Introduction
Primary vaginal cancer is a rare disease of the female gynecological tract and mainly affects postmenopausal women. It accounts for less than 0.5% of female cancers.\(^1,2\)

Uterine prolapse combined with vaginal cancer is an extremely rare condition. Until now, only less than 20 cases of primary vaginal cancer complicated by uterine prolapse have been reported.\(^3-9\) Squamous cell carcinoma is the most common type in this entity.\(^3-9\) However, to the best of our knowledge vaginal warty squamous cell carcinoma (WSCC) has never been reported in this rare combination. WSCC is a rare neoplasm that can be misdiagnosis as verrucous carcinoma.\(^10\) Here we describe a case of vaginal WSCC occurred in an elderly woman with uterine prolapse.

Case Presentation
A 77-year-old postmenopausal, gravida 8, para 8, with vaginal delivery, not sexually active and without significant medical history, was referred to our department with third-degree uterine prolapse and a non-healing ulcer of the vagina. For 20 years, she had a third-degree prolapsed uterus and she did not use a pessary. Her first sexual intercourse was at the age of 11. The patient underwent an examination under anesthesia. Physical examination revealed a uterine prolapse with an ulcer-budding lesion located on the medium and lower third of the left lateral vaginal wall. The lesion had 6 cm in the greater axis. The mass was mobile. The vaginal cul-de-sac were smooth and both lateral parametrium and rectovaginal septum appeared free of disease. The cervix was normal. There were no palpable inguinal lymph node. We performed a cystoscopy whereas we found a sore in the left wall of the bladder. We carried out a biopsy for both the vaginal and bladder lesion. The histopathological assessment revealed a warty surface and low-power architecture analogous to a condyloma lesion (Figure 1). The surfaces were contiguous and occupied by papillary vegetations and supported by fibrovascular axes (Figure 2). Cells in the tumor nest had large, wrinkled, hyperchromatic nuclei with koilocytosis, horn pearl was present, and there was a deep stromal invasion (Figures 3 and 4). The diagnosis of a well-differentiated warty squamous cell carcinoma was made. The CT scan excluded distant metastasis. We staged the patient as IVA according to FIGO classification of primary carcinoma of the vagina. We decided surgical treatment despite the advanced stage because warty subtypes should not be exposed to radiation due to the risk of rapid transformation in a more malignant tumor. We opted for a laparotomic technique. Preoperative investigations showed suspicious pelvic lymph nodes that have not been objectified on the radiological assessment. The patient underwent a total hysterectomy, bilateral salpingo-oophorectomy, bilateral pelvic node dissection, left partial cystectomy with left ureteral reimplantation and total vaginectomy. Postoperative management was straightforward. The final histological examination concluded to a warty squamous cell carcinoma of the vagina (WSCC) with bladder involvement. The parametrium, the
paracervix, the cervix, and all the pelvic lymph nodes were free of disease. The surgical margins were free. Due to the lack of publications for this rare entity and the locally aggressive behavior, the patient had adjuvant radiotherapy with a total dose of 50 Gy. The patient was asymptomatic and had no recurrence during 8 years of regular follow-up. The overall survival was 93 months. She died of pulmonary infection.

Discussion
Primary vaginal cancer is a rare disease of the female gynecological tract and mainly affects postmenopausal women. It accounts for 2% to 3% of gynecological cancers, 10% of vaginal cancers and even less than 0.5% of female cancers.1

This rarity may be due to the restrictive criteria of the FIGO classification, excluding other coexistent gynecologic cancers.2

Uterine prolapse combined with vaginal cancer is an extremely rare condition. Until now, only less than 20 cases of primary vaginal cancer complicated by uterine prolapse have been reported.3-9 The most common histological type observed is squamous cell carcinoma.2,3,6 However, WSCC of the vagina associated with uterine prolapse has never been reported previously.

Great multiparity, postmenopausal status, also chronic cough, obesity, and chronic constipation are known as risk factors for uterine prolapse. Moreover, multiparity, postmenopausal status, and prolapse also represent risk factors for the development of vaginal cancer. Hence, early sexual intercourses, Human Papilloma Virus (HPV) infection, chronic vaginal irritation are also risk factors for vaginal cancer.10 In our case, the patient had early sexual intercourse and was a great multiparous and postmenopausal woman with a history of third-degree of the prolapsed uterus for 20 years.

Great multiparity, postmenopausal status, also chronic cough, obesity, and chronic constipation are known as risk factors for uterine prolapse. Moreover, multiparity, postmenopausal status, and prolapse also represent risk factors for the development of vaginal cancer. Hence, early sexual intercourses, Human Papilloma Virus (HPV) infection, chronic vaginal irritation are also risk factors for vaginal cancer.10 In our case, the patient had early sexual intercourse and was a great multiparous and postmenopausal woman with a history of third-degree of the prolapsed uterus for 20 years.

However, WSCC is correlated with a history of intraepithelial neoplasia, a young age, and HPV infection.10 In our case, the patient was old, which contrasts with what is known, but unfortunately, the HPV status wasn’t done due to the lack of materials.
WSCC is a rare variant of invasive squamous cell carcinoma, commonly described as a hybrid characteristic of condyloma and invasive cell carcinoma. Its occurrence in the vulva, uterine cervix, penis, anus, oral mucosa, and urinary bladder has been described. It is essential to differentiate WSCC from verrucous carcinoma. WSCC is HPV induced but verrucous carcinoma is not. This condition leads to consider HPV vaccination to provide HPV induced neoplasms.

Verrucous carcinoma is a very well-differentiated squamous cell carcinoma, with hyperananchosis, hyperkeratosis and tumor buds that repel the stroma in depth. This type exhibits exophytic and endophytic patterns. The epithelial papillae have no connective axis. The nuclei are round. Some atypia may be seen in the basal epithelial layer. There are no koilocytes, which differentiates it from the giant condyloma. It’s a tumor with local malignancy. It does not give lymph node metastasis.

Warty carcinoma is an infiltrating tumor that was first described in the vulva. It is multifocal and multifactorial. It includes poor hygiene, pre-existing condyloma acuminatum, squamous intraepithelial lesions with warty features, and HPV infection.

The presence of papillomatous exophytic growth with rounded papillae, prominent fibrovascular cores contrary to verrucous carcinoma, irregular infiltrative tumor interface, and conspicuous koilocytosis, are typical characteristics to diagnose WSCC. Koliocytic atypia can be seen on the surface in giant condyloma, but it is a mean feature of WSCC, however, it is absent in verrucous and papillary carcinoma. The second feature is the fibrovascular cores that are seen in WSCC, unlike verrucous carcinoma.

Vaginal bleeding, discharge, or ulceration are warning signs in a woman with uterine prolapse. WSCC is known as exophytic patterns. However, patients with externalized uterine prolapse are exposed to local repetitive strain injuries, that increase the risk to develop vaginal cancer. Vaginal carcinoma is classically presented as an ulcerative lesion. The etiopathogenesis of these forms, and in particular the role of HPV, is poorly established. It is assumed that irritation and chronic inflammation of the exposed vagina contribute to these ulcerative lesions as we reported in our case.

WSCC can express aggressive behavior, such we reported, despite it appears to be less aggressive than the typical well-differentiated squamous cell carcinoma. The aggressive behavior that we reported may be explained to the anatomy change of the vaginal wall.

The anterior middle and lower third of the vagina in uterine prolapse become closer to the bladder, which induces the early involvement of the bladder such we reported in our case.

Due to the rarity of this entity, there are very few publications on the subject, and it is essentially unique cases that are reported. There is no consensus on the appropriate treatment of these cancers on genital prolapse.

This case is unique because it presents a rare entity with a rare histological subtype. In our case, treatment guidelines have been extrapolated from studies of vaginal carcinoma with uterine prolapsed and warty WSCC.

The usual treatment for stage IV for vaginal cancer is radiation therapy. Chemotherapy may be combined with radiation helping it work better.

Electrocautery was the main therapy used to control warts at six-monthly intervals. Several other wart treatments, including cryosurgery, laser surgery, topical podophyllin, imiquimod, and surgical resection have been attempted.

In this case, with an unusual histological subtype, surgery may be considered for many reasons. Local treatment can’t be used, due the bladder involvement, moreover radiotherapy is generally avoided in order to avoid the risk of secondary cancers related to radiotherapy for benign gynecological conditions.

The incidence of malignant condylomatous warty lesion is estimated to be around 30% and is suspected to be more severe with the coexistence of carcinogens such as immunosuppressive factors, HIV infection, and poor nutrition. While some studies showed that radiotherapy tends to potentize the malignant transformation of warts, some case reports showed a total resolution of the small tumors.

Moreover, radiotherapy for elderly patients with uterine prolapse is associated with side effects as rectovaginal fistula, vesicovaginal fistula, or fibrosis, which reduces the quality of life for the patients, moreover, uterine prolapse will still exist. Nevertheless, more invasive operations cannot be endured by older patients. The physician has to weigh the pros and cons of every treatment choice modeling the comorbidities of those patients.

We opted for surgery as a first treatment, because our patient was without significant comorbidities. Despite the relative benignity of the WSCC, we indicated radiotherapy as adjuvant treatment due to the locally aggressive behavior.

**Conclusion**

The physician has to keep in mind the diagnosis of WSCC of the vagina in uterine prolapse, despite the older age and the ulcer-budding patterns. For the treatment of those unusual cases, the physicians have to discuss on a case-by-case basis. Further reports are encouraged to understand the physiopathology of this rare entity.

**Ethics Approval**

Our institution does not require ethical approval for reporting individual cases or case series.

**Informed Consent**

Verbal informed consent was obtained from the patient for their anonymized information to be published in this article.
REFERENCES

1. Howlader NNA, Krapcho M, Garshell J, et al. SEER Cancer Statistics Review 1975–2012. National Cancer Institute. http://seer.cancer.gov/csr/1975_2012/. Accessed May 5, 2019.

2. Benedet JL, Bender H, Jones H 3rd, Ngan H, Pecorelli S. FIGO staging classifications and clinical practice guidelines in the management of gynecologic cancers. FIGO Committee on Gynecologic Oncology. Int J Gynaecol Obstet. 2000;70:209-262.

3. Karateke A, Tugrul S, Yakut Y, Gürbüz A, Cam C. Management of a case of primary vaginal cancer with irreducible massive uterine prolapse – a case report. Eur J Gynaecol Oncol. 2006;27:528-530.

4. Gupta N, Mittal S, Dalmia S, Misra R. A rare case of primary invasive carcinoma of vagina associated with irreducible third degree uterovaginal prolapse. Arch Gynecol Obstet. 2007;276:563-564.

5. Rao K, Kumar NP, Geetha AS. Primary carcinoma of vagina with uterine prolapse. J Indian Med Assoc. 1989;87:10-12.

6. Lavazza C, Vorgias G, Vecchini G, Katsoulis M, Akrivos T. Vaginal carcinoma in a completely prolapsed uterus. A case report. Arch Gynecol Obstet. 2007;275:503-505.

7. Ghosh SB, Tripathi R, Mala YM, Khurana N. Primary invasive carcinoma of vagina with third degree uterovaginal prolapse: a case report and review of literature. J Gynecol Obstet. 2009;279:91-93.

8. Kim HG, Song YJ, Na YJ, Choi OH. A case of vaginal cancer with uterine prolapse. J Menopausal Med. 2013;19:139-142.

9. Wang Y, Li Q, Du H, Lv S, Liu H. Uterine prolapse complicated by vaginal cancer: a case report and literature review. Gynecol Obstet Invest. 2014;77:141-144.

10. DiSaia PHJ, Creasman WT. Invasive cancer of the vulva. In: DiSaia PHJ, Creasman WT, editors. Clinical Gynecologic Oncology. 6th ed. Mosby; 2002:211-219.

11. Erman-Vlahovic M, Vlahovic J, Mrcela M, Hrgovic Z. Coexistence of condylomata acuminata with warty squamous cell carcinoma and squamous cell carcinoma. Med Arch. 2017;71:72-75.

12. Campaner AB, Cardoso FA, Fernandes GL, Veasey JV. Verrucous carcinoma of the vulva: diagnosis and treatment. An Bras Dermatol. 2017;92:243-245.

13. Rastkar G, Okagaki T, Twigg LB, Clark BA. Early invasive and in situ warty carcinoma of the vulva: clinical, histologic, and electron microscopic study with particular reference to viral association. Am J Obstet Gynecol. 1982;143:814-820.

14. Tarbunou Y, Davis CL, Costa J, Williams C. Warty condylomatous squamous cell carcinoma of the penis in a 19-Year-Old. Urol Case Rep. 2014;2:79e8181.

15. Thapa S, Ghosh A, Shrestha S, Ghartimagar D, Narasimhan R, Talwar OP. Warty carcinoma penis: an uncommon variant. Case Rep Pathol. 2017;2017;293792.

16. Cho MK, Kim CH, Kim YH. Primary invasive carcinoma of the vagina after Le Fort partial colpocleisis for stage IV pelvic organ prolapse: a case report. Int Urogynecol J. 2011;22:1459-1461.

17. Bezerra AL, Lopes A, Landman G, Alencar GN, Tosloni H, Villa LL. Clinico-pathologic features and human papillomavirus and prevalence of warty and squamous cell carcinoma of the penis. Am J Surg Pathol. 2001;25:673-678.

18. Jang YH, Kim YC, Lee WS. Warty squamous cell carcinoma of the vulva in older women: association with human papillomavirus. Yonsei Med J. 2005;46:155-158.

19. Dhadda AS, Anand A, Boynton C, Chan S. External beam radiotherapy for extensive genital condyloma acuminate: a role in selected patients. Clin Oncol (R Coll Radiol). 2008;20:91-92.

20. Moodley M, Gowender PS. Radiotherapy in genital warts. Does it work? Eur J Gynaecol Oncol. DOI: 10.12892/ejgo4413.2019.

21. Creasman C, Haas P, Fox T, et al. Malignant transformation of anorectal giant condyloma acuminate. Dis Colon Rectum. 1989;32:481.

22. Sobrado CVV, Mester M, Nadalin VV, et al. Radiation-induced total regression of a highly recurrent giant perianal condyloma: report of a case. Dis Colon Rectum. 2000;43:257.