International Journal of Reproduction, Contraception, Obstetrics and Gynecology
Almeida GV et al. Int J Reprod Contracept Obstet Gynecol. 2023 May;12(5):1212-1216
www.ijrcog.org
pISSN 2320-1770 | eISSN 2320-1789

DOI: https://dx.doi.org/10.18203/2320-1770.ijrcog20231200

Original Research Article

Risk of progression to vaginal cancer after successful treatment of high-grade cervical intraepithelial neoplasia: a long-term cohort study in a single institution

Gisela Vicente Almeida[1]*, Margarida Bernardino[2], Ana Francisca Jorge[2], Catarina Luís[1], Nadia Charepe[3]

[1]Gynecology and Obstetrics Service of Centro Hospitalar de Setúbal, EPE, Setúbal, Portugal, Portugal
[2]Gynecology Service of the Portuguese Institute of Oncology, Lisbon, Portugal
[3]Gynecology and Obstetrics Service at Maternidade Dr. Alfredo da Costa, CHLC, Lisbon, Portugal

Received: 10 March 2023
Revised: 15 April 2023
Accepted: 17 April 2023

***Correspondence:**
Dr. Gisela Vicente Almeida,
E-mail: giselavicalmeida@gmail.com

ABSTRACT

Background: Studies on the long-term risk of treated cervical intraepithelial neoplasia (CIN), have shown that these women have a higher risk of invasive cancer in the remaining cervix or vagina, when compared to the general population. This risk persists, for at least, ten years after initial treatment.
Methods: Retrospective cohort study to evaluate the long-term risk of vaginal cancer after treatment of high-grade cervical intraepithelial neoplasia.
Results: The data comprised 460 women with high-grade cervical intraepithelial neoplasia treated at our institution, from January 2012 to December 2020. Three women developed vaginal cancer. The rate of invasive cancer during this period was 181 per 100 000 woman-years. The increased risk of developing cancer was noticed during the first 5 years of follow-up, in women older than 50, and with human papillomavirus (HPV) 16 infections.
Conclusions: Women previously treated for high-grade lesions, are at an increased risk of developing invasive vaginal cancer. This risk is higher in older women. Follow-up of these women should be based on risk, by a combination of co-testing and clinical evaluation.

Keywords: High-grade intraepithelial neoplasia, HPV, Vaginal cancer

INTRODUCTION

Carcinoma of the cervix is the leading cause of female cancer mortality in the developing world.[1] Infection with high-risk human papillomavirus (hrHPV) is the necessary cause of cervical intraepithelial neoplasia (CIN), which can progress to cervical cancer if left untreated.[2]

In developed countries, the implementation of cervical screening has had a significant impact on the incidence of cervical cancer, since preinvasive lesions can be detected and treated effectively. Management methods for high-grade intraepithelial lesions include excision, destructive techniques, or hysterectomy.[3,4] Long-term follow-up of women who have undergone conservative treatment suggests that, although these procedures are effective, these women have a higher risk of developing invasive cervical cancer after treatment, when compared to the general population. This risk persists for at least 25 years.[5-7]

American Cancer Society (ACS) 2020 guidelines recommend continued surveillance with HPV testing or co-testing at 3-year intervals for at least 25 years, after high grade lesion treatment.[8]

The recurrence rate for high-grade preinvasive disease can be as high as 5-10%.[7] In 2006, Soutter published a systematic review and meta-analysis that showed that the rate of invasive disease remained about 56 per 100,000-woman years for at least 20 years after treatment, corroborating Kalliala et al findings in 2005. This rate was shown to be approximately 2.8 times greater than the expected in the general population.[4,7]

It is known that lack of treatment or incomplete excision of preinvasive cervical lesions is associated with a higher risk of invasive cervical cancer. This increase in risk may be caused by persistent or recurrent human papillomavirus (HPV) infections, reinfection, inadequate follow-up, or residual preinvasive disease that can be more difficult to detect.[9] Women who have had cervical cancer are also at significantly increased risk of developing vaginal cancer.[9,10] Smoking is also known to be a strong risk factor for cervical neoplasia.[11]

The aim of this review was to estimate the risk of developing cervical or vaginal squamous cell carcinoma (SCC) after cervical high grade intraepithelial neoplasia treatment in our center, and to further explore how this compares to the risk reported in literature.

METHODS

Study design

A retrospective study on patient data of women treated at our institution. The study population consisted of women who had been surgically treated for cervical high-grade intraepithelial neoplasia, between January 2012 and December 2020.

Based on the archived data, we identified patients who had an excisional treatment between 2012 and 2020. The diagnostic HPV tests and the histopathological evaluation were performed at our department of pathology. Both cervical intraepithelial neoplasia (CIN) II and III (ICD-O: 8077/2) and carcinoma in situ (CIS) (ICD-O: 8070/2) diagnoses were recorded according to the international guidelines for cancer registration.[12]

Large loop excision of the transformation zone (LLETZ) was the method of treatment for high grade dysplasia. The specimen was analysed to ensure the lesion was excised totally with a safety margin. Follow-up surveillance was from six months after the first visit until death, or September 30, 2021.

The main outcome of the follow up was assessed by the progression to squamous cell carcinoma (SCC).

This study was in accordance with the Declaration of Helsinki, as revised in 2013.

Eligibility criteria

All women with a high-grade cervical lesion and documented effective treatment of cervical lesion.

Women were initially treated by LLETZ. We included woman who had additional procedures to complete high-grade lesion excision (second LLETZ or hysterectomy after an excisional procedure without total excision of the lesion). Patients with simultaneous vaginal or vulvar high-grade lesions who had undergone laser vaporization or excision, were also included. Women with no recorded treatment were excluded from the analysis.

Patients with positive margins after LLETZ who did not have a second LLETZ or hysterectomy, were excluded. We also excluded women who had histological diagnosis of invasive cancer within 6 months of a biopsy examination with a result of CIN, as we considered to have missed an existence invasive cancer at initial diagnosis.

Statistical analysis

Statistical analysis was done using Statistical Package for Social Sciences (IBM SPSS), version 27.0.

RESULTS

The CIN cohort consisted of 652 women, treated for high-grade lesions from January 1, 2012, through December 31, 2020, identified from our institution database.

We excluded 108 women with incomplete records or concomitant invasive disease of the vagina or vulva and 43 women with a LLETZ without clear margins and no subsequent treatment.

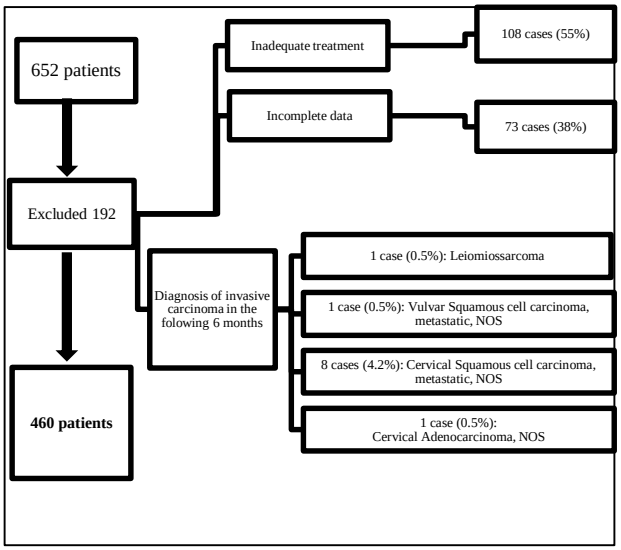

Figure 1: Flow chart of recruitment.

After applying our exclusion criteria, 460 patients remained for analysis, as shown in Figure 1.

We identified 3 cases (0.7%) of cancer among 460 women treated for cervical high grade intraepithelial neoplasia.

The standardised incidence ratio for women with previous cervical intraepithelial neoplasia grade 3 to develop invasive cervical cancer was shown to be 2.29 (95% confidence interval 2.07 to 2.52), compared with the general female population.[5] In our study, the risk was 1.3 times higher than the standardised incidence ratio.

Table 1: Baseline characteristics of the patients.

Variables	
Age (years)	46.2±12.6
Coitarche (years)	17.8±2.5
Time of follow-up* (years)	3.6±2.1
Risk factors, n (%)	
Smoking	89 (19.3)
Immunosuppression	78 (16.9)

Time (years) of follow-up after initial treatment for high-grade lesion. Values are presented as mean±standard deviation or number (percentage)

All three patients had, as initial treatment, a LLETZ excision procedure followed by a hysterectomy within one year. The three patients had residual high-grade lesion in the hysterectomy piece, with clear margins.

These patients were post-menopausal and aged 50 years or older. The diagnosis of recurrence was confirmed by biopsy in all three cases. The invasive cancer diagnosis was made 36, 48 and 60 months after initial treatment.

One patient, had been referred to her local hospital, after hysterectomy and returned to our center after five years, after being diagnosed with of invasive disease in the vaginal vault. She has an autoimmune disease, treated with chronic corticotherapy.

The other two patients-maintained follow-up at our institution after the hysterectomy. Both had persistent HPV 16 infection.

One patient underwent a partial vaginectomy 18 months after the hysterectomy, for histologic VaIN3, and subsequent two CO_2 laser treatments, for high grade vaginal lesion persistence. Diagnosis of invasive lesion was made 48 months after initial treatment after a pelvic mass was palpated. Diagnosis was confirmed based on suspicious findings on imaging, and confirmed by a tomography guided biopsy. No invasive cancer was evident on vaginoscopy.

The third patient had a partial vaginectomy 48 months after the hysterectomy for high-grade lesion on the vaginal biopsy, after abnormal colposcopic findings. The histopathological result was low-grade intraepithelial lesion on the surgical specimen.

As described, in all cases, the progression to carcinoma arose in the vaginal vault. All patients were asymptomatic at the time of the diagnosis.

All patiens were treated with chemoradiotherapy and are, currently, without signs of disease recurrence, with an average of 15 months (9-24 months) follow-up.

DISCUSSION

It has been reported in the literature that women who have undergone hysterectomy and have a history of high-grade cervical lesion are at some risk of developing female genital tract cancers.[13,14] The rate of invasive cervical cancer after treatment of CIN depends on the effectiveness of the primary treatment and the rigour of follow-up to detect and treat recurrent preinvasive disease.

The rate of invasive cervical cancer among women treated for cervical intraepithelial neoplasia was estimated to be 85 per 100 000 woman-years, in a previous large study on long term outcomes after treatment.[15] We found that the incidence of vaginal cancer among women treated for cervical intraepithelial neoplasia in our study was about 181 per 100 000 woman-years.

All our patients were initially treated with what can be considered a complete treatment and were compliant with the post-treatment follow-up program. However, they still progressed to cancer.

We should also consider the persistence of risk factors common to pre-malignant lesions such as immunosuppression, lifestyle habits, such as smoking or HPV persistence.[2,16-18] Women aged more than 50 years at diagnosis seem to have a higher risk of developing an invasive cervical cancer.[18]

HPV vaccine might have beneficial effects against new infections and reinfections from the same HPV subtype before treatment It is less likely that vaccination promotes clearance of an existing infection.[19-21] Unfortunately, the cost of the HPV vaccine is still not supported by the state and many patients do not have the economic means to do so.

Also, evidence shows that, even after cervical screening and treatment, women who are immunosuppressed, are at high risk of HSIL or invasive cervical lesions. These findings highlight the importance of reflecting upon the appropriate post-treatment follow-up of this population.[22]

Strengths and weaknesses

In our study, there are some limitations to be noted: clinical data was observational and limited to a single institution. A small number of cases was included, and treatment patterns shifted during the study period.

Another limitation is lack of information on other risk factors, such as HPV persistent infection, or deleterious daily habits.

Implications

The clinical implication of our findings is that women treated for cervical intraepithelial neoplasia need long term follow-up with cytology and testing for human papillomavirus. Stopping such a programme in women aged 60 may be premature if they were aged more than 35-40 when treated.

CONCLUSION

Vaginal cancer is a rare HPV-related malignancy. Persistent infection with HPV 16, as well as coexistence of immunosuppression seem to be factors for progression to carcinoma.

Our results are consistent with previous literature. Women treated for high grade intraepithelial neoplasia have an increased incidence of HPV-related female genital tract cancers, compared to the general population. This reinforces a systematic screening for women treated for high-grade intraepithelial neoplasia.

Currently, HPV testing is included for the follow-up after treatment for cervical intraepithelial neoplasia.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Almeida GV, Bernardino M, Jorge AF, Luís C, Charepe N. Risk of progression to vaginal cancer after successful treatment of high-grade cervical intraepithelial neoplasia: a long-term cohort study in a single institution. Int J Reprod Contracept Obstet Gynecol 2023;12:1212-6.