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High-grade vaginal intraepithelial neoplasia and risk of progression to vaginal cancer: a multicentre study of the Italian Society of Colposcopy and Cervico-Vaginal Pathology (SICPCV)

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Abstract. – OBJECTIVE: The aim of this study was to analyze the women with high grade vaginal intraepithelial neoplasia (HG-VaIN), in order to identify a subset of women at higher risk of progression to invasive vaginal cancer.

PATIENTS AND METHODS: The medical records of all the women diagnosed with HG-VaIN, and subsequently treated, from January 1995 to December 2013 were analyzed in a multicentre retrospective case series. The rate of progression to invasive vaginal cancer and the potential risk factors were evaluated.

RESULTS: 205 women with biopsy diagnosis of HG-VaIN were considered, with a mean follow up of 57 months (range 4-254 months). 12 cases of progression to vaginal squamocellular cancer were observed (5.8%), with a mean time interval from treatment to progression of 54.6 months (range 4-146 months). The rate of progression was significantly higher in women diagnosed with VaIN3 compared with VaIN2 (15.4% *vs*. 1.4%, $p < 0.0001$). Women with HG-VaIN and with previous hysterectomy showed a significantly higher rate of progression to invasive vaginal cancer compared to non-hysterectomised women (16.7% *vs*. 1.4%, $p < 0.0001$). A higher risk of progression for women with VaIN3 and for women with previous hysterectomy for cervical HPV-related disease was confirmed by multivariable logistic regression analysis.

CONCLUSIONS: A higher rate of progression to vaginal cancer was reported in women diagnosed with VaIN3 on biopsy and in women with previous hysterectomy for HPV-related cervical disease. These patients should be considered at higher risk, thus a long lasting and accurate follow up is recommended.

Key Words:
Vaginal Intraepithelial neoplasia, VaIN, Vaginal cancer.

Introduction

Vaginal Intraepithelial Neoplasia (VaIN) is a rare histological lesion of the vaginal epithelium, typically diagnosed through a colposcopy-guided biopsy of suspicious areas after an abnormal referring pap smear. Its development is due to a

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persistent high risk human papillomavirus (HPV) infection[1,2]. Multiple sexual partners and early stage at sexual debut[3], smoking[1,4] and immunosuppression[5], increasing the likelihood of HPV infection, are described as further risk factors.

These lesions are characterised by dysplastic changes in the vaginal epithelium, without stromal invasion[2] and, accordingly to the depth of the tissue involved, they are classified in VaIN1 (mild dysplasia), VaIN2 and VaIN3 (moderate and severe dysplasia, respectively).

VaIN1, also defined "low-grade VaIN", can be considered as the transient expression of HPV infection, with no potential of progression to vaginal cancer and with a high rate of spontaneous regression[6,7], while VaIN3 can be properly considered "high-grade VaIN" (HG-VaIN), due to its potential progression to vaginal cancer. The VaIN2 category is not a reproducible histopathologic category among pathologists[8,9] and the risk of progression for lesions classified as VaIN2 is supposed to be intermediate between VaIN1 and VaIN3[9]. However, since the real potential of progression to invasive cancer of VaIN2 is still discussed, some Authors encompass VaIN2 in the HG-VaIN category[7,10-12]. Globally HG-VaIN account for only 0.4% of female lower genital tract intraepithelial lesions[13,14], with an incidence from 0.2 to 2 per 100,000 women/year[8]. Therefore, HG-VaIN is a rare condition and its natural history is not well known, as well as its real potential to progress towards invasive squamous cell vaginal cancer[6,7,10-12,15-17]. Moreover, even because of the lack of a complete knowledge of its natural history, the optimal management of HG-VaIN actually remains a "therapeutic dilemma"[8]. Various treatment modalities have been employed with varying success among women with HG-VaIN[16,18]; current practice include immediate surgical treatment with excisional or ablative procedures.

To our knowledge, only few studies analyzed the rate of invasive vaginal cancer in women treated for HG-VaIN and a rate of progression to cancer from 2% to 7% was reported[10,11,16,17].

The aim of this study was to analyse the rate of progression to cancer in women with HG-VaIN, in order to identify a subset of women at higher risk.

Patients and Methods

This study was sponsored by the Italian Society of Colposcopy and Cervico-Vaginal Pathology (SICPCV) and seven hospitals in the central and northern Italy participated to data collection.

All the women with histological diagnosis of VaIN2 and VaIN3 consecutively referred to the institutions involved, from January 1995 to December 2013, were considered. These women were diagnosed with HG-VaIN through biopsy of suspicious areas detected on colposcopy after an abnormal pap-smear. Colposcopic examinations were recorded accordingly to the 2011 revised colposcopic terminology of the International Federation for Cervical Pathology and Colposcopy (IFCPC)[19]. The colposcopies performed before the introduction of the 2011 IFCPC terminology were revised accordingly.

All the colposcopies and the vaginal biopsies were performed by gynecologic oncologists with particular expertise in the diagnosis and management of pre-invasive and invasive lesions of the lower female genital tract. Similarly all the biopsies and the surgical specimens obtained after surgical excision procedures were analyzed by pathologists with particular expertise in the pre-invasive and invasive lesions of the female lower genital tract.

All the women considered were diagnosed with HG-VaIN for the first time, thus women with previous diagnosis and/or treatments for HG-VaIN were excluded, in order to avoid potential confounders. Similarly, women with synchronous squamocellular cervical invasive cancer (SCC) or vaginal invasive cancer were excluded.

Patients were identified by searching the clinical databases of the institutions involved, and the medical records of women fulfilling the study in0clusion criteria were analyzed in a retrospective case series. Data obtained included information regarding pertinent medical and surgical history, sociodemographic characteristics of each woman and clinical outcome at follow up.

Women diagnosed with HG-VaIN were treated with ablative therapies (CO_2-laser ablation, electrofulguration, radiotherapy, photodynamic therapy – PDT – or topic 5-FU) or with excisional procedures (CO_2-laser excision or CO_2-laser skinning colpectomy, radio-frequency excision, cold-knife local excision or traditional cold-knife upper colpectomy, with vaginal or abdominal access).

After the initial diagnosis of HG-VaIN and the subsequent first line treatment, all the women underwent a routine follow up with pap test and

colposcopy every 6 months for the first 2 years, then yearly. From 2010 a HR-HPV test was performed 6 or 12 months after the first line procedure, depending on the internal guidelines of each institution.

In case of gynecologic symptoms (e.g. vaginal bleeding) a prompt gynecologic evaluation, was performed. Suspicious areas detected during follow up colposcopic examinations were biopsied. Progression is defined as the histopathological evidence of invasion after the first line treatment.

All the women with progression to vaginal invasive cancer, fulfilling the other study inclusion/exclusion criteria were considered, regardless the length of follow up. In case of negative follow up, only women with a minimum follow up of six months were included in the analysis.

Each woman with histopathological evidence of HG-VaIN during the routine follow up examinations, underwent one or more additional treatments as required.

Statistical Analysis

Statistical analysis was performed using IBM SPSS version 22.0 (IBM Corporation, Armonk, New York, USA). The χ^2 testing, the Fisher exact test and Mann Whitney U test were used, as appropriate, to evaluate associations. A p-value < .05 was considered as statistically significant.

Institutional Review Board approval (CRO IRB n. 17/2013) was obtained.

Results

From January 1995 to December 2013, 288 women were diagnosed with HG-VaIN for the first time in the institutions involved in the present study. Among them, 205 women fulfilling the study inclusion criteria, were considered. The mean age of these women was 46 years old (SD ± 13.7, range 19-78 years) and, in particular, 92 women (44.9%) were in post-menopausal status. Tobacco use was reported in 42 women of 163 on which this datum was available (25.8%) and HIV infection was present in 14 cases (6.8%). Previous diagnosis of HPV-related cervical disease (CIN, carcinoma *in situ* or invasive cancer) was reported in 95 cases (46.3%). Sixty women (29.3%) previously underwent hysterectomy; in particular hysterectomy was performed because of CIN/CIS or invasive cervical cancer in 45 cases. In the remaining 15 cases the hysterectomy was performed because of benign conditions or non HPV-related malignancies. However, two of these patients showed a history of CIN before the hysterectomy.

In the whole study cohort, 140 women were diagnosed with VaIN2 on biopsy (68.3%), while the remaining 65 women were diagnosed with VaIN3 (31.7%).

The first line treatments performed after the diagnosis of HG-VaIN in the study population are reported in Table I.

A mean follow up of 57 months (range 4-254 months) after the first-line treatment was reported.

Twelve cases of progression to vaginal invasive cancer were observed in the whole study cohort (5.8%), with a mean time interval from treatment to progression of 54.6 months (range 4-146 months).

Women with progression to vaginal cancer were older (57.7 ± 14.5 vs 45.3 ± 13.3 years old, $p = 0.002$) and more likely to be in menopause (75% *vs*. 42.5%, $p = 0.001$).

In 2 cases, the progression to vaginal invasive cancer was observed after an initial diagnosis of VaIN2 (with 4 and 38 months of follow up, respectively), while in the remaining 10 cases the initial diagnosis on biopsy was VaIN3. Thus in women with VaIN3 compared to women with VaIN2, the rate of progression to invasive disease was significantly higher (15.4% *vs*. 1.4%, $p < 0.0001$).

In ten cases, the progression to vaginal cancer was observed in hysterectomized women and, in particular, in 9 of these cases, the hysterectomy was performed for HPV-related cervical disease (CIN/CIS or SCC). Moreover, in these 9 women, the vaginal dysplastic lesion leading to invasive carcinoma developed in the vaginal cuff or in the

Table I. First line therapy after diagnosis of HG-VaIN in the study population (n = 205).

Ablative procedures	**n = 120**
CO_2-laser ablation	80
Electrofulguration	37
Radiotherapy	1
Photodynamic therapy	1
Topic 5-FU	1
Excisional procedures	**n = 85**
CO_2-laser excision	51
Radiofrequency excision	30
Cold knife upper colpectomy	4

lateral recesses. In one case, the progression to vaginal invasive cancer was detected after hysterectomy for benign condition, but this patient had a history of HR-HPV related disease of the uterine cervix.

The progression to invasive vaginal cancer was observed in 10 women up 60 with previous hysterectomy, while only 2 cases of progression among the remaining 145 women were reported (16.7% *vs*. 1.4%, $p < 0.0001$). Considering only the 45 women with previous hysterectomy for CIN/SCC, the progression to invasive cancer was reported in 20% of cases (9/45 cases).

All women with progression to invasive vaginal cancer had a history of HPV-related cervical diseases and the risk of progression was significantly higher in women with previous CIN or SCC (12.6% *vs*. 0%, $p < 0.0001$).

The time of progression appear to be independent from the grade of VaIN or previous hysterectomy for CIN or SCC ($p > 0.6$ Mann Whitney U test).

The clinical and histopathological characteristics of women with progression to invasive vaginal cancer are reported in Table II.

By multivariate logistic regression analysis (Table III), only previous hysterectomy for CIN/SCC and VaIN3 on biopsy showed an independent significant association with the progression to invasive vaginal cancer (OR = 5.61, 95% CI 1.28-24.63 and OR = 5.61, 95% CI 1.06-29.76, respectively).

Discussion

Vaginal cancer is a rare disease, accounting for less than 2% of all the gynecologic malignancies with an incidence of approximately 3000 new cases per year in the United States[20]. Approximately 80-90% of primary vaginal cancers are squamous cell carcinomas[21] and most of them seems to be preceded by HG-VaIN[22]. However, even the HG-VaIN is quite rare and, therefore, its natural history, and especially its true malignant potential of progression to invasive cancer, is actually on debate[6,10,11,21].

In the present series, during a long follow up period, a overall rate of progression to vaginal cancer of 5.8% was reported; this datum appear to be similar to those of the few previous published studies, reporting a rate of progression to cancer from 2% to 7%[10,11,16,17]. However, the factors influencing the risk of progression of

Table II. Clinical and histopathological characteristics of women with progression to vaginal cancer.

	VaIN (first diagnosis)	VaIN (before prgression)	Age	Menopause	Previous hysterectomy	Previous diagnosis of cervical HPV-related disease	First line treatment	Localization of invasive lesion	Further therapies before progression	Follow up before progression (months)
1	3	3	41	Yes	Yes (CIN)	Yes	Laser CO_2 excision	Upper third	2 (ablative)	63
2	3	1	61	Yes	Yes (CIN)	Yes	Laser CO_2 excision	Inferior third	2 (ablative)	75
3	3	3	66	Yes	Yes (CIN)	Yes	Laser CO_2 excision	Upper third	–	105
4	3	3	39	No	Yes (CIN)	Yes	Upper colpectomy	Upper third	–	8
5	3	2	66	Yes	Yes (CA)	Yes	Laser CO_2 vaporization	Upper third	1 (ablative)	53
6	3	3	54	Yes	Yes (CIN)	Yes	Laser CO_2 excision	Upper third	5 (excisional) + 4 (ablative)	146
7	3	3	77	Yes	Yes (CA)	Yes	Laser CO_2 excision	Upper third	2 (ablative)	63
8	3	3	66	Yes	Yes (CIN)	Yes	Laser CO_2 vaporization	Upper third	–	15
9	3	3	62	Yes	Yes (fibroids)	Yes	Laser CO_2 excision	Upper third	2 (excisional) + 1 (ablative)	82
10	2	2	47	No	No	Yes	Electrosurgical ablation	Upper third	–	4
11	2	2	34	No	No	Yes	Electrosurgical ablation	Upper third	–	38
12	3	3	77	Yes	Yes (CA)	Yes	Electrosurgical excision	Upper third	–	4

Table III. Multivariable logistic regression of risk factors for progression to squamocellular invasive vaginal cancer in women with biopsy diagnosis of HG-VaIN.

Characteristics	Progression to vaginal cancer n = 12 (5.8%)	No progression to invasive vaginal cancer n = 193 (94.2%)	Adjusted* Odds Ratio (95% CI)	*p*-value
Previous hysterectomy for CIN/SCC	9 (75%)	36 (18.6%)	5.61 (1.28-24.63)	0.02
VaIN3 on biopsy	10 (83.3%)	55 (28.5%)	5.61 (1.06-29.76)	0.04

*Adjusted for age, previous hysterectomy, treatment modality and previous HPV-related disease of the lower genital tract.

HG-VaIN to cancer are still not known and, differently from other previous studies, we tried to stratify the risk of progression to cancer in different subsets of patients.

In our series a significantly higher rate of progression to cancer emerged in women previously diagnosed with VaIN3 compared to women with VaIN2 (15.4% *vs*. 1.4%, $p < 0.0001$). This datum appear of particular interest if we consider the actual debate on the natural history of HG-VaIN. VaIN2 and VaIN3 have been both considered as HG-VaIN by several authors[7,10-12] just because of their potential progression towards vaginal cancer. However, some Authors don't encompass VaIN2 in this category, considering only VaIN3 as the true precursor of invasive vaginal cancer[8,9].

In our cohort we observed a over 10 times higher risk of progression in women with VaIN3 compared to women with VaIN2; for this reason, in our opinion, VaIN3 should be considered as the true precursor of vaginal cancer.

A previous hysterectomy seems to be another important risk factor for progression to cancer and a higher risk of progression in these women emerged, especially in women with hysterectomy for CIN/CIS/SCC, as confirmed by multivariable logistic regression.

A possible interpretation of this datum is that, in women with HPV-related cervical disease, vaginal dysplastic lesions can coexist. After hysterectomy these lesions could spread in the context of the scar on the cuff, remaining clinically undetectable for long time, and thus invasive cancer can grow.

Therefore, among patients with HG-VaIN, hysterectomized women with previous HPV-related disease of the lower genital tract should be considered a higher risk subset of patients. In this cases one of the most important issue is the possibility of occult invasive disease at the time of diagnosis of HG-VaIN. For this reason, in these patients, an accurate colposcopic evaluation with biopsy is mandatory and an excisional treatment of HG-VaIN should be preferred, in order to detect otherwise occult invasive lesions.

In the present study, we observed an extremely variable time interval from treatment for HG-VaIN towards progression to cancer, with one cases of progression occurred more than 12 years after the first treatment. Therefore, we recommend a close follow up every six months for the first two years, then yearly, for at least fifteen years.

From 2010 we have introduced the HR-HPV test in the follow up of these patients, but the potential correlation with the risk of progression to cancer is unclear. Since the HG-VaIN and the vaginal squamocellular cancer are related to a persistent HR-HPV infection[1,2], a negative HR-HPV test could be helpful in reducing the need for follow up in these patients. However, the negative predictive value of the test seems to be very low, especially when the lesion do not reach the mucosal surface[8] and further studies are needed before we can make specific recommendations about the use of HR-HPV test in the follow up of women treated for HG-VaIN.

In 2 cases the progression to invasive cancer was detected only 4 months after the first line treatment. The routine follow up at our institutions include a gynecologic examination with cytology and colposcopy 6 months after the first line treatment. These 2 women were examined before the scheduled follow up because they referred vaginal bleeding. They were both treated with electrosurgical ablation and probably the rapid progression to cancer can be considered expression of insufficient depth of ablation during treatment; it is possible to suppose that, in these cases, the vaginal dysplastic lesions harbored occult invasive disease.

The retrospective nature of this study limited the clinical data to those already collected in the

medical charts and it was not possible to identify the factors that influenced the choice of treatment modality in all the patients. Some of the factors considered included location of the lesions and multifocality, patients comorbidities as well as patient's or physician's preference. However, in this study, we analyzed the rate of progression to cancer in women with HG-VaIN regardless to the treatment performed, even because HG-VaIN and mostly vaginal cancer are quite rare.

Thus further studies analyzing the potential role of different therapeutic strategies in the progression to invasive disease are needed.

Conclusions

Women with HG-VaIN should always be carefully evaluated by gynecologic oncologists with particular expertise in the diagnosis and management of pre-invasive and invasive lesions of the lower female genital tract. A long lasting and accurate follow up is recommended, especially in women at higher risk of progression to invasive vaginal cancer (VaIN3 and previous hysterectomy for HPV-related cervical disease).

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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