be considered as a prognostic marker, but further research that correlates p53 expression in cervical carcinoma, sorted by HPV dependent and HPV independent cervical carcinomas, is needed.

DECLARATIONS

Competing interest

The authors declare no competing interests in this study.

Ethics approval and consent to participate

This research was approved by Denpasar Health Polytechnic Health Research Ethics Committee, with reference number DP.04.02/F.XXXII.25/ 0742 /2023.

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