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Prognostic Impact of Human Papilloma Virus Infection on Cervical Cancer Outcome in Egyptian Referral Center- Retrospective Cohort Study

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Abstract

BACKGROUND

Cervical cancer remains a major global health challenge. Although p16^INK4a^ (p16) is a well-established diagnostic surrogate marker for high-risk HPV-related carcinogenesis, its prognostic value in invasive cervical cancer remains controversial. This study evaluated the prognostic significance of p16 expression in combination with the 2018 FIGO stage.

METHODS

A retrospective cohort study was conducted at a single tertiary referral center, including 122 patients with histologically confirmed cervical carcinoma treated between January 2020 and December 2024. Epidemiological and clinicopathological characteristics, with particular emphasis on the 2018 FIGO stage and p16 immunohistochemical expression, were evaluated. Overall survival (OS) and disease-free survival (DFS) were analyzed using Kaplan–Meier survival analysis and Cox proportional hazards regression.

RESULTS

Among the 122 patients, p16 expression was significantly associated with histopathological subtype ($p < 0.001$), with squamous cell carcinoma predominating in the p16-positive group and adenocarcinoma in the p16-negative group. During follow-up, 31.1% of patients died and 40.2% developed recurrence. However, p16 expression was not significantly associated with overall or disease-free survival. Multivariate Cox regression identified age > 55 years and FIGO stage IV as independent predictors of poorer survival and increased recurrence.

CONCLUSION

In cervical cancer, p16 expression was not an independent prognostic marker. Instead, FIGO stage and patient age were the primary predictors of survival and recurrence. Although p16 remains a valuable biomarker for tumor classification, larger prospective studies are needed to better define its prognostic utility.

1 Introduction

Cervical cancer is one of the most common malignancies affecting women and a leading cause of cancer-related mortality, particularly in low resource settings(Arbyn et al. 2020; Sung et al. 2021). This ongoing burden reflects not only limited access to preventive and screening strategies, but also the biological heterogeneity of cervical cancer, highlighting the need for reliable prognostic markers to guide management(Denny 2012; Sharma et al. 2020).

At the molecular level, persistent infection with high-risk human papilloma virus (HR-HPV) drives carcinogenesis through the integration of viral oncogenes E6 and E7 into the host genome(Bosch et al. 2002; Walboomers et al. 1999). The E7 oncoprotein inactivates retinoblastoma protein (pRb) pathway, leading to dysregulation of the cell cycle and subsequent overexpression of the cyclin -dependent kinase (CDK) inhibitor P16INK4a(Huang et al. 2014; McLaughlin-Drubin et al. 2013; Wu et al. 2024). Consequently, P16 immunohistochemistry (IHC) has become a surrogate biomarker for identifying HPV infection and helps distinguish true precancerous lesions and HPV-associated carcinomas from benign and HPV-independent tumors(Bergeron et al. 2010; Darragh et al. 2012; Klaes et al. 2001; Tsoumpou et al. 2009; Wentzensen and von Knebel Doeberitz 2007).

For prognostic assessment and treatment planning, the International Federation of Gynecology and Obstetrics (FIGO) staging system has long been the cornerstone in cervical cancer. However, because FIGO staging is based on clinical and radiological findings than tumor biology, it inherently lacks molecular precision(Soares et al. 2022). More recent classifications(Giannella et al. 2022; Stolnicu et al. 2018) have highlighted the distinction between HPV-associated tumors, including most squamous cell carcinomas (SCC) and usual type adenocarcinomas (AC), typically show diffuse P16 overexpression and HPV- independent tumors such as gastric-type, clear cell, and mesonephric adenocarcinomas, often show absent or focal P16 expression and tend to follow more aggressive course(Galic et al. 2012; Nicolas et al. 2019; Park et al. 2011).

Despite this diagnostic role, the value of P16 in cervical cancer prognosis is still debated. While some studies suggest that strong P16 expression is associated with improved with better response to treatment and improved survival(Lin et al. 2014; Schwarz et al. 2012), others have reported no significant association or even poorer prognosis(Alfsen et al. 2003; Chong et al. 2025). Therefore, this study aims to evaluate the prognostic value of P16 expression alongside FIGO staging in patients with cervical cancer. We specifically examined its relationship with clinicopathological features, survival outcomes and recurrence.

2 Patients and Methods

2.1 Study Design and Patient Population

This retrospective cohort study included 122 patients diagnosed with cervical cancer. Eligibility criteria included histologically confirmed cervical carcinoma with documented P16 IHC analysis and availability of complete follow-up data. Patient with synchronous malignancies or incomplete staging information were excluded.

2.2 Data collection

Demographic and clinical data were extracted from medical records for the period from January 2021 to December 2024, including age at diagnosis, FIGO stage (2018 revision), and treatment modality. Treatment was selected according to the stage at diagnosis and included extrafascial hysterectomy,

radical hysterectomy, or concomitant chemoradiation consisting of external beam radiotherapy with weekly cisplatin as a radiosensitizer followed by brachytherapy. Patients were then followed for survival assessment based on follow-up findings. Additional variables included parity, number and duration of marriages, menstrual status, and smoking history. Pathological data included tumor size, histological subtype (squamous cell carcinoma, adenocarcinoma, neuroendocrine carcinoma), and P16 expression. FIGO staging was determined using clinical examination, imaging modalities (MRI, CT, PET-CT), and surgical-pathological findings when available. Patients were categorized into P16-negative and P16-positive groups.

2.3 P16 immunohistochemistry

Immunohistochemical assessment of p16 was performed because p16 is a cyclin-dependent kinase inhibitor that is characteristically overexpressed in cervical epithelial cells affected by transforming high-risk human papillomavirus (HPV) infection. Consequently, p16 immunohistochemistry is widely used as a surrogate biomarker for oncogenic HPV activity and is particularly valuable in distinguishing HPV-associated cervical carcinomas from HPV-independent tumors when routine histopathological examination alone is insufficient.

Formalin-fixed, paraffin-embedded (FFPE) tissue blocks from eligible cervical carcinoma cases, together with non-neoplastic cervical tissue controls, were sectioned at a thickness of 4 μm and mounted on poly-L-lysine-coated slides. Immunohistochemical staining was performed using a ready-to-use monoclonal mouse anti-human p16 antibody (clone E6H4; Roche). Staining was carried out on a Ventana BenchMark GX automated immunostainer (Roche/Ventana Medical Systems, Tucson, AZ, USA) according to the manufacturer's recommended protocol. Appropriate positive and negative control tissues were included with each staining run to ensure assay quality and reliability.

The primary antibody was incubated for 12 minutes, followed by visualization using the ultraView Universal DAB Detection Kit (Ventana Medical Systems, Tucson, AZ, USA). Slides were subsequently counterstained with hematoxylin for 12 minutes, treated with bluing reagent for 4 minutes, dehydrated, and permanently mounted. p16 immunoreactivity was considered positive when cervical tumor cells demonstrated brown nuclear staining, with or without accompanying cytoplasmic staining, regardless of staining intensity, consistent with established pathological interpretation criteria.

2.4 Statistical Analysis

Data analysis was performed using IBM SPSS Statistics version 20.0. Continuous variables were tested for normality using the Shapiro–Wilk test and presented accordingly. Categorical variables were compared using the chi-square test or Fisher's exact test when appropriate. Survival outcomes were evaluated using Kaplan–Meier analysis and compared with the log-rank test. Univariate and multivariate Cox regression models were used to identify factors associated with mortality and recurrence, with results expressed as hazard ratios (HR) and 95% confidence intervals (CI). Variables with $p < 0.05$ in univariate analysis were included in multivariate models. A p-value < 0.05 was considered statistically significant.

2.5 Outcome Measures

The primary outcomes were overall survival (OS), defined as the time from diagnosis to death from any cause, and disease-free survival (DFS), defined as the time from treatment completion to recurrence or death. Patients without events were censored at the last follow-up. Secondary outcomes include association between P16 expression and clinicopathological features.

2.6 Ethical consideration

The study was conducted in accordance with the Declaration of Helsinki. Patient confidentiality was maintained though anonymization of all data. The study protocol was approved by Alexandria University Ethical committee (IRB number: 0307907) and consent was waived due to the retrospective nature of the study.

3 Results

The study included 122 patients, P16-negative (n = 24) and P16-positive (n = 98), with a mean age of 53.97 ± 12.39 years. A statistically significant association was observed between p16 expression and histopathological subtype ($p < 0.001$). Squamous cell carcinoma was the most common histology (78.7%), accounting for 85.7% of the p16-positive group compared to 50.0% in the p16-negative group. In contrast, adenocarcinoma was more frequent in the p16-negative cohort (50.0%) than in the p16-positive group (12.2%). Significant differences between p16 groups were also noted for the FIGO stage ($p = 0.034$), menstrual status ($p = 0.009$), and number of marriages ($p = 0.022$), table 1.

Regarding clinical outcomes, 31.1% of patients died by the end of the study period and 40.2% experienced recurrence. However, p16 expression was not significantly associated with overall survival ($p = 0.214$) or recurrence ($p = 0.091$) as shown in table 2. In univariate cox analysis, age > 55 years ($p = 0.045$), postmenopausal status ($p = 0.022$), and FIGO stage IV ($p = 0.017$) were associated with mortality, whereas p16 was not ($p = 0.262$). In multivariate analysis, FIGO stage remained the only predictor for mortality, patients with Stage IV disease had an HR of 2.481 (95% C.I.: 1.016–6.055, $p = 0.046$) compared to Stage I patients (Table 3). Kaplan-Meier survival curves for overall survival (Fig. 1, Table 4) confirmed this, showing a sharp drop in 36-month survival from 63.9% in Stage I to 0% in Stage IV (Log Rank $p = 0.012$).

A similar trend was observed in the analysis of disease recurrence, Age > 55 years ($p = 0.018$) and FIGO stage IV ($p = 0.011$) were significant in the univariate analysis, while p16 expression remained statistically insignificant ($p = 0.107$). The multivariate COX regression model confirmed that both older age (HR 2.352, $p = 0.023$) and FIGO stage IV (HR 3.241, $P = 0.014$) were the most critical parameters affecting recurrence (Table 5). Kaplan-Meier curves for disease-free survival further illustrated this disparity, with mean recurrence-free survival times dropping from 31.8 months in Stage I down to 12.86 months in Stage IV (Log Rank $p = 0.050$) (Fig. 2).

4 Discussion

In this study, p16 expression showed a clear association with histopathological subtype, supporting its role as a marker of HPV-driven carcinogenesis and reflects shifting global understandings of cervical cancer biology, particularly the division between HPV-associated and HPV-independent pathways(Darragh et al. 2012; Stolnicu et al. 2018). The predominance of adenocarcinomas within the p16-negative subgroup aligns with existing literature establishing that rare, HPV-independent adenocarcinomas (such as gastric-type and mesonephric adenocarcinomas) fundamentally lack the HPV E6/E7 viral oncoproteins that drive diffuse p16 overexpression(Giannella et al. 2022; Park et al. 2011; Selenica et al. 2021). In contrast, most squamous cell carcinomas were p16-positive, supporting its role as a surrogate marker of HPV-driven carcinogenesis(Chong et al. 2025; de Sanjose et al. 2010; Pirog et al. 2000)

Despite this, p16 expression was not associated with survival or recurrence outcomes in our cohort. This finding is in line with some previous studies(da Mata et al. 2021; Ismail et al. 2023), although others have reported either improved outcomes in p16-positive tumors(Lin et al. 2014; Schwarz et al. 2012) or negative impact on survival(Alhamlan et al. 2021; Chong et al. 2025). The variability in reported results may reflect differences in study populations, treatment approaches, and methodological factors, including variability in immunohistochemical assessment, particularly the lack of standardized cut-off values for defining p16 positivity which has been historically noted to confound prognostic interpretations(Tsoumpou et al. 2009; Wentzensen and von Knebel Doeberitz 2007)

Biologically, p16 plays a central role in cell cycle regulation by inhibiting CDK4/6 and preventing phosphorylation of the Rb protein. In the context of HR-HPV infection, however, this pathway is disrupted, leading to paradoxical overexpression of p16 (de Sanjose et al. 2010; Pirog et al. 2000; Selenica et al. 2021). Abnormal p16 expression results in excessive cell division and rapid deterioration(Fernandes et al. 2022) (Agarwal et al. 2013; Volkova et al. 2021). Loss of p16 expression in certain tumors may occur through alternative mechanisms such as CDKN2A mutations or epigenetic silencing(da Mata et al. 2021).

Schwarz et al. (2012) reported that p16-positive tumors are associated with improved survival and better response to chemoradiation, whereas p16-negative tumors tend to occur in older patients and carry a poorer prognosis. Similarly, Sara da Mata et al. (2021) described p16-negative tumors as more aggressive, presenting at advanced stages, although p16 expression did not retain independent prognostic significance in multivariate analysis(da Mata et al. 2021). Evidence from previous meta-analyses indicates that p16 overexpression is linked to favorable features, including absence of lymph node metastasis and improved OS and DFS(Huang et al. 2014; Lin et al. 2014). At the same time, it does not appear to correlate with conventional parameters such as TNM stage, tumor grade, size, or vascular invasion(Lin et al. 2014). This pattern suggests that p16-positive tumors reflect an HPV-driven pathway that is generally less aggressive and more responsive to treatment, while p16-negative tumors may follow multiple complex genetic alterations in cell cycle regulatory pathways associated with treatment

resistance and higher metastatic potential(Lin et al. 2014). Supporting this, low p16INK4A expression, particularly when combined with stem cell markers such as SOX2 and ALDH1A1, has been associated with poorer outcomes and increased chemoradioresistance(Fu et al. 2018).

However, findings remain inconsistent. Alhamlan et al.(2021) reported improved survival in HPV-positive patients but paradoxically found worse outcomes with p16 overexpression (HR 3.2), highlighting variability across studies and suggesting that the prognostic value of p16 may differ by population and context and suggests that exceeding certain expression levels may correlate with poorer prognoses(Huang et al. 2014). More recent meta-analytic data have also linked elevated p16 expression to metastatic behavior, particularly lymphatic and vascular spread, while remaining independent of tumor size, depth of invasion, and histological subtype (Chong et al. 2025). These results were supported by Begg's test, with symmetrical funnel plots indicating no significant publication bias.

In contrast, our findings emphasize that FIGO stage(Bhatla et al. 2019; Matsuo et al. 2019) and patient age remain the most important predictors of outcome. The high hazard ratios observed for Stage IV disease, together with the absence of long-term survival in advanced stages, suggest that once invasive disease is established, anatomical extent outweighs molecular markers in prognostic relevance. In line with this, Ismail et al. found no significant association between p16 expression and survival outcomes, whereas lymph node metastasis remained an independent predictor of worse prognosis (Ismail et al. 2023). Nevertheless, FIGO staging alone does not fully capture tumor biology, as it does not incorporate molecular features, tumor burden, or HPV-related factors(Long et al. 2023; Mendaza et al. 2020).

Taken together, while p16 remains essential for pathological classification and may have a role in guiding targeted approaches, traditional clinical staging and demographic factors continue to be the most reliable predictors of outcome. There is growing evidence that combining molecular markers with clinicopathological variables, such as integrating p16 with cancer stem cell markers or other molecular signatures, may improve risk stratification(Fahmi et al. 2021; Fu et al. 2018). Larger prospective studies with standardized assessment methods are still needed to better define the prognostic value of p16.

The present study has some limitations, including its retrospective design, relatively small sample size, and the absence of HPV genotyping. These factors may have limited the ability to detect subtle associations and further stratify patients biologically.

5 Conclusion

In this cohort, p16 expression did not demonstrate independent prognostic significance in cervical cancer. Instead, FIGO stage and patient age were the primary determinants of survival and recurrence. These findings reinforce the importance of early detection and appropriate staging. While p16 remains valuable for tumor classification, its role as a prognostic marker appears limited when used alone. Future studies incorporating larger cohorts, standardized methodologies, and combined biomarker approaches are needed to better define its clinical utility.

Declarations

Acknowledgement

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Statement and Declarations:

Consent for Publication Not applicable.

Data Avaialbility: The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request

Ethical approval and consent to participate

The study approval was obtained from the Research Ethics Committee, Faculty of Medicine, Alexandria University (IRB number: 0307907). All subjects gave their informed consent to participate prior to their involvement in the study.

Conflict of interest: The authors declare no conflict of interest.

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Author Contributions

All authors contributed to the study idea and design. Criteria for subject selection were decided by [AE], [HS] and [AS]. Material preparation, data collection was performed by [HS]. Methodology was performed by [AE] and [HS]. Data analysis and interpretation were performed by [HS], [AE] and [AS]. The first draft of the manuscript was written by [HS] and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Abbereviations

AC	Adenocarcinoma
ALDH1A1	Aldehyde Dehydrogenase 1 Family Member A1
CDK	Cyclin-Dependent Kinase
CDK4/6	Cyclin-Dependent Kinases 4 and 6
CDKN2A	Cyclin-Dependent Kinase Inhibitor 2A
CI	Confidence Interval
CT	Computed Tomography
DAB	3,3'-Diaminobenzidine
DFS	Disease-Free Survival
FFPE	Formalin-Fixed, Paraffin-Embedded
FIGO	International Federation of Gynecology and Obstetrics
HPV	Human Papillomavirus
HR	Hazard Ratio
HR-HPV	High-Risk Human Papillomavirus
IBM	International Business Machines
IHC	Immunohistochemistry
IRB	Institutional Review Board
MRI	Magnetic Resonance Imaging
OS	Overall Survival
p16INK4a	Cyclin-Dependent Kinase Inhibitor 2A
PET-CT	Positron Emission Tomography–Computed Tomography
pRb	Retinoblastoma Protein
Rb	Retinoblastoma Protein
SCC	Squamous Cell Carcinoma
SOX2	SRY-Box Transcription Factor 2
SPSS	Statistical Package for the Social Sciences
TNM	Tumor–Node–Metastasis

Tables

Table (1): Comparison between the two studied groups according to patient characteristics

Patient characteristics	Total (n = 122)	P16/IHC		Test of sig.	p
		Negative (n = 24)	Positive (n = 98)		
Age (years)					
Mean ± SD.	53.97 ± 12.39	58.17 ± 10.23	52.94 ± 12.70	t = 1.871	0.064
Number of marriages					
I	101 (82.8%)	17 (70.8%)	84 (85.7%)	χ^2= 6.969*	0.022*
II	19 (15.6%)	5 (20.85%)	14 (14.3%)		
III	2 (1.6%)	2 (8.3%)	0 (0%)		
IV	0 (0%)	0 (0%)	0 (0%)		
Min – Max.	1.0–3.0	1.0–3.0	1.0–2.0	U = 987.0	0.063
Mean ± SD.	1.19 ± 0.43	1.38 ± 0.65	1.14 ± 0.35		
Median (IQR)	1.0 (1.0–1.0)	1.0 (1.0–2.0)	1.0 (1.0–1.0)		
Age of marriage (years)					
Mean ± SD.	22.06 ± 4.85	22.79 ± 5.63	21.88 ± 4.65	U = 1137.0	0.800
Duration of marriage (years)					
Mean ± SD.	28.63 ± 12.67	30.50 ± 12.12	28.17 ± 12.83	U = 1050.5	0.418
Parity					
Mean ± SD.	1.53 ± 1.35	1.33 ± 1.34	1.58 ± 1.35	U = 1005.5	0.130
Menstrual state					
Premenopausal	49 (40.2%)	4 (16.7%)	45 (45.9%)	χ^2=6.864*	0.009*
Postmenopausal	73 (59.8%)	20 (83.3%)	53 (54.1%)		
Smoking	13 (10.7%)	3 (12.5%)	10 (10.2%)	χ^2=0.107	^{FE}p=0.718
Tumor size (cm)					
Mean ± SD.	5.09 ± 2.08	5.29 ± 2.16	5.04 ± 2.07	U = 1114.5	0.688

Patient characteristics	Total (n = 122)	P16/IHC		Test of sig.	p
		Negative (n = 24)	Positive (n = 98)		
Age (years)					
Histopathology type					
Squamous cell carcinoma	96 (78.7%)	12 (50.0%)	84 (85.7%)	χ^2= 14.802*	< 0.001*
Adenocarcinoma	24 (19.7%)	12 (50.0%)	12 (12.2%)		
Neuroendocrine	2 (1.6%)	0 (0.0%)	2 (2.0%)		
FIGO stage					
I	34 (27.9%)	5 (20.8%)	29 (29.6%)	χ^2= 8.145	^{MC}p= 0.034*
II	55 (45.1%)	15 (62.5%)	40 (40.8%)		
III	18 (14.8%)	0 (0%)	18 (18.4%)		
IV	15 (12.3%)	4 (16.7%)	11 (11.2%)		

Table (2): Comparison between the two studied groups according to Management and survival outcomes

Management and survival outcomes	Total (n = 122)	P16/IHC		Test of sig.	p
		Negative (n = 24)	Positive (n = 98)		
Treatment					
Surgical	29 (23.8%)	5 (20.8%)	24 (24.5%)	χ^2=0.461	0.862
Chemo Radiotherapy (CRT)	85 (69.7%)	17 (70.8%)	68 (69.4%)		
Combined	8 (6.6%)	2 (8.3%)	6 (6.1%)		
Overall survival (OS)					
Alive	84 (68.9%)	14 (58.3%)	70 (71.4%)	χ^2=1.542	0.214
Died	38 (31.1%)	10 (41.7%)	28 (28.6%)		
Overall survival (OS) time					
Mean ± SD.	17.18 ± 11.21	17.04 ± 11.95	17.21 ± 11.08	U = 1127.50	0.754
Recurrence					
No	73 (59.8%)	18 (75%)	55 (56.1%)	χ^2=2.859	0.091
Yes	49 (40.2%)	6 (25%)	43 (43.9%)		
Disease free survival (DFS) time (months)					
Mean ± SD.	12.78 ± 11.14	13.58 ± 12.22	12.58 ± 10.92	U = 1145.000	0.841

Table (3): Univariate and multivariate COX regression analysis for the parameters affecting mortality for total sample (n = 122)

Mortality	Univariate		#Multivariate	
	p	HR (95%C.I)	p	HR (95%C.I)
Age category				
< 45®	1.000	–	1.000	–
45–55	0.626	1.281 (0.473–3.473)	0.731	0.756 (0.154–3.719)
> 55	0.045*	2.399 (1.018–5.652)	0.860	1.171 (0.202–6.795)
Menstrual state				
Premenopausal®	1.000	–	1.000	–
Postmenopausal	0.022*	2.400 (1.132–5.091)	0.353	2.087 (0.442–9.851)
Smoking				
No®	1.000	–		
Yes	0.081	0.170 (0.023–1.242)		
Parity				
Nullipara	1.000	–		
Para 1	0.460	1.970 (0.326–11.92)		
Para 2–6	0.455	1.580 (0.476–5.243)		
Histopathology type				
Squamous cell carcinoma®	1.000	–		
Adenocarcinoma	0.896	1.052 (0.495–2.233)		
Neuroendocrine	0.948	0.935 (0.126–6.923)		
P16.IHC				
Negative ®	1.000	–		
Positive	0.262	0.662 (0.321–1.363)		
FIGO stage				
I®	1.000	–	1.000	–
II	0.631	0.825 (0.375–1.812)	0.440	0.731 (0.330–1.619)
III	0.849	0.895 (0.285–2.810)	0.827	0.879 (0.277–2.794)
IV	0.017*	0.895 (0.285–2.810)	0.046*	2.481 (1.016–6.055)

Mortality	Univariate		#Multivariate	
	p	HR (95%C.I)	p	HR (95%C.I)
Age category				
Treatment				
Surgical ®	1.000	–		
Chemo Radiotherapy (CRT)	0.719	1.143 (0.551–2.372)		
> 1 treatment modality	0.370	0.390 (0.05–3.055)		
Recurrence	0.074	1.800 (0.944–3.432)		

Table (4): Univariate and multivariate COX regression analysis for the parameters affecting Recurrence for total sample (n = 122)

Recurrence	Univariate	#Multivariate		
	P	HR (95% CI)	p	HR (95% CI)
Age category				
< 45®	1.000	–	1.000	–
45–55	0.675	1.199 (0.514–2.796)	0.680	1.197 (0.509–2.816)
> 55	0.018*	2.426 (1.161–5.054)	0.023*	2.352 (1.128–4.903)
Menstrual state				
Premenopausal®	1.000	–		
Postmenopausal	0.056	1.820 (0.985–3.362)		
Smoking				
No®	1.000	–		
Yes	0.488	1.441 (0.512–4.054)		
Parity				
Nullipara	1.000	–		
Para 1	0.951	1.046 (0.252–4.348)		
Para 2–6	0.095	0.128 (0.011–1.430)		
Histopathology type				
Squamous cell carcinoma®	1.000	–		
Adenocarcinoma	0.561	0.553 (0.075–4.068)		
Neuroendocrine	0.443	0.444 (0.056–3.527)		
P16.IHC				
Negative ®	1.000	-		
Positive	0.107	2.030 (0.859–4.798)		
FIGO stage				
I®	1.000	–	1.000	–
II	0.202	1.589 (0.780–3.239)	0.289	1.475 (0.719–3.025)
III	0.743	1.195 (0.411–3.480)	0.667	1.267 (0.432–3.717)
IV	0.011*	3.347 (1.320 – 8.489)	0.014*	3.241 (1.272–8.263)

Recurrence	Univariate	#Multivariate		
	P	HR (95% CI)	p	HR (95% CI)
Age category				
Treatment				
Surgical ®	1.000	–		
CRT	0.052	2.089 (0.994–4.390)		
> 1 treatment modality	0.515	1.552 (0.413–5.828)		

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Figures

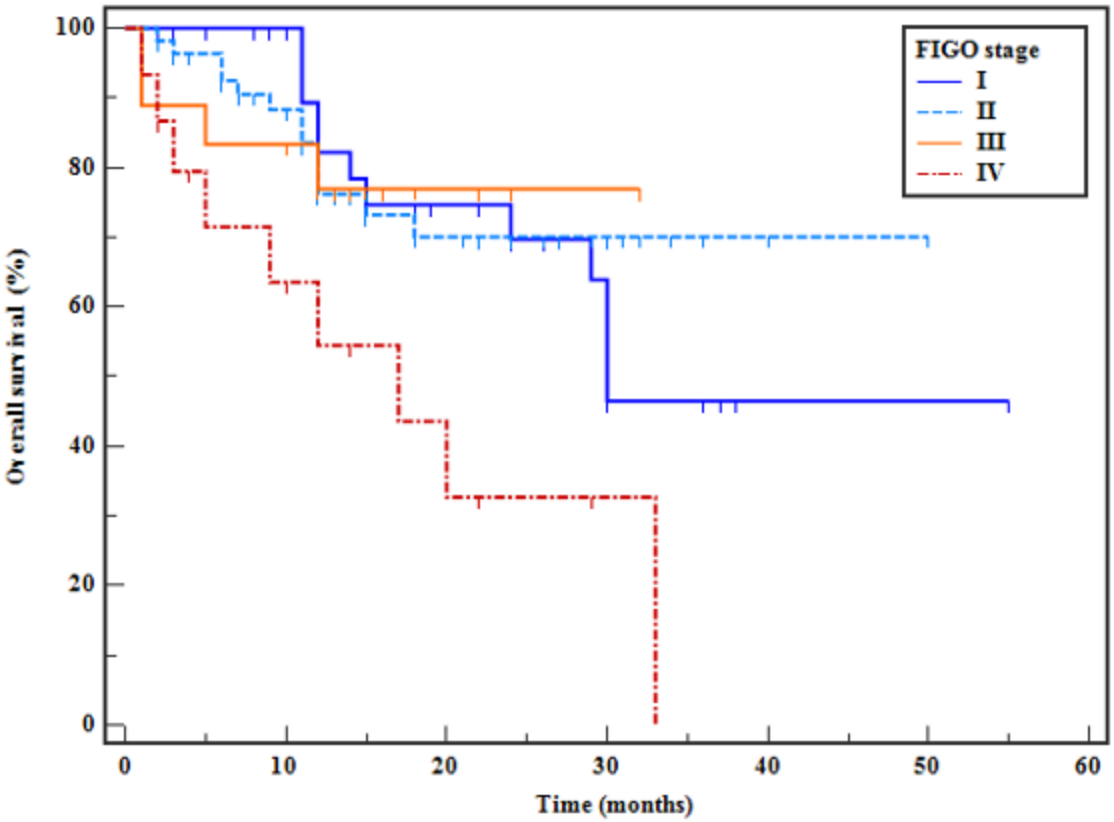


Figure 1

Kaplan-Meier survival curve for Overall Survival, study of the OS based on the FIGO staging

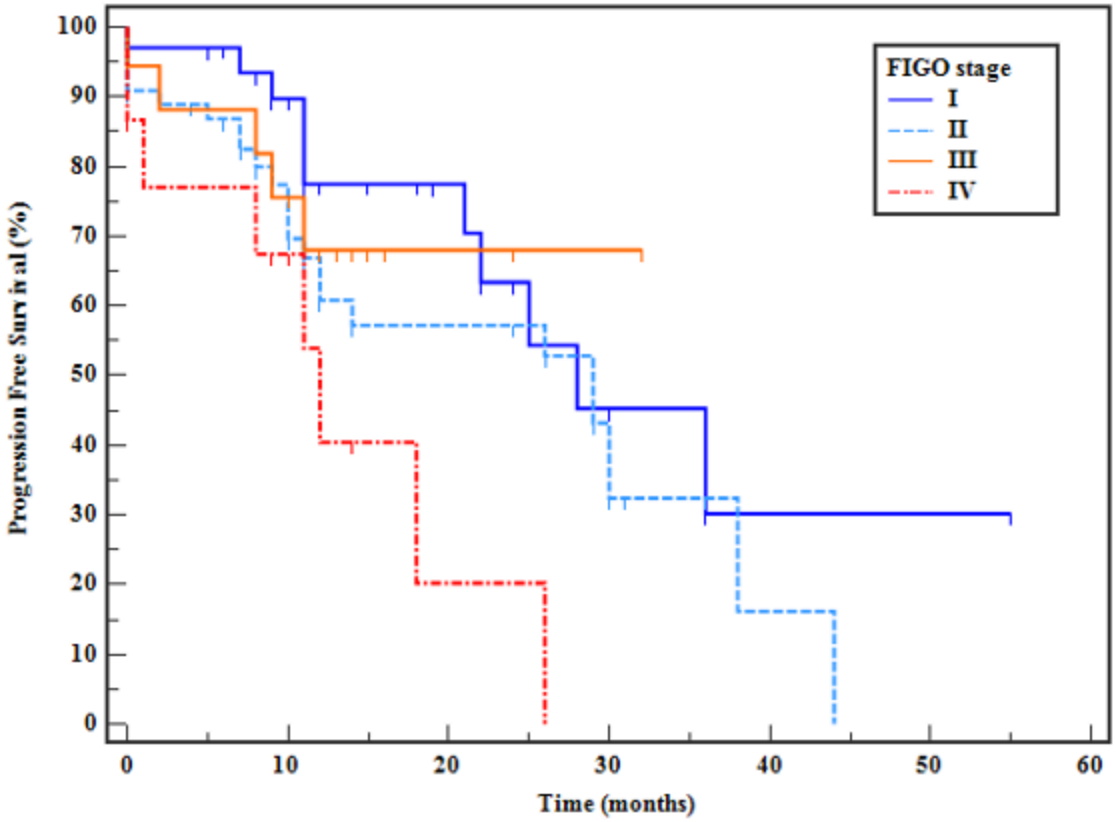


Figure 2

Kaplan-Meier survival curve for Recurrence, study of the DFS, based on the FIGO staging

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