


Successful treatment of locally advanced bulky cervical cancer complicated by irreducible complete uterine prolapse

A case report

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Abstract

Rationale: Cervical cancer complicated by irreducible complete uterine prolapse in elderly patients is extremely rare. No standard treatment has been established for these conditions.

Patient concerns: A 74-year-old woman with a 30-year history of pelvic organ prolapse presented with irreducible complete uterine prolapse and a large exophytic mass involving the cervix and vaginal wall.

Diagnosis: Biopsy of the mass was performed at the referring institution and showed invasive verrucous-type squamous cell carcinoma.

Interventions: A prolapsed uterus with a tumor mass could not be manually reduced. After completion of concurrent chemoradiotherapy, the tumor mass in the prolapsed uterus decreased and could be reduced manually. Subsequently, the patient underwent hysterectomy and intra-abdominal uterosacral ligament suspension.

Outcomes: At 19 months of postoperative follow-up, the patient remained disease-free and had no evidence of vault prolapse.

Lessons: This study has important clinical implications and may provide a therapeutic strategy to address unmet medical needs in combination with locally advanced cervical cancer complicated by irreducible complete uterine prolapse. These conditions were successfully treated using a multidisciplinary approach of chemoradiotherapy followed by radical hysterectomy and uterosacral ligament suspension.

Abbreviations: CCRT = concurrent chemoradiotherapy, EBRT = external beam radiotherapy, HPV = human papilloma virus, LACC = locally advanced cervical cancer, POP = pelvic organ prolapse, SCC = squamous cell carcinoma.

Keywords: advanced bulky carcinoma, cervical cancer, uterine prolapse

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SYH and KHK contributed equally to this work.

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1. Introduction

Cervical cancer remains the most common gynecological malignancy worldwide, although its incidence and mortality rates have declined in most areas of the world during the past few decades. In Korea, it is the most common female genital malignancy; in 2017, the age-standardized incidence rate was 8.4 cases per 100,000 women. The numbers of newly diagnosed cervical cancer cases and deaths from cancer were 3469 and 868, respectively.^[1] Pelvic organ prolapse (POP) is a far more common disease than cervical cancer and is estimated to occur in 40% to 60% of parous women.^[2] Uterine prolapse is a common condition in elderly women and is mainly associated with increasing age, obesity, and high parity. Among parous women, 40% to 60% have varying degrees of POP and up to 20% require surgery during their lifetime.^[2,3]

The concurrence of cervical cancer with irreducible uterine prolapse is rare. Treatment options for cervical cancer are well established according to disease stage. One of the challenges in the treatment of cervical cancer is the coexistence of uterine prolapse. Uniform management is not well established when these 2 conditions coincide.

Herein, we present an unusual case of locally advanced bulky squamous cell carcinoma of the cervix, complicated by irreducible complete uterine prolapse, in an elderly woman. The patient underwent chemoradiotherapy followed by modified

radical hysterectomy and uterosacral ligament suspension. A multidisciplinary approach involving a gynecological oncologist, a urogynecologist, and a radiation oncologist resulted in successful outcomes.

2. Case presentation

A 74-year-old woman (gravida 5, para 4) with a known history of progressively worsening POP for approximately 30 years was referred to Pusan National University Hospital by another institution for uterine prolapse accompanied by an irregularly shaped large protruding mass. The patient reported an inability to reduce prolapse during the 3 months prior to the referral visit. The patient also complained of nocturia, associated with incomplete bladder emptying. Biopsy of the mass was performed by the referring institution and revealed an invasive verrucous squamous cell carcinoma (SCC) (Fig. 1). Pelvic examination revealed a large exophytic mass with complete uterovaginal prolapse (Fig. 2A and B). The prolapsed uterus with the tumor mass could not be reduced manually. She had a medical history of hyperlipidemia and surgical history of mastectomy for breast cancer. The patient's height and weight were 150 cm and 50 kg, respectively. The serum SCC antigen level at the initial visit increased (6.88 ng/mL). Neither high- nor low-risk human papilloma viruses (HPV) were detected at either the referring or our institution. Contrast-enhanced axial T1-weighted magnetic resonance imaging revealed an approximately 8.0 cm mass with marked enhancement in the prolapsed vagina and cervix (Fig. 3). Positron emission tomography-computed tomography (PET-CT) revealed avid 18F-fluorodeoxyglucose (FDG) uptake in the cervicovaginal region and the inguinal, external iliac, and obturator lymph nodes (Fig. 3). No evidence of distant metastases was observed. According to the International Federation of Gynecology and Obstetrics classification, the disease is clinically classified as stage IIIc1r.

Concurrent chemoradiotherapy (CCRT) consisting of 50.4 Gy whole pelvis irradiation in 28 fractions and 6 weeks of cisplatin (40 mg/m²/wk) was administered. On contrast-enhanced CT of the pelvis after CCRT completion, the tumor mass at the prolapsed uterus decreased (6.0 cm) and changed from a hard, irregular mass to a pinkish, soft smooth mass (Fig. 2C). The serum SCC antigen levels were normalized (1.09 ng/mL). At that

time, the prolapsed uterus was manually reduced (Fig. 2D). Four weeks after CCRT, the mass had decreased significantly (4.5 cm) (Fig. 2E).

Subsequently, the patient underwent type II radical hysterectomy with bilateral salpingo-oophorectomy and intra-abdominal uterosacral ligament suspension without mesh placement. Pelvic lymphadenectomy was performed to assess the persistence of suspicious pelvic lymph nodes. No adhesions or fibrosis was observed in the operative field. Postoperative pathological examination showed residual SCC measuring 0.3 × 0.2 cm in size. The residual protruding masses in the uterine cervix and vagina were confirmed to be inflamed granulation tissues. Both the adnexa and pelvic lymph nodes were free of tumor cells. No lymphovascular invasion was observed. She tolerated radiation therapy and surgery well, and had no significant morbidity. At 19 months of postoperative follow-up, the patient remained disease-free and had no evidence of vault prolapse (Fig. 2F). Written informed consent was obtained from the participant for publication of the details of her medical case and any accompanying images.

3. Discussion

Cervical cancer complicated by complete uterine prolapse is rare. Squamous cell carcinoma of the female tract, the verrucous type (formerly named), is rare, described as a well-differentiated and slowly growing tumor, and is unlikely to metastasize to lymph nodes or distant areas.^[4] In 2020, the WHO classification of female genital tumors classified invasive squamous lesions into 2 main categories: HPV-associated and HPV-independent. The vast majority of cervical SCCs (>90–95%) are HPV-associated.^[5] Although the role of HPV in the etiology of this neoplasm has been suggested, HPV DNA has not been detected in 75% of reported cases of SCC (verrucous type).^[4] A clear relationship between SCC, verrucous type, and HPV is yet to be described, and HPV infection tends to be infrequent in cases in which uterine prolapse is present.^[6] In our case, HPV was not detected at either the referring hospital or our institution. A systematic review has demonstrated the clinicopathological characteristics of these coexisting conditions.^[7] That review reported the mean age and median duration of prolapse were 63.7 years and 147.9 months, respectively, while the mean tumor size was 8.9 cm. Most patients

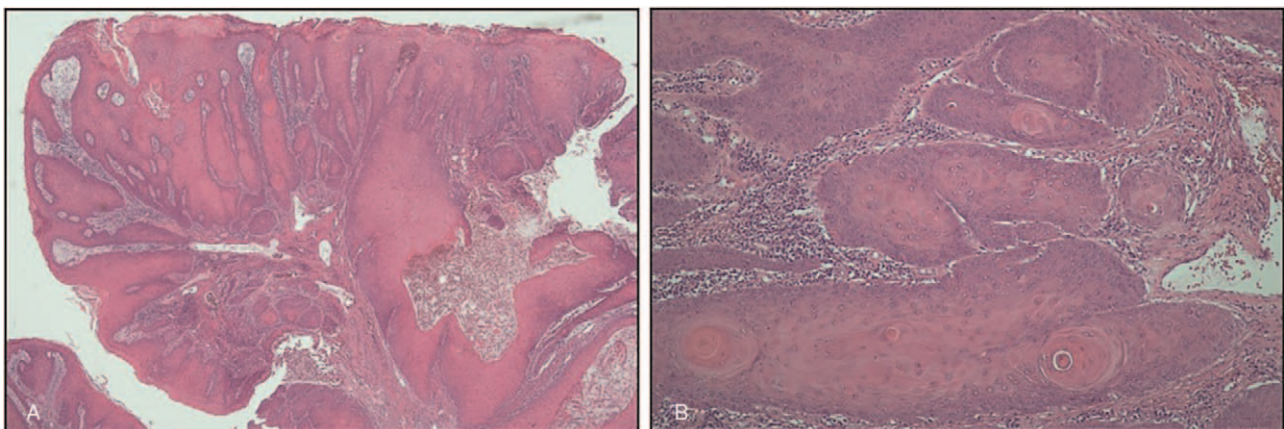


Figure 1. Microscopic findings of the squamous cell carcinoma (verrucous) of the cervix. (A) Exophytic acanthotic squamous epithelium shows pushing invasive growth (H&E, ×40); (B) tumor cells show abundant cytoplasm, minimal cytologic atypia, and rare mitoses (H&E, ×200).



Figure 2. Pelvic examination findings. (A, B) Squamous cell carcinoma of the cervix and complete uterine prolapse at initial visit, (C) immediately after CCRT, (D) manually reduced state preoperatively, at 3 weeks after CCRT, (E) preoperatively before operation, at 4 weeks after CCRT, (F) postoperative, at 6 months. Radiation dermatitis of the genitalia was noted after the prolapsed uterus was irradiated (D&E). CCRT=concurrent chemoradiotherapy.

were diagnosed with stage 1 disease (56.2%) and had an SCC type (83.9%). The pathophysiology of coexisting conditions remains unclear. Studies have shown that uterine prolapse itself may protect against cervical cancer or it can predispose to malignant transformation of the uterine cervix.^[8] Some authors have suggested that epithelial cornification during uterine prolapse may decrease the risk of malignant transformation.^[6,7] Others postulated that irritation of the cervix by being outside the body might promote the development of cancer. Women presenting with complete uterine prolapse are predisposed to a long process of chronic inflammation and direct mechanical irritation of the prolapsed areas, increasing the risk of cancer development.^[6,9] In this respect, the prolapse duration may be important for the development of cancer. Prolapse for >10 years

may be associated with an increased risk of cancer development.^[10] In our case, the patient had progressively worsening POP that persisted for approximately 30 years. The patient did not seek medical attention because of uterine prolapse; thus, cervical carcinoma was not diagnosed until the disease had progressed. Owing to its rarity, no standard recommendations have been established for the treatment of these coexisting conditions. Optimal management options include surgery, radiotherapy (RT) alone, or a combination of these 2 modalities. Treatment strategies vary considerably among reports and should be tailored according to the stage of cervical cancer and degree of pelvic prolapse. Surgery should be considered as the preferred option whenever possible to avoid serious visceral injuries from RT. In addition, surgical treatment for POP can

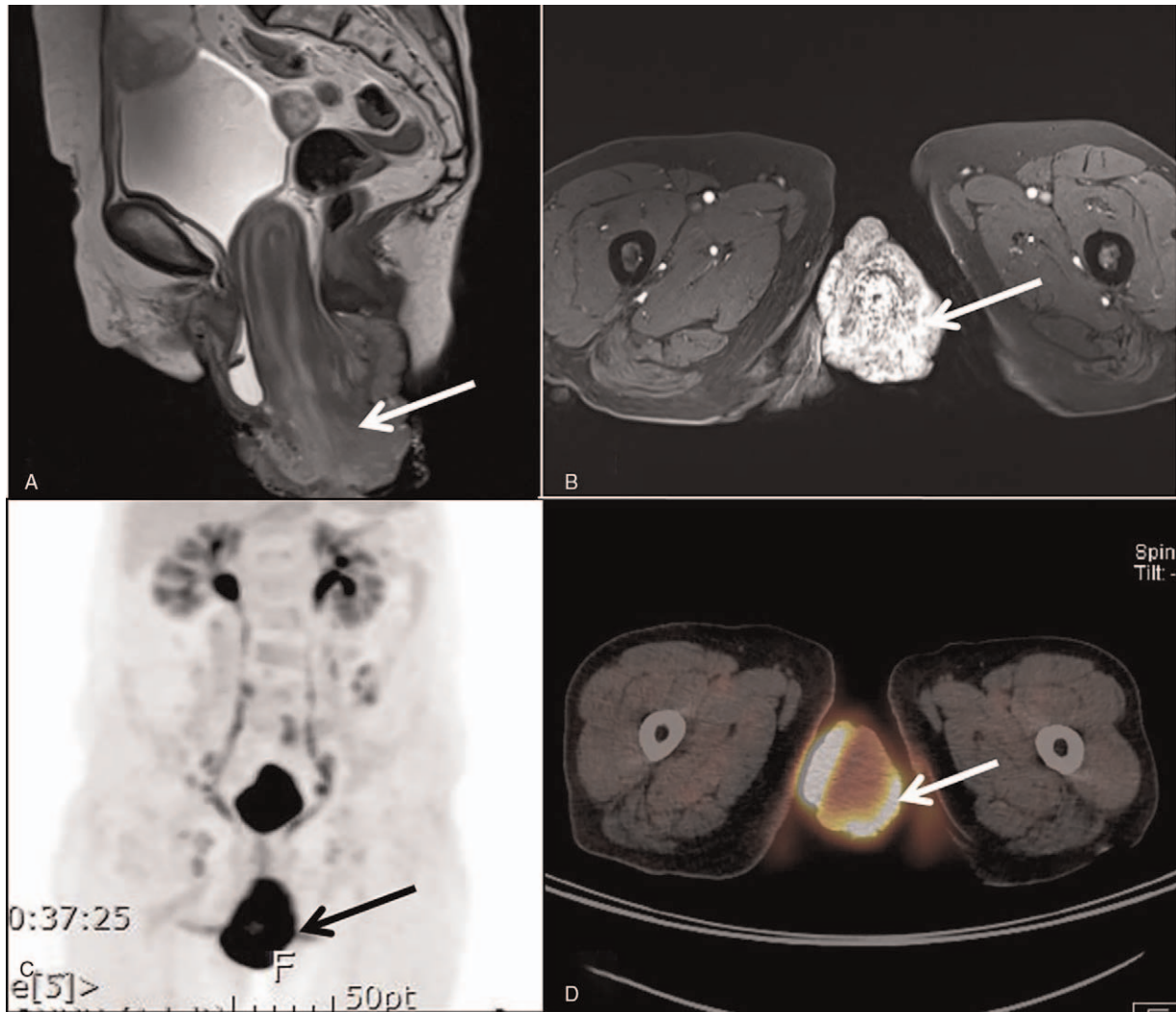


Figure 3. Imaging findings of squamous cell carcinoma (verrucous) of cervix and complete uterine prolapse. (A) T2-weighted sagittal magnetic resonance (MR) image showing complete prolapse of uterus and vagina (arrow). (B) Contrast-enhanced axial T1-weighted MR image showing marked enhancement in the prolapsed vagina and cervix (arrow). (C, D) FDG PET/CT images showing increased FDG uptake (arrow) in the prolapsed vagina and cervix. FDG=18F-fluorodeoxyglucose, PET-CT=positron emission tomography-computed tomography.

effectively improve health-related quality of life. Matsuo et al^[8] reported treatment patterns and survival outcomes in patients with cervical cancer complicated by complete uterine prolapse. Surgery alone or RT alone was performed in 33.3% and 38.5% of patients, respectively, while neoadjuvant RT followed by surgery was performed in 11.5% of patients. Survival outcomes were more favorable with surgery-based treatment than with radiation-based treatment, in terms of recurrence-free survival and disease-specific overall survival. Surgery alone or in combination with RT as a neoadjuvant or adjuvant method was considered the preferred option in 72% of cases of cervical cancer with irreducible uterine prolapse.^[7] In cases where immediate surgery is not feasible, chemoradiotherapy followed by surgery with curative intent has been reported to have good results in terms of both oncological and functional outcomes,^[11,12] as in our case. Some authors have mentioned that when external beam radiotherapy (EBRT) is planned, reduction of uterine prolapse and hysterectomy are recommended before EBRT to reduce the risk of visceral injury. Karateke et al^[13]

managed vaginal cancer and a massive uterovaginal prolapse that could not be repositioned under general anesthesia, but was repositioned by surgical intervention prior to RT. Despite this recommendation, Reimer et al^[11] reported successful EBRT treatment for an irreducible uterovaginal prolapse combined with cervical cancer, a case similar to ours. In our case, after the completion of chemoradiotherapy, the prolapsed uterus became reducible, and a minimal residual tumor was confirmed after surgery. We performed CCRT followed by salvage hysterectomy and uterosacral ligament suspension to control locally advanced cervical cancer (LACC) and irreducible complete uterine prolapse. CCRT is the standard treatment for LACC. However, the 5-year-overall survival (OS) remains at approximately 70%, and histopathologic residual tumors are observed in 40% to 50% of patients. Salvage hysterectomy is a treatment specifically for patients in whom tumors persist after definitive RT/CCRT. Gosset et al^[14] reported that salvage hysterectomy causes a high rate of postoperative complications (approximately 25%) and this surgical procedure did not prevent locoregional or distant

Table 1**Studies comparing survival outcomes between CCRT followed by hysterectomy and CCRT alone.**

Author	Study design	Subjects	Comparison	Outcome in CCRT+HT group
Albert et al (2019)	Retrospective	IB2 to IIA2 cervical cancer	CCRT+HT vs CCRT alone	No difference in OS
Yang et al (2020)	Retrospective	Locally advanced cervical adenocarcinoma	CCRT+HT vs CCRT alone	Improve OS and PFS
Takekuma et al (2020)	Retrospective	Persistent cancer after RT/CCRT	RT/CCRT+HT vs RT/CCRT+CT	Improve OS and PFS
Yoshida et al (2020)	Retrospective	IB2 to IIB cervical cancer	CCRT+HT vs CCRT alone	Improve OS and PFS reduce the risk of recurrence
Shim et al (2018)	Meta-analysis	Locally advanced cervical cancer	CCRT+HT vs CCRT alone	Not improve OS, reduce the risk of recurrence
Shi et al (2018)	Meta-analysis	Locally advanced cervical cancer	RT/CCRT+HT vs RT/CCRT+CT	Not improve OS, reduce the risk of recurrence
Lu et al (2021)	Meta-analysis	Locally advanced cervical cancer	CCRT+HT vs CCRT alone	Improve OS and PFS (subgroup analyses* did not show significant benefit) reduce the risk of recurrence

CCRT+CT=chemotherapy after CCRT, CCRT+HT=hysterectomy after CCRT, CCRT=concurrent chemoradiotherapy, CT=chemotherapy, HT=hysterectomy, OS=overall survival, PFS=progression free survival, RT=radiotherapy.

* Subgroup analyses of studies based on similar treatment protocols.

recurrences. Conversely, Takekuma et al^[15] demonstrated that salvage hysterectomy for patients with persistent cervical cancer after definitive RT/CCRT reduced the mortality rate by approximately 60% compared with systemic chemotherapy and could be a curative treatment for these patients. PET-CT may play a role in the selection of patients for salvage hysterectomy following CCRT for LACC.^[16,17] Further prospective clinical trials on salvage HT after RT or CCRT are required. The benefits of adjuvant hysterectomy (AH) after definitive CCRT for LACC are controversial because of unclear survival benefits and associated complications (Table 1).^[18–23] Three recent meta-analyses compared survival outcomes between CCRT followed by AH and CCRT alone.^[21–23] An updated review by Lu et al^[21] demonstrated that AH after CCRT may positively affect survival outcomes. In contrast, 2 previous meta-analyses reported no difference in the OS between the 2 groups.^[22,23] Most gynecologic oncologists agree that AH may be effective in patients with persistent residual disease after CCRT. The major clinical issue associated with surgical treatment after RT/CCRT is the high incidence of postoperative complications in the irradiated pelvis, which must be balanced against the potential benefits of treatment. Complication rates depend on the radicality of the surgery, accompanying procedures, tumor stage, residual tumor, time interval from CCRT completion to AH, and the surgeon's skill.^[22] Routine use of AH should be avoided because of its significant morbidity.

In conclusion, our study has important clinical implications and may provide a therapeutic strategy to address unmet medical needs in combined conditions, such as LACC complicated by irreducible complete uterine prolapse. To date, no standard treatment for these conditions has been established. This case presents an unusual combination of these 2 conditions, leading to a treatment dilemma. In our case, chemoradiotherapy followed by salvage hysterectomy was effective, without adverse events. This approach may be a treatment option for locally advanced bulky cervical carcinoma and irreducible complete uterine prolapse in carefully selected patients. Physicians should be aware of the optimal treatment for uterine prolapse with cervical cancer, because these coexisting conditions may become more prevalent.

4. Patient consent statement

The patient has provided informed consent for the publication of this case.

Author contributions

Conceptualization: Dong Hyung Lee, Ki Hyung Kim.

Resources: Byung Sup Shin.

Supervision: Jong Kil Joo.

Writing – original draft: Dong Hyung Lee.

Writing – review & editing: Dong Soo Suh, Seo Yoon Hwang, Ki Hyung Kim.

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