

Fifteen Years' Experience with Vulvar Verrucous Carcinoma at a Single Norwegian Academic Cancer Center

Sharma S¹, Davidson B^{2,3}, Jensen TS¹ and Wang Y^{1*}

¹Department of Gynaecologic Oncology, Oslo University Hospital-Radium Hospital, Oslo, Norway

²Department of Pathology, Oslo University Hospital-Radium Hospital, Oslo, Norway

³Faculty of Medicine, Institute of Clinical Medicine, University of Oslo, Oslo, Norway

***Corresponding author:** Wang Y, Department of Gynecological Oncology, Oslo University Hospital-Radium Hospital, Oslo, Norway, Tel: +47 45217069, E-mail: yunwang@ous-hf.no

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Abstract

Objective: Vulvar verrucous carcinoma (VVC) is extremely rare, accounting for less than 1% of vulvar cancer cases. The purpose of this study was to report our experience with this disease.

Methods: This is a retrospective study of patients with VVC who were treated at Oslo University Hospital - Radium Hospital between 2003 and 2018. Clinicopathological characteristics, treatment and follow-up were extracted from the medical records.

Results: Seven patients were identified through pathology databases and verified as having VVC. The average age at diagnosis was 70 years. Four patients had previous lichen sclerosus. Primary surgery was performed in all patients, including 3 who underwent wide local excisions, 1 simple local excision and 3 simple vulvectomies. Ipsilateral groin lymphadenectomy was performed in 1 patient because of an uncertain histological result before surgery showing negative lymph nodes. Tumor size and invasion depth ranged from 15 to 45 mm and 1 to 12 mm, respectively. Tumor-free histopathological margins were achieved in 5 out of 7 patients. Invasive disease extended to the histopathological margin in 2 patients, re-excision was performed in 1 patient after primary simple local excision and the other patient was followed up without reoperation because of negative biopsy after primary wide local excision. The mean follow-up was 68 months with no recurrence in those 7 patients.

Conclusion: VVC is defined by slow growth, no metastasis or lymph node involvement. The prognosis is good, with low recurrent rate if wide local excision is performed. Overtreatment should be avoided. Patients with lichen sclerosus in the vulva may show a risk of VVC.

Keywords: Vulvar Verrucous Carcinoma; Vulvar Squamous Carcinoma; Lichen Sclerosus; Treatment

Abbreviations: VVC: Vulvar Verrucous Carcinoma; SCC: Squamous Cell Carcinomas; VIN: Vulvar Intraepithelial Neoplasia; uVIN: Usual VIN; dVIN: differentiated VIN; VLS: Vulvar Lichen Sclerosus; PV: Human Papillomavirus; CT: Computed Tomography

Introduction

Vulvar cancer is rare and accounts for about 1% of all malignancies occurring in women and 5% of the gynaecological cancers. Most of these cases are histologically confirmed to be squamous cell carcinomas (SCC) [1]. Verrucous vulvar carcinomas (VVC) are rare and comprise only 1% of vulvar cancers. They have been found to be a slow-growing tumour that seldom metastasizes to the lymph nodes [2]. Such tumours can often grow considerably in size and preferably push membranes and margins rather than break through, compared to SCC, which have an infiltrating nature [3]. They are also often described as exophytic in appearance. Possible symptoms include itching, pain, ulceration, or bleeding from the tumour [1]. Our study aims to review the cases of VVC treated at the Department of Gynaecologic oncology, Oslo University Hospital-Radium Hospital, Norway. The department has a regional function for gynaecological malignancies and receives patients from the whole of southeastern Norway, but also a national function for pelvic exenteration and fertility-sparing operation for cervical cancer treatment.

Methods

This study is a retrospective study. The study population consisted of all patients diagnosed and treated for VVC at the Department of Gynaecologic oncology, Oslo University Hospital - Radium Hospital from 2003 to 2018. Patients diagnosed with VVC were

identified from the hospital pathology database. All histologic specimens were re-reviewed and the diagnosis was confirmed by an experienced gynaecologic pathologist (Ben Davidson). Information regarding the past medical history, clinical presentation, histopathology, treatment regime and follow-up have been extracted from their medical records. This study was approved by the local data protection officer at Oslo University Hospital (No. 18/22578). A request to waive written informed consent was approved.

Results

In total, seven patients were verified as having VVC. Histopathological images at different magnification are shown in Figures 1 & 2. Presence of papillomatosis, mild basal atypia and absence of koilocytosis were identified in all cases, while only 4 cases showed hyperkeratosis. All patients were Caucasian and had a body mass index ranging from 18, 6 to 28, 8. The average age at diagnosis was 70 years, with the youngest patient being 42 years, and the oldest 95 years. VVC occurred in several vulva locations (Table 1), with 3 in the area of clitoris, 2 on labium major, 1 on labium minor and 1 on mons pubis. Four patients had previous lichen sclerosus (No. 2-5). Three of our patients had previously been treated for SCC in the vulva (No. 4-6), but they all had SCC on a different side than the later diagnosed VVC. The elapsed time from primary SCC to the later diagnosed VVC was 4, 8 and 12 years, respectively. Two of the four patients with previous lichen sclerosus had SCC prior to VVC (no. 4 and 5). Patient no. 1, who had a medical history of kidney transplantation, condyloma and positive HPV, was diagnosed with SCC on the right side of labium major 4 years after treatment for VVC. There was no lymph node involvement in any of the cases, as had been confirmed by computed tomography (CT) examination previous to the operation.

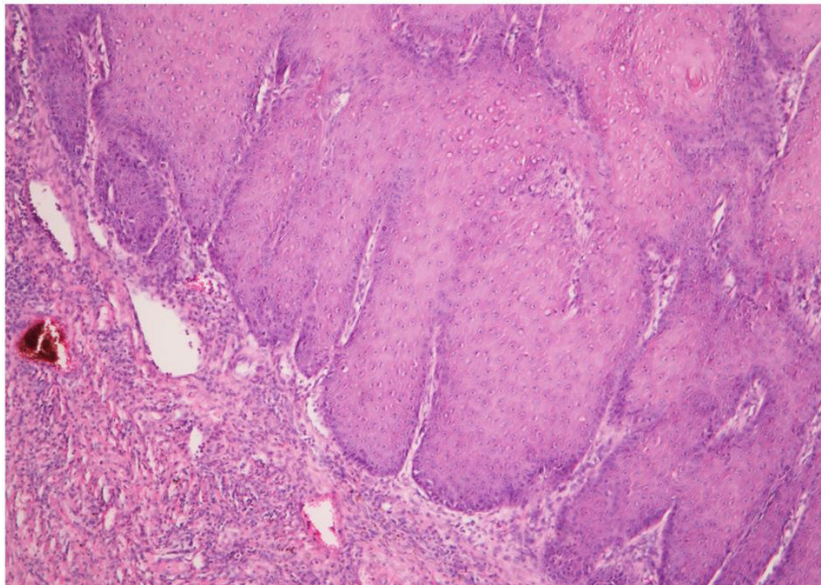


Figure 1: Histopathological image (magnification x 100)

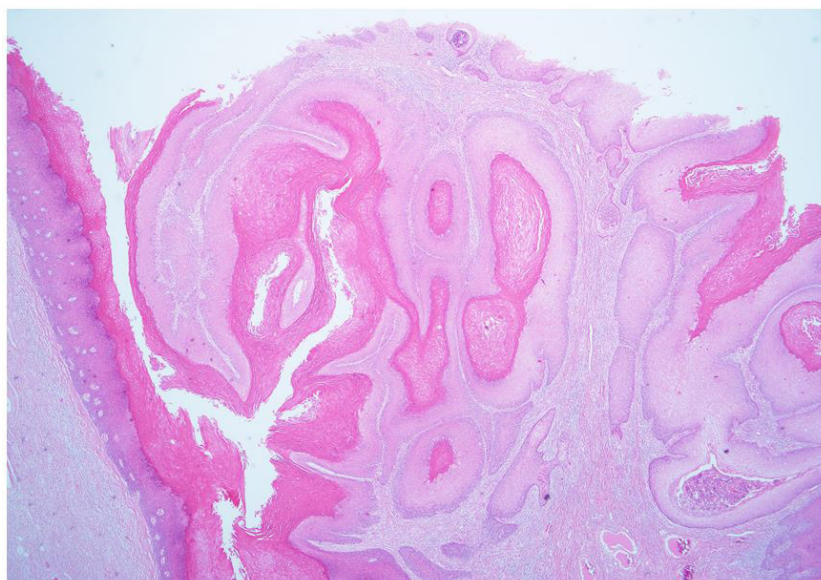


Figure 2: Histopathological image (magnification x 25)

case	Age	Previous LS	Procedure	Location	Tumor size (mm)	Margin (mm)	ID (mm)	Follow-up (months)	Recurrence
1	42	No	WLE	Mons pubis	45	>10	<1	181	NED
2	81	Yes	SV	Clitoris	20	7	<1	118	NED***
3	76	Yes	SV+IGL	Right labium minor	23	3	12	108	NED
4	95	Yes	WLE	Clitoris	33	1	6	27	NED
5	60	Yes	SLE	Left labium major	15	Positive*	3	21	NED
6	67	No	WLE	Right side of clitoris	41	Positive**	4	21	NED
7	68	No	SV	Left labium major	21	>10	5	3	NED

Table 1: Clinicopathologic features

Primary surgery was performed on all of the patients, including 3 who underwent wide local excisions, 1 who had simple local excision and 3 simple vulvectomies. Ipsilateral groin lymphadenectomy was performed in one case (no. 3) because of uncertain histological results prior to surgery, and was confirmed VVC with negative lymph nodes. Tumor size and invasion depth ranged from 15 to 45mm and 1 to 12mm, respectively. Tumor-free histopathological margin was achieved in 5 of 7 patients. Invasive disease extended to the histopathological margin in 2 patients (nos. 5 and 6). Re-excision was performed on 1 patient (no. 5) after primary simple local excision and on the other patient (no. 6) having a tumor located near the clitoris; this was not followed up with reoperation because of repeated negative biopsies after primary wide local excision. The mean follow-up time was 68 months with no recurrence in those 7 patients. One patient (no.2) died around 9 years after the VVC diagnosis, however of other disease and without evidence of VVC recurrence.

Discussion

The incidence of vulvar cancer in Norway is 4.66 per 100,000/year and about 80 patients are newly diagnosed with vulvar cancer each year [4]. Around 2/3 of these patients are treated in our hospital (on average 50 patients per year). We identified and verified 7 cases with VVC in our hospital pathology database during a 15-year period from 2003 to 2018, corresponding to approximately 1% of overall vulvar cancer patients who were treated in our hospital. This is equivalent to previous reports [2,5] concluding that VVC is rare and comprises only 1% of vulvar cancers.

The vulvar intraepithelial neoplasia (VIN) is well documented to be a precursor of SCC [6]. While usual VIN (uVIN) is associated with human papillomavirus (HPV) infection, differentiated VIN (dVIN) develops in areas with chronic inflammation, like lichen sclerosus [7-10]. Lichen sclerosus often presents in women over the age of 40 and has a higher occurrence in Caucasian women. It has been differentiated between vulvar lichen sclerosus (VLS) and lichen simplex chronicus with a verruciform architecture as a precursor and risk factor for VVC or SCC [10,11]. While lichen simplex chronicus usually occurs after trauma or infection, VLS can occur spontaneously and can be classified as an autoimmune disease. Oxidative stress, DNA damage and TP53 mutations have also been shown to facilitate VLS and the progression to malignancy [8]. Women with VLS have an increased risk of developing SCC [9,10,12]. In a retrospective study from the UK in 2010, Wang, *et al.* [9] reported that 5 out of 5 women with VVC had coexisting VLS.

While the occurrence of VIN/Condyloma was low in our study (1/7), we found a rather high number of patients with VLS (4/7). VVC is rare and one might therefore be reluctant to say that there is a definite association between VLS and VVC, but these findings strongly suggest that patients with lichen sclerosus in the vulva do tend to show a higher risk of developing VVC. As the number of patients in all studies remains small, however, further studies will be needed to confirm this theory. Previous study has shown that VVC does not break the basal membranes and infiltrate and does not metastasize to lymph nodes or other structures [1]. However, VVC can grow rather considerably in size if mistaken for condyloma and left untreated.

The recommendation of primary treatment is surgical excision with good resection margins and without removal of lymph nodes [1,2,13]. In our study, surgical excision was performed in all patients. Among the two patients where invasive disease extended to the resection margin, re-excision was performed in 1 patient after primary simple local excision. The other patient had a tumor located near the clitoris, and repeated new biopsies after primary surgery were negative. In order to preserve the function of the clitoris, she was followed intensively without reoperation. There was no evidence of recurrence after 21 months of follow-up in all these 7 patients. Our study confirms that surgical excision with good margin and without removal of lymph nodes is adequate. We conclude that follow-up is acceptable in order to preserve genital function if biopsies prove negative after primary operation with positive margin. Overtreatment should be avoided in VVC.

It has been shown that existence of VVC and SCC can occur simultaneously. Haidopoulos *et al.* [14] found in their study from 2005 that a total of 6 out of 17 patients had coexisting SCC and VVC. 3 out of 6 patients had both well differentiated SCC and VVC in the vulvar biopsy. In the remaining 3 patients this cooccurrence was diagnosed after the operative treatment. Liu, *et al.* [2] reported a 15% (10/67) occurrence of coexisting SCC and VVC. None of the 7 patients had coexisting SCC and VVC in our study, but 3 patients had previously been treated for SCC in the vulva, while 1 was diagnosed with SCC in the vulva 4 years after treatment for VVC. The latter patient had confirmed condyloma/HPV before treatment for VVC. Although VVC does not involve the lymph nodes, inflammatory enlargement is

not unusual, and can provide a pitfall during diagnostics, possibly leading to overtreatment. Optimal vulvar biopsy and a biopsy from an enlarged inguinal lymph node are crucial in establishing a correct diagnosis and choosing the proper course of treatment [14,15].

If vulvar biopsy confirms the diagnosis of VVC, lymphadenectomy can be abandoned safely. If vulvar biopsy confirms coexistence of VVC and SCC, an evaluation of inguinal lymph node either by sentinel lymph node extirpation or lymphadenectomy is necessary. In our study, no inguinal intervention was done for the six patients with a preoperatively confirmed VVC diagnosis, while lymphadenectomy was performed in one patient due to unclear diagnosis in the vulvar biopsy. In the latter case, histologic examination detected no metastasis in the removed lymph nodes. If treated adequately, VVC represents minimal risk of recurrence. However, a previous study showed that the risk of recurrence in VVC is relatively high, about 30%, if treated incorrectly [3]. Considering the shown correlation between VLS and VVC, and SCC and VVC, one might not only recommend regular interval check-ups [13,15], but also extra examinations if the patient presents with symptoms.

Conclusion

VVC is defined by slow growth, no metastasis or lymph node involvement. The prognosis is relatively good, with low recurrent rate if wide local excision is performed. Overtreatment should be avoided. Patients with lichen sclerosus in the vulva may show high risk of VVC and should therefore be included in a follow-up regime with regular check-ups.

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