Impact of cervical cancer treatment on micturition and sexual function

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Abstract
Context: Cervical cancer is the second most common tumor in women worldwide and due to diagnostic and therapeutic advances, the overall survival rates at 5 years is approaching 70%. Disorders in micturition, defecation, sexuality and quality of life have been described, frequently caused by different treatments. Addressing these comorbidities in the medical follow-up is often limited or nonexistent.

Methods: A systematic review of studies to identify the articles related with urogynecological sequels from cervical cancer treatment was carried out.

Summary of evidence: During radical hysterectomy, disruption of the autonomic nerve fibers which innervate the bladder appears to be the main cause of voiding dysfunction. Up to 36% of women report voiding dysfunction; from 10 to 80%, stress urinary incontinence (SUI), due to the decrease in urethral closure pressure. After radical hysterectomy and/or radiotherapy, vaginal shortening and stenosis is often observed. Sexual function is altered in these women and those who are sexually active women after the surgery frequently report sexual dysfunction due to lack of lubrication and pain.

Conclusions: Voiding dysfunction and urinary incontinence are the most frequent urinary problems that occur in patients treated for cervical cancer. Systemic urogynecologic assessment of the symptoms suggestive of micturition dysfunctions during oncologic follow-up may be useful to detect the cases that can be evaluated and treated in an Urogynecology Unit.

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Impacto del tratamiento del cáncer de cérvix sobre la función miccional y sexual

Resumen
Contexto: El cáncer de cérvix es el segundo tumor más frecuente en mujeres, y debido a los avances diagnósticos y terapéuticos las cifras de supervivencia global a 5 años se aproximan al 70%. Se han descrito trastornos en la función miccional, defecatoria, sexual y en la calidad
Impact of cervical cancer treatment on micturition and sexual function

<table>
<thead>
<tr>
<th>Incontinencia urinaria; Disfunción sexual; Dispareunia</th>
</tr>
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</table>

Introduction

Because of the improvements in the early diagnosis and therapeutic advances, the overall survival of cervical cancer is close to 70%, affecting younger women when compared to other gynecological malignancies. Despite this, it remains the second most common tumor in the world after breast cancer, and the surviving affected women face the consequences in the short and long term, caused by cancer treatments. Alterations in the voiding and defecatory function have been described secondary to radical surgeries and radiotherapy, as well as impairment of sexual function with changes at the level of elasticity and vaginal capacity, decreased lubrication, fibrosis, and vaginal stenosis. In addition, chemotherapy may cause ovarian damage causing premature menopause and decreased sex drive.

Innervation of the female lower urinary tract

Currently, radical surgery remains the first choice of treatment of cervical cancer, and radical hysterectomy is preferred in the initial stages of cervical carcinoma (Ia2/Ib1/Ila1). Radical hysterectomy with pelvic lymphadenectomy is often accompanied by postoperative morbidity, particularly on the pelvic floor.

A paracervical resection or an extensive lymphadenectomy may cause partial disruption of the sympathetic and parasympathetic nerve fibers which cross the paracervix to innervate the urinary bladder. This denervation appears to be the major cause of long-term postoperative voiding dysfunction, with a prevalence ranging between 8 and 80%. This wide range is due to the different surgical techniques and the different ways to assess the symptoms.

The sympathetic fibers arise from the T11-L2 segments of the spinal cord and are well directed either toward the inferior mesenteric plexus and hypogastric nerve or to the paravertebral chain to be part of the pelvic nerves that innervate the urinary bladder and urethra.

Parasympathetic preganglionic fibers originate in the S2–S4 segments of the spinal cord, and they are directed toward the sacral roots and pelvic nerves, to the pelvic plexus lymph nodes and the bladder detrusor wall. The somatic motor nerves that innervate the external urethral sphincter originate in the S2–S4 segment motor neurons and form the pudendal nerve (Fig. 1).

The sympathetic postganglionic fibers release noradrenaline, which activates the β-3 adrenergic receptors that relax the detrusor muscle, causing at the same time the contraction of the urethral rhabdosphincter activating the α-1 adrenergic receptors. The parasympathetic postganglionic axons release acetylcholine, which performs the functions contrary to the sympathetic system: they cause contraction of the detrusor due to the stimulation of the M-3 muscarinic receptors. In addition, they also release ATP which equally contracts the bladder smooth muscle; and nitric oxide, which relaxes the urethral sphincter. Finally, the somatic axons of the pudendal nerve release acetylcholine, which causes contraction of the external urethral sphincter activating the cholinergic nicotinic receptors (Fig. 2).

The anatomy and physiology of these nerve fibers may explain that the surgical involvement thereof is translated into symptoms of voiding dysfunction and/or urinary incontinence.

Voiding dysfunction and cervical cancer

The most frequent voiding dysfunctions after surgery are loss of sensation of desire to void and the inability to get a spontaneous voiding. Both disorders are associated with altered sympathetic and parasympathetic neurological control, and they can go with or without urinary incontinence.

Voiding dysfunction

Between 4 and 15% of the patients require indwelling bladder catheter for more than 30 days after radical
hysterectomy. This early voiding dysfunction is usually temporary and depends on the severity of autonomic denervation in the surgery. In contrast, the late voiding dysfunction, which presents with decreased bladder compliance and detrusor overactivity, may persist up to one year after surgery.\(^8,9\)

Axelsen published in 2006 the urinary symptoms of a cohort of more than 300 women undergoing radical hysterectomy for cervical cancer.\(^3\) A validated questionnaire, as well as the presence of urogynecologic symptoms, was assessed before and after radical surgery. The mean age of the patients included in the study was 52.5 (± 12.2) years, and the mean postsurgical follow-up time 9.6 (± 7.7) years. Among the obtained results, it was emphasized that up to 36% of the patients reported symptoms of radical surgery voiding dysfunction (Table 1).

Later, in 2010, Hazewinkel\(^10\) published the follow-up results of the follow-up of a cohort of 242 women who underwent surgery for cervical cancer. Among them, 146 were operated by hysterectomy and pelvic lymphadenectomy; 49 received postsurgical adjuvant radiotherapy, and in 47 radiotherapy was the primary treatment. In turn, a control group of healthy women between 20 and 70 years was selected. The mean interval between the treatment received and the completion of the questionnaires selected for the study (Urogenital Distress Inventory and Defecatory Distress Inventory) was 6 years (range 1–11 years), and the women treated in an interval of less than 12 months were excluded from the study. When assessing the symptoms of voiding dysfunction, the prevalence in the treatment group was 30–45%. All the treated patients had a significantly higher risk of developing bladder emptying difficulty compared to the control group, with an odds ratio (OR) of 6.2 (2.0–5.3) in the women undergoing radical hysterectomy and radical pelvic lymphadenectomy; an OR of up to 7.2 (2.4–21.2) in women with hysterectomy, lymphadenectomy, and adjuvant radiotherapy, and, finally, an OR of up to 4.7 (1.4–15.6) in the women who received radiation therapy as the only treatment. 45–51% of women left a pathological postvoid residual, with an OR of 3.2 (2.0–5.3) in the patients undergoing surgery (hysterectomy and pelvic lymphadenectomy); 2.5 OR (1.1–5.9) where they also received adjuvant radiotherapy and an OR of 4.3 (1.6–11.1) in those treated with radiotherapy alone.

The findings of Hazewinkel coincide with those published by Oda in 2011, concluding that the women who apart from surgery receive radiation therapy have a higher risk of voiding dysfunction symptoms.\(^11\)

Finally, Manchana followed a cohort of 30 women undergoing radical hysterectomy for cervical cancer, compared to urodynamic studies those who suffered voiding dysfunction symptoms in the immediate postoperative period, to those who did not report these symptoms. The criterion of voiding dysfunction in the immediate postoperative period was the need for an indwelling urinary catheter for more than 30 days after the hysterectomy. He described a prevalence of 12% preoperative voiding dysfunction (3/25), compared to 47% prevalence in the postoperative period (14/30). Among the urodynamic findings, the fact that there were no significant differences between both study groups in terms of the indicators of the voiding function stood out. It was observed that most patients used the contraction of the abdominal muscles to promote urination, or they needed a double voiding to empty the bladder without residue.\(^8\)

In conclusion, the published studies indicate a significant association between radical hysterectomy and bladder voiding dysfunction, especially in women who also receive radiation therapy (Table 1).
### Stress urinary incontinence

Besides the voiding dysfunction, stress urinary incontinence (SUI) is another urinary symptom associated with cervical cancer treatment.

In the cohort of patients followed by Axelsen\(^3\) only 6\% reported SUI symptoms preoperatively (20/333), while 19.5\% (65/333) did so after radical hysterectomy. In turn, Hazewinkel\(^10\) again found that the patients treated by radical hysterectomy, pelvic lymphadenectomy, and adjuvant radiotherapy had a significantly higher risk of developing SUI than the control group, with an OR of 3.5 (1.5–8.2).

Recently, Plotti\(^6\) has published a review of the literature on urinary dysfunctions reflected in the urodynamic study associated with radical surgery of cervical cancer. After identifying 477 articles, only 19 were selected for a systematic review. These articles were published between 1980 and 2010, and they amounted to a sample size of 652 women. In 16 articles, a urodynamic study was carried out pre and post-surgically; 15 of them were prospective studies, and only 4 had a sample size greater than 50 patients. The most relevant result was the finding of urodynamic alterations in 72\% of the patients.\(^5\) The prevalence of SUI after radical hysterectomy, according to the results of these studies, ranges from 10 to 81\%. Eight of the 19 studies objectified decreased urethral closure pressure, comparing the urodynamic study prior to hysterectomy to the postoperative one. The review shows that the urogynecologic symptoms are reflected in the urodynamic study.

Currently, it is unknown whether there is anatomical involvement of the pelvic floor after radical surgery with or without radiotherapy. In this context, urogynecologic ultrasound might be useful. In the literature, only the presence of urethral hypermobility was assessed by transperineal ultrasound in a case-control study of 100 patients after radical hysterectomy.\(^12,13\) Contrary to the urodynamic study, in which differences were objectified in urethral closure pressure, no significant differences were found in the bladder neck mobility between groups (Table 1).

### Other voiding dysfunctions

The overactive bladder is another urodynamic entity associated with treatment of cervical cancer. Although in the study by Axelsen\(^3\) the overactive detrusor symptoms were not modified after radical hysterectomy, Hazewinkel\(^10\) described a lower risk of overactive bladder symptoms, such as urinary frequency (with a 0.6 [0.3–0.9] OR), or urinary urgency (0.2 [0.1–0.4] OD). It seems that the denervation caused by surgery might have a protective effect against the uninhibited detrusor contractions. The prevalence of overactive bladder symptoms in postoperated patients was 23\% (frequency) and 19\% (urgency). However, when assessing the patients treated with primary radiotherapy, the relative risk of developing symptoms of detrusor overactivity was higher than the control group, with a 7 (2.8–17.5) and 3.5 (1.4–8.7) OR for frequency and urgency, respectively.

<table>
<thead>
<tr>
<th>Year</th>
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<th>Sample size</th>
<th>Follow-up</th>
<th>Results</th>
</tr>
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<td>Axelsen(^3)</td>
<td>Retrospective case series</td>
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<td>242</td>
<td>6 years (1–11)</td>
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</tr>
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<td>Manchana(^8)</td>
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<td>2 years</td>
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<td>Frequency: OR = 0.6 HL group, OR = 7.0 RT group</td>
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<td></td>
<td></td>
<td>Urge urinary incontinence: OR = 3.0 HL group, OR = 3.7 RT group</td>
</tr>
</tbody>
</table>

HL: radical hysterectomy plus pelvic and/or para-aortic lymphadenectomy; OR: odds ratio of the subgroup of cases compared to the control group; RT = radiotherapy.

## Table 1

Major published studies that analyze the voiding function in women treated for cervical cancer.

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</tbody>
</table>
Regarding urge urinary incontinence (UUI), the preoperative prevalence described by Axelsen was 2.7% (9/333), while it increased to 8.1% (27/333) postoperatively. Similarly, the three treatment groups of Hazewinkel’s cohort had a higher risk of UUI than the control group, with a 3 (1.8–5) OR in the group treated with radical hysterectomy and lymphadenectomy, 4.3 (1.8–10.3) OD in the group that besides surgery received adjuvant radiotherapy, and 3.7 (1.4–8.7) OR in the group with primary radiotherapy.

One of the urodynamic findings that would explain the symptoms of urgency/frequency is decreased bladder compliance, whose prevalence in women treated for cervical cancer ranges between 15 and 57%. Radical hysterectomy without nerve sparing and adjuvant radiotherapy to surgery are risk factors for persistent low bladder compliance, with 3.4 (1.1–11.0) and 10 (2.5–43–5) OR, respectively (Table 1).

### Sexual dysfunction and cervical cancer

On the other hand, the alteration of sexuality is one of the comorbidities associated with gynecological malignancies, especially cervical cancer. Several studies have shown sexual function disorders, such as decreased libido or dyspareunia, which adversely affect the quality of life of women (Table 2). However, despite the extensive research on sexual dysfunctions secondary to the treatment of cervical cancer, there is still uncertainty about the nature and extent of these sexual problems. Sexuality is often studied as an isolated domain, which should not dissociate itself from the comprehensive psychological assessment. Pelvic surgery can cause vaginal dryness, early menopause, infertility, and sense of loss of femininity.

In a retrospective study that assessed 332 women treated for cervical cancer, it was objectified that up to 25% of these patients had a lack of lubrication and short and inelastic vagina, compared to a control group, up to 5 years after the treatment. Again, 26% reported concern about these changes in sexual function, although the percentage of sexually active women and the frequency of orgasms was similar in both groups. The most consistent predictors of sexual health in cervical cancer survivors were the time interval since the diagnosis, the treatment with radiation therapy, partner relationships, the vaginal changes previously described, and the perceived physical appearance.

A sexuality questionnaire was provided to 860 Korean women treated for cervical cancer at any stage and to 494 controls. The affected women reported more severe climacteric symptoms, worse body image, worse sexual and vaginal functioning, and concern for the alterations in sexuality.

Jensen selected 173 patients treated by hysterectomy and pelvic lymphadenectomy for cervical cancer at early stages. Prospectively, the patients answered a sexuality questionnaire at 5 weeks, 3, 6, 12, 18 and 24 months after surgery; and so did a control group from the general population in the same age group. The affected women reported severe difficulties in sexual relations and orgasm, due to the vaginal shortening during the first 6 months after surgery. The dyspareunia was severe during the first 3 months, and the lack of interest in sexuality and insufficient vaginal lubrication persisted up to 2 years after the treatment. These results agree with those published by Pieterse in 2008. In addition, radiation therapy worsens the vaginal elasticity, atrophy, and stenosis, causing dyspareunia and further hindering sexual relations.

By following a cohort of 107 women treated exclusively with pelvic radiotherapy, we noted a decrease in the sense of vaginal dryness and a higher proportion of sexually active patients, comparing the results the first 6 months post-radiotherapy to the results after 3 years of treatment.

Finally, Lindau showed that up to 62% of the women treated for cervical cancer had never discussed their sexual dysfunctions with their oncologist in the follow-up visits, and 74% said it was necessary to talk about this subject. The discussions with health professionals about the treatment effects on sexuality are associated with a lower likelihood of having long-term sexual morbidity in the surviving patients with cervical cancer.

### New surgical techniques

The new classification of cervical cancer surgery proposed by Querleu and Morrow not only takes into account the curative effect, but it also assesses the adverse effects, such as bladder dysfunction. It considers the extent of the resection of the parametrium as determinant of long-term

<table>
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<th>Year</th>
<th>Type of study</th>
<th>Follow-up results</th>
<th>Sample size</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1999</td>
<td>Case-controls</td>
<td>5 years</td>
<td>332</td>
<td>25% lower lubrication + short vagina 26% concern about sexual dysfunction</td>
</tr>
<tr>
<td>2004</td>
<td>Case-controls</td>
<td>2 years</td>
<td>173</td>
<td>Severe dyspareunia up to 3 months after treatment Loss of interest and lubrication up to 2 years after treatment</td>
</tr>
<tr>
<td>2007</td>
<td>Case-controls</td>
<td>–</td>
<td>860</td>
<td>Worse climacteric syndrome Worse body image Worse sexual and vaginal function Preoccupation with sexual dysfunction</td>
</tr>
<tr>
<td>2011</td>
<td>Prospective cohorts</td>
<td>3 years</td>
<td>107</td>
<td>After 3 years post-radiotherapy, improved vaginal dryness, and increased sexual activity (compared to results at 6 months post-radiotherapy)</td>
</tr>
</tbody>
</table>

**Table 2** Major studies published that analyze the sexual function in women treated for cervical cancer.
morbidity, mainly due to the autonomic nervous system damage. Techniques for preserving these nerves (nerve-sparing) have been described in the literature. In turn, the development of imaging techniques, particularly nuclear magnetic resonance and ultrasound in the assessment of stromal infiltration, will allow for a more individualized treatment option, thereby reducing radicalism in a selected group of patients. Thus, women with tumors smaller than 2 cm, or with stromal infiltration below 50%, could undergo less radical surgery in the paracervical resection. A study has been published in which it is postulated that nerve-sparing surgery might improve vaginal lubrication, although the sample size is small and the results lack statistical significance.

Radical tracheectomy, a surgery that allows for preservation of fertility, is being recognized as the safe oncological alternative to radical hysterectomy in female patients of childbearing age and gestational desire. The comorbidities associated to this recent surgical technique are unknown, but a possible improvement in the area of psychology and sexuality is postulated. With regard to the urogynecologic involvement, there are no comparative studies with radical hysterectomy.

Conclusions

The lower urinary tract dysfunctions are common after radical surgery and radiotherapy for cervical cancer. Although it is accepted that the assessment of the voiding, sexual, and psychological function should be integrated into the follow-up visits of oncological patients, currently it does not always seem to be applied in clinical practice.

The healthcare professionals who treat these patients should assess the importance that urogynecologic dysfunctions have on the quality of life of the patients operated on for cervical cancer. Many of them are young, with an excellent prognosis for survival, but with a greatly affected quality of life.

The pre- and posttreatment assessment is essential to identify potential risk factors and to inform the patient of the comorbidities associated to the therapies and of how to reduce the risk.

Conflict of interest

The authors declare that they have no conflict of interest.

References


