

Radical Hysterectomy for Cervical Cancer in Patients With Uterine Prolapse

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Abstract. *Background/Aim: Association between cervical cancer and uterine prolapse represents a scarce eventuality. This is a case series of 11 patients diagnosed with different stages of cervical cancer in association with uterine prolapse. Patients and Methods: Between 2014 and 2020, 11 patients were diagnosed with cervical cancer on prolapsed uterine cervix. Results: The mean age of patients at the time of uterine cervix diagnosis was 68 years. In six cases, the first intent treatment was surgery, while in the remaining five cases it consisted of radio-chemotherapy, followed by radical surgery. The perioperative and postoperative outcomes were compared to those reported in a similar series of patients diagnosed in similar stages of the disease, but in the absence of uterine prolapse, no significant differences being*

encountered. Conclusion: Although it represents an unusual situation, malignant transformation of the uterine cervix might be encountered even in cases presenting uterine prolapse. In such cases, the therapeutic strategy should be tailored according to the stage of the disease.

Chronic inflammation is widely accepted to be associated with the development of certain malignancies such as skin, liver or lung cancer (1). When it comes to cervical cancer patients, the relationship between chronic inflammation, malignant transformation, viral infection and uterine prolapse is a controversial one. Women presenting a complete uterine prolapse are predisposed to a long process of chronic inflammation and direct mechanical irritation of the prolapsed areas, increasing in this way the risks of cervical cancer development; therefore, in such cases, special attention should be given to this aspect, and the patients should be routinely submitted to more specific investigations, such as colposcopy, endocervical and exocervical examination, in order to achieve an early diagnosis of the neoplastic disease whenever it develops (1). Furthermore, virology studies have underlined the fact that the displacement of the uterine cervix in cases in which

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pelvic prolapse is associated might confer a degree of protection against malignisation by decreasing the risk of viral infection (2, 3). However, association of these two pathologies is rather uncommon, as scarce cases have been reported so far (2-4).

The aim of this paper is to report a case series of 11 patients diagnosed with different stages of cervical cancer in association with uterine prolapse.

Patients and Methods

Between 2014 and 2020, 11 patients were diagnosed with complete uterine prolapse in association with cervical cancer and submitted to surgery with curative intent. Classification of uterine prolapse was performed according to the Pelvic Organ Prolapse Quantification (POP-Q) system, while cervical cancer staging was performed according to the 2019 National Comprehensive Cancer Network guidelines (5, 6). After obtaining the approval of the ethical committee (no 34/March 2020), data of these patients were retrospectively reviewed. Postoperative complications were classified according to Dindo-Clavien scale (7). Perioperative outcomes were compared to those reported in a similar group of patients diagnosed with similar stages of neoplastic transformation of the uterine cervix, but in the absence of uterine prolapse.

Results

The mean age of patients diagnosed with cervical cancer in association with genital prolapse was 68 years (range=63-74 years), while the mean number of vaginal births was 5 (range=3-7). All cases were investigated for post-menopausal bleeding in association with various degrees of pelvic pain; nine patients were also associated with altered urinary habits, while seven cases associated with altered digestive habits; all cases were associated with complete uterine prolapse. All but two cases presented ulcerous or necrotic lesions at the level of the uterine cervix. Cervical biopsies were retrieved from all cases and demonstrated the presence of squamous cell carcinoma; among the 11 patients, two cases presented well differentiated lesions, five cases moderately differentiated lesions and four cases poorly differentiated lesions. Once the diagnosis of the malignancy was established, in all cases, pelvic magnetic resonance imaging in association with chest and upper abdominal computed tomography were performed in order to establish the extent of the disease and obtain proper staging. Preoperative details are shown in Table I.

An interesting aspect which should be mentioned is the fact that all patients were carriers of pelvic prolapse for a long period of time; the mean interval from the moment in which the patient observed the apparition of uterine prolapse to the moment in which cervical bleeding occurred was 9.5 years (range=8-12 years).

Once the diagnosis of malignancy was established, the five cases diagnosed with locally advanced cervical cancer were submitted to neoadjuvant therapy consisting of

Table I. *Preoperative details of patients diagnosed with complete uterine prolapse and cervical cancer.*

Parameter	No. of cases
Symptoms	
Post-menopausal bleeding	11
Pelvic pain	11
Urinary symptoms	9
Digestive symptoms	7
Local signs	
Ulcerous/necrotic lesions	9
Histopathological findings	
Squamous cell carcinoma	11
Grade	
Well differentiated	2
Moderately differentiated	5
Poorly differentiated	4
Stage at the time of diagnostic	
I	3
II	3
III	5
IV	0

radiotherapy alone or in association with chemotherapy, followed by surgery with curative intent, while the remaining six cases were submitted per primam to surgery. Intraoperative details are shown in Table II. In all cases, surgery for cervical cancer consisted of total radical hysterectomy *en bloc* with bilateral adnexectomy and pelvic lymph node dissection, while in eight of the 11 cases para-aortic lymph node dissection was also performed. The treatment procedures used for prolapse included anterior colporrhaphy (in five cases) followed by perineorrhaphy (in three cases) or posterior repair (in three cases). Two of the 11 cases also benefited from mesh placement; both cases were diagnosed with stage I cervical cancer and did not undergo radiotherapy.

Postoperatively, two patients developed grade 2 Dindo-Clavien complications represented by urinary tract infections, while one case developed a febrile syndrome of unknown origin. In order to investigate if the association between uterine prolapse and cervical cancer influenced the intraoperative and early postoperative complications, data of these patients were compared to the ones reported in a similar group of patients diagnosed with cervical malignancies in the absence of uterine prolapse.

Therefore, 11 similar cases diagnosed with squamous cell cervical cancer in the absence of uterine prolapse were identified; there were no significant differences in terms of age (the mean age being of 63 years, range=56-73 years, $p=0.32$) and cancer staging between the two groups. However, patients diagnosed with cervical cancer in the presence of uterine prolapse had a significantly higher

Table II. Intraoperative aspects of cases submitted to surgery for complete genital prolapse and cervical cancer.

Parameter	Value
Length of surgery	160 min (range=120-200 min)
Estimated blood loss	250 ml (range=100-350 ml)
Number of retrieved pelvic lymph nodes	18 (range=11-23 lymph nodes)
Number of retrieved para-aortic lymph nodes	6 (range=0-10 lymph nodes)
Length of hospital in stay	5 days (range=3-13 days)
Prolapse repair	11 cases
Mesh placement	2 cases

number of vaginal births when compared to cases with no degree of prolapse (5 *versus* 1, $p<0.0001$).

No significant differences were observed in terms of estimated blood loss (250 ml *versus* 210 ml, $p=0.34$), number of pelvic retrieved lymph nodes (18 *versus* 19, $p=0.44$) para-aortic retrieved lymph nodes (6 *versus* 8 nodes, $p=0.78$), and postoperative complications (27% *versus* 18%, $p=0.09$). However, cases with pelvic prolapse necessitated a significantly longer operative time due to the fact that in these cases synchronous surgical procedures for correction of the urinary and/or rectal prolapse were performed (160 minutes *versus* 100 minutes, $p=0.04$).

Discussion

Association of uterine cervix neoplastic transformation in patients with pelvic prolapse is a scarce eventuality, isolated cases being reported so far. However, a wide implementation of screening tests has led to a decrease in the incidence of the malignancy in the last decades. In our country, unfortunately, cervical cancer still represents a significant health problem affecting women in all ages (8-13). When it comes to the possibility of association of these two entities, different theories have been proposed so far. While certain authors consider that prolapse itself predisposes to chronic inflammation and possible malignant transformation of the uterine cervix, other studies sustain the idea that the prolapsed surfaces develop a process of cornification, which diminishes the risk of malignant transformation. However, other authors consider that this cornification seem to induce an acid secretion, which might predispose to malignant transformation. As for the role of human papilloma virus infection, it seems that this infection is less frequent in cases in which uterine prolapse is present (14, 15). Another interesting aspect which should be taken into consideration in such cases is related to the risk of cancer cell spread in such cases; therefore, certain authors consider that lymphatic spread might be prevented by the distortion of the lymphatic stream, because of the anatomical modifications that occur due to the pelvic prolapse (16).

When it comes to the incidence of pelvic organ prolapse, it has been estimated that up to 50% of women are affected by this pathology, increasing trends being reported so far (17). Moreover, it seems that women worldwide, have an 11% life-time risk of requiring a surgical procedure for this pathology, the most commonly affected cases being represented by patients older than 50 years of age (18, 19). In this respect, attention has been focused on creating surgical techniques which could best manage this condition.

During the last decades research has focused on developing organ sparing surgical procedures in order to treat different types of pelvic prolapses; however, in such cases the risk of preserving a viscera with a premalignant or even malignant condition has to be considered. In this respect, in the study conducted by Renganathan *et al.* on 517 patients submitted to vaginal hysterectomy for uterine prolapse, the authors reported four cases in which the histopathological studies of the specimen confirmed the presence of a uterine malignancy, although preoperatively malignancy was not suspected in any of these cases (20). Therefore, the authors underlined the fact that conserving a prolapsed uterus should be performed only after excluding the possibility of a malignant uterine condition. In a similar study conducted by Grigoriadis *et al.* in 2015 the authors reported that the incidence of cervical cancer among patients submitted to hysterectomy for pelvic organ prolapse was 0.3% (21).

As for the group age at risk of developing the combination of the two pathologic entities, another discussion should be carried out. While patients at risk of developing cervical cancer usually originate from younger age groups, cases who develop pelvic prolapse usually originate from older age groups, which are thought to be at a lower risk of developing malignant conditions. Moreover, certain authors consider that patients who will develop cervical cancer will experience uterine fixation at the level of the pelvic area preventing in this way uterine procidentia. However, it seems that in cases in which these two pathological conditions are associated, initially uterine prolapse occurs, and, after some years malignant transformation of the uterine cervix develops.

Therefore, in a study conducted by da Silva *et al.*, the authors reported two cases in which the two pathologies were associated, and the interval between the diagnosis of uterine prolapse and cervical cancer was more than 10 years (22). Similarly to da Silva's study, in our case series the mean interval between the diagnosis of the two pathologies was 9.5 years; these data demonstrate that a long period of mechanical aggression and inflammation is needed in order to induce a premalignant and even a malignant transformation of the uterine cervix.

As for the modifications which might occur at the level of a procident uterine cervix, ulceration is a frequently encountered finding; however, in all such cases biopsy of this lesion is needed in order to exclude the presence of a synchronous malignant transformation (23).

As for the therapeutic strategies in such cases, no clear guidelines have been established so far due to the low number of cases diagnosed with this association of pathologic conditions. Moreover, the stage of the uterine cervix malignancy and the degree of pelvic prolapse should be considered when establishing the type of treatment. In consequence, tailored, personalized treatment should be taken into consideration in all cases presenting this association of pathological findings (3, 22, 24).

However, radical surgery seems to be the option of choice in order to prevent the development of serious adverse events (3, 22, 24, 25). Therefore, whenever possible, surgery should be preferred instead of radiation therapy due to the risk of visceral injury by ionizing radiation administration (26). In cases in which surgery is feasible, it consists of total radical hysterectomy *en bloc* with bilateral adnexectomy alone or in combination with pelvic and para-aortic lymph node dissection or sampling, depending on the stage of the tumoral process. This type of surgical procedure can be routinely performed in such cases via a vaginal or open approach. Therefore, in Matsuo's review, surgery alone or in combination with radiotherapy as neoadjuvant or adjuvant method has been considered the option of choice in 72% of cases (27). In certain cases in which lymph node dissection or sampling is needed, the minimally invasive route such as the laparoscopic approach has been proposed with encouraging results (2). Moreover, the minimally invasive approach seems to be safer in cases in which complete prolapse and secondarily anatomic modifications of the ureters might be encountered.

In cases in which extended surgery is not feasible due to the fragility of the patient, neoadjuvant chemo-irradiation followed by surgery with curative intent has been reported with good results in terms of both oncological and functional outcomes (24, 28). Moreover, in cases in which surgery is not feasible, palliative radiochemotherapy might be performed; however, in such cases attention should be paid on tailoring the doses with the degree of rectal and urinary

bladder prolapse, an important local toxicity being expected if standard doses of irradiation are applied on the prolapsed visceral areas (16).

The largest study published so far regarding cervical cancer in patients with complete uterine prolapse was a review conducted by Matsuo *et al.* in 2016 and included 78 patients; the mean age at the time of the diagnosis of cervical cancer was 63.7 years, while the median duration of prolapse was 147.9 months (27). Most often, patients were diagnosed with stage one disease (56.2%), while the most commonly encountered histopathological subtype was squamous cell carcinoma (83.9%). As for the types of treatment, in 33.3% of cases surgery alone was the treatment of choice, while in 11.5% of cases neoadjuvant radiotherapy followed by surgery was performed. Furthermore, radiotherapy alone was performed in 38.5% of cases, and as for the long-term outcomes, the authors underlined the fact that surgery was associated with significantly better outcomes (in terms of disease-free survival and overall survival) when compared to radiation therapy in both univariate and multivariate analysis. Another prognostic factor associated with the long-term outcomes was represented by the uterine cervix malignancy stage at the time of diagnosis. In regards to the surgery for pelvic prolapse, it consisted of anterior colporrhaphy (in 55.6% of cases) followed by perineorrhaphy (in 33.3% of cases), posterior repair (in 11.1% of cases) or colpocleisis (in 11.1% of cases). Mesh placement for treating pelvic prolapse was performed in a single case in which radiation therapy was not performed. However, none of the cases in which surgery for pelvic prolapse was also performed experienced recurrent pelvic prolapse after surgery or radiation therapy (27).

Conclusion

Although both cervical cancer and pelvic prolapse represent commonly encountered health problems affecting women worldwide, the association of these two pathologies represents an uncommon situation. In such cases, a standard therapeutic strategy has not been established yet; however, it seems that surgery should be considered as the option of choice whenever possible, due to the fact that in such cases performing radiation therapy might predispose to serious visceral injuries of the other prolapsed viscera.

Conflicts of Interest

The Authors have no conflicts of interest to declare regarding this study.

Authors' Contributions

NB, GG, AN performed the surgical procedure; IH, Ciprian B reviewed literature data, CD, LI preoperative investigation the patient, IB, Cristian B prepared the draft of the manuscript, IB was

advisor of the surgical oncology procedures. NB, DC reviewed the final version of the manuscript. All Authors read and approved the final version of the manuscript.

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