Lower urinary tract function after postoperative radiotherapy in the treatment of cervical cancer

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Summary

Objective: The aim of this study was the urodynamic assessment of lower urinary tract disturbance intensity (especially urinary incontinence) among irradiated women after the surgical treatment of cervical cancer.

Study design: The analysis included 34 patients after radical hysterectomy and following radiotherapy for cervical cancer in clinical Stage Ib. Only patients without any previous urogynecological disorders were included. Urodynamic diagnostics was performed two weeks after oncological treatment termination.

Results: Urodynamic parameter changes were clearly present at all stages of functional diagnostics.

The most remarkable changes included decreased bladder capacity (mean 196 ml) and residual urine volume (mean 19 ml). The mean value of maximal urine flow rate obtained from uroflowmetry was 26 ml/s, but for 20 women it was lower than 20 ml/s. Voiding time and flow time were abnormally delayed with the significant difference of five seconds. Bladder sensation points were increased and maximum cystometric capacity was decreased to 270 ml during filling cystometry. Bladder compliance was 28 ml/cm H_2O on average; for the majority of patients it was below 20. Detrusor pressure was increased in 23 cases above 20 cm H_2O and mean isometric pressure was 34 cm H_2O. Urethral pressures were low, especially while taking effort. Urinary incontinence was diagnosed in 30% of the cases.

Conclusions: The obtained results allow us to conclude that voiding disorders after combined radiotherapy and surgery are often and mainly apply to the detrusor muscle with the domination of functional disturbances. It seems that early quantitative and qualitative changes *depend* on combined therapy with a standard dose pattern. The presence of functional disorders after oncological treatment should be considered in the planning of prevention and further treatment. Urinary incontinence restricts patients' activity, affects the quality of their lives and is the cause of patient discomfort. Many patients suffering from lower urinary tract pathologies pose a therapeutic problem caused by lack of information.

Key words: Urodynamics; Urinary incontinence; Cervical cancer; Radiotherapy; Bladder.

Introduction

Radiotherapy and surgical treatment as invasive methods cannot be free of complications. Radiation of the pelvis aimed at neoplastic cells also results in destruction of healthy cells of the surrounding organs. Some patients present urological complications, which occur more often than gastroenterological ones. Dean and Lytton report the frequency of bowel and bladder lesions to be as high as 20% of treated women [1].

The reaction of healthy tissues of the bladder and urethra consists of the cell destruction phase with the following repair process, which starts after several days. Both of these processes are running concurrently. Radiated cells, however, lose their repair abilities, therefore early and late lesions appear [2].

The early postradiation period is characterized by hyperemia of the submucosa and intercellular edema with distinctive degenerative changes. Epithelium defects are the sources of bleeding.

Further vascular changes lead to the constriction of capillary vessels. Damaged smooth muscle cells are replaced by fibroblasts.

Revised manuscript accepted for publication April 8, 2003

Arteriocapillary fibrosis results in ischaemia of the bladder wall and decrease of bladder capacity.

Although the clinical symptoms and complications of irradiation are well known, the functional assessment of lower urinary tract postradiation activity is usually lacking.

The late phase of postradiation changes result from generalized proliferative vascular inflammation with lumen obliteration and interstitial fibrosis. Since these changes progress slowly but continuously and irreversibly, complications may occur years later in the form of ulceration and fistulas [3]. Ureter lesions are rare using modern radiotherapeutic techniques, but occur more often after surgical treatment.

Postradiation complications are easy to observe in the course of treatment and therefore can be immediately treated. However, functional disturbances are often wrongly considered as temporary and underestimated [4]. Although they are not life-threatening they can make life much more difficult for women after the treatment of neoplastic diseases.

Bladder filling and voiding disturbance intensity is not the simple sum of surgical treatment and radiation complications, as functional defects are influenced by various factors.

Modern diagnostic techniques allow us to detect the subtle changes of different parameters for the quantitative and qualitative analysis and to differentiate the types of urinary incontinence [5, 6].

Aim of the study

The aim of this study was to assess lower urinary tract disturbance intensity (particulary urinary incontinence) among irradiated women after surgical treatment for cervical cancer.

Materials and Methods

The analysis included 34 patients after radical hysterectomy and following radiotherapy because of cervical cancer in clinical Stage Ib.

The interval between surgery and radiotherapy lasted four to five weeks and depended on wound healing.

Therapy and brachytherapy procedures were performed at the HDR Laboratory of the Gynecology-Obstetrics Hospital, four to five weeks after surgery performed at the Division of Gynecological Surgery Gynecology-Obstetrics Hospital of the Medical University of Poznań, Poland.

Radiation doses were within standard values and isodoses were drawn individually.

Brachytherapy consisted of three to five fractions of 800 cGy each and was completed with teletherapy to reach a total dose of 6000 cGy.

The "box" technique from four external fields was used for pelvic radiation till the L_3 level, with a high energy linear accelerator (2-35 MeV) using a total dose of 4300-5000 cGy divided into the fractions of 200 cGy, five times a week.

Urodynamic diagnostics was performed two weeks after oncological treatment termination. All procedures – uroflowmetry, water cystometry and urethral pressure profiles – were performed according to the International Continence Society standards [7].

Urodynamic procedures were performed at the Urodynamics Laboratory of the same hospital using Medtronic Duet^R Logic MultiP.

Residual urine volume was measured by Bladder Scan BVI-3000.

None of the patients qualified for this study presented any previous urological or gynecological surgery history.

Results

None of the treated women presented urinary tract infection symptoms before radiotherapy.

During the radiation treatment the first symptoms were reported in the second week of the treatment in the case of three patients, in the third week they were reported by another ten and by 13 patients at the end of the oncological treatment. The total number of the affected patients was 26, which made up 74% of all cases (Table 1).

Table 1.

Frequencies of subjective symptoms:
- Urgency - 26 women (76%)
- Frequency - 28 women (82%)
- Dysuria - 21 women (62%)
- Nocturia - 9 women (26%)

The reported complaints were similar: urgency, frequency and dysuria. The intensity was insignificant for 20 women, however six patients required pharmacological treatment.

The complete set of the aforementioned complaints was diagnosed for 21 women, i.e., 62% of all treated with radiotherapy. Nocturia was reported in nine cases.

Urine culture resulted in significant bacteruria (10^5/ml) in one case, in three cases concentration was 10^2/ml, however pathogenic *Escherichia coli* and *Staphyloococcus saprophiticus* were cultured. All symptoms reversed after two to three days of anti-inflammatory treatment without pausing radiotherapy.

The mean age of the patients was 45, delivery count was 2.5.

Questioned on QoL all 26 women confirmed that urological complaints limited their activity; in 19 cases in a significant way (Table 2). Moreover, half [13] were afraid of intensification of these complaints after the completion of oncological treatment.

Changes in the analysed urodynamic parameters were clear at all stages of functional diagnostics (Table 3). The most remarkable ones included decreased bladder capacity (mean 196 ml) and residual urine volume (mean 19 ml). The mean value of maximal urine flow rate obtained from uroflowmetry was 26 ml/s, but for 20 women it was lower than 20 ml/s.

Table 2.

QoL questions in patient questionnaire:
A) Are bladder and urethra disturbances limiting your normal activities?
   - Not much - 7 women (27 %)
   - Very much - 19 women (73%)

B) Are you afraid of intensification of these complaints after completion of oncological treatment?
   - Yes - 13 women (50%)
   - No - 13 women (50%)

Table 3. — *Mean values of evaluated urodynamic parameters.*

Parameter name*	Mean value
Qmax	26 (11) ml/s
Vcomp	196 (102) ml
VT	41 (9) s
FT	36 (8) s
Vres	19 (12) ml
FS	80 (65) ml
ND	120 (78) ml
SD	150 (65) ml
CysCapmax	270 (98) ml
C	28 (9)
Pdet	19 (7) cmH_2O
Piso	34 (9) cmH_2O
Puramax	47 (14) cmH_2O
Puradif	42 (19) cmH_2O
Puradif stress	23 (6) cmH_2O
FL	28 (7) mm
FL stress	24 (6) mm

*All symbols according to ICS standardization [7].

Also voiding time and flow time were abnormally delayed with a significant difference of 5 sec.

Bladder sensation points were increased and maximum cystometric capacity was decreased to 270 ml during filling cystometry. Bladder compliance is 28 ml/cm H_2O on average, but for the majority of patients it was below 20.

Detrusor pressure was increased, in 23 cases above 20 cm H_2O.

Urethral pressures were low, especially with effort, and urgency urethral closure pressure was 23 cm H_2O. Urethral length was also below normal values in 23 cases - mean at urgency was 24 cm H_2O.

Urinary incontinence was diagnosed in 11 cases (30%): five cases of urge incontinence, two cases of stress incontinence and four cases with the mixed form of urine incontinence.

Discussion

Lower urinary tract dysfunction was observed in 26 of the 34 patients after surgery and radiotherapy because of cervical cancer. It is 74% of the study group and, despite the small group size, it emphasizes the scale of the problem. Patients willing to return to normal life and society require support in their attempts [8].

A very important purpose of comprehensive diagnostics is to distinguish between treatment side-effects and cancer symptoms.

Pathological changes were confirmed by all urodynamic tests – uroflowmetry, cystometry and urethral pressure profiles.

Such results show dysfunction of both the filling and voiding phase.

Some authors describe increased daytime frequency, urgency and nocturia as the urethral syndrome, often associated with different pathologies and characteristic of lower urinary tract irritation [6].

This syndrome is distinctive of the pelvic radiation phase, catheterization (especially multiple), but also of inflammation.

The highest level of symptom intensity was observed at the end of treatment.

Small bladder capacity, clearly seen in our study, is characteristic of both early postradiation defects and postoperative ones.

Buchali *et al.* confirm Tamussino's theory that reduced bladder capacity after postoperative radiotherapy lasts several weeks [9].

These authors reported bladder volume during the treatment at the level of 190 ml. Changes of bladder capacity during radiotherapy can be reflected in bladder sensation and should be taken into account while calculating the total dose.

Limitation of pelvic organ mobility is very important during irradiation and shortly thereafter, and does not cause any serious late complications, as confirmed by Buchali *et al.* and Kim *et al.* [9, 10].

Although it is confirmed that bladder capacity is decreased after radiotherapy and associated with other pathologies, the exact mechanism is still unclear [11].

The fibrosis process starts shortly after irradiation. Other causes are also possible.

The influence of involuntary instable detrusor contractions on bladder capacity decrease is known; it is also said that submucosal edema can deteriorate the condition [12]. Venrooij *et al.* hint the that ureterovesical junction injury, e.g., due to radiation or surgical treatment, can trigger detrusor muscle contractions [13]. The assumption that this region is a source of detrusor instability is not common though. Most authors focus on the quality of the smooth muscle fibres of the detrusor [6].

Branding and Turner [12] found that increased thickness of the bladder wall is caused by smooth muscle hypertrophy as confirmed by others [9, 14]. Although its connection with bladder outlet obstruction is certain, it is not considered as proof of direct denervation or detrusor instability. However, Gabella strongly emphasizes a significant influence of workload on muscle fibre hypertrophy and resulting functional changes [15].

The foregoing data, being in accordance with irritated bladder dysfunction, demonstrate urethrovesical dysfunction and clinical symptoms such as detrusor hyperactivity as confirmed by the abnormal results of uroflowmetry, cystometry and urethral pressure profiles. The observed changes confirm subjective complaints and show their causes, as well as detect "alleged" symptoms [16].

Uroflow curves with irregular shapes characteristic of obstructed bladder outlets were observed in 27 patients (79%). Voiding time was longer than flow time in 30 cases (88%), thus confirming urine flow dysfunction.

All symptoms of irradiation cystitis, including urgency episodes caused by increased detrusor sensibility and detrusor hyperactivity, are of complex origin.

Many authors mention the influence of released tissue mediators, but exposed nerve endings and their higher excitability also matter [2].

Sensory sensibility is increased, which is confirmed by the bladder filling phase parameters - increased first sensation (FS), normal (ND) and strong (SD) desire to void.

References on bladder function after radiotherapy are scant, especially those concerning parameters describing current activity. Thus it is important to correlate urodynamic parameters and subjective and objective symptoms.

Small capacity and compliance of bladder walls can suggest that these low values are the effect of direct tissue injury [13].

Lowering of the foregoing parameters and changes of intravesical and urethral pressures combined with other anatomical injuries can result in different functional symptoms and atypical urodynamic curves [17].

Frequent coexistence of involuntary contractions, increased detrusor pressure above 15 cm H_2O and urgency episodes were sufficient for diagnosis of urinary urge incontinence. In that case low compliance was observed. Urinary stress incontinence was reported for patients with higher intravesical pressure, low values of the urethral profile and increased compliance. Diagnostics and the therapy of mixed forms of urinary incontinence is the most complex.

More frequent involuntary contractions confirming detrusor instability can be caused by rapid urethral pressure falls [14]. Unstable urethra reactions with small fluctuations of abdominal pressure may be the reason for the increased number of detrusor contractions [5, 18]. It follows that anatomical injury of the urethrovesical junction is not the direct cause of urinary incontinence in the analysed group. Coughing, laughing and other causes of increased abdominal pressure result in involuntary detrusor contractions. Increased sensitivity is recorded, although patient feeling is often impaired. The detrusor muscle is both overactive and hypersensitive. It results in decreased contraction strength while voiding, which is confirmed by lowered pressure of isometric contraction. Slightly increased voiding time is necessary to empty the bladder, but it is ineffective. Urine retention is over 10% and even 20%. Patients are upset about the prolonged voiding time and use abdominal straining, but the feeling of incomplete bladder emptying remains.

Accumulation of irradiation and surgical side-effects result in changes of the elastic and mechanical characteristics of the bladder wall [19].

Individual variation seems to be of great importance.

Structural and functional traits are influenced by the genetically determined characteristics of connective tissue, collagen, muscle efficiency and general fitness [11]. It may be presumed that it is very similar to genital prolapse and increased urethra mobility, during which individual variations of muscle and tissue joining occur. Some authors have considered the effects of the local innervation injury of the irradiated region [9, 19]. Correlating risk factors like the number of deliveries, low estrogen level and high abdominal pressure is very important in the therapy of all urogynecological disorders [13]. While discussing the risk of complications structural pathologies should be considered. The Ehlers-Danlos syndrome (different types) and the Marfan syndrome confirm the role of inheritance and define abnormalities of elastin microfilament structures as an autosomal dominant trait. A similar mechanism of inheritance is described for collagen, especially types I and III. It can be one of the explanations for the susceptibility of some patients to connective tissue hypersensitivity, hypermobility and other disturbances that may intensify complaints. Ten to 20% of adult women are estimated to be affected by these problems; race and age are also factors. Environmental influences, diet and the quality of life must be taken into account as well [6].

Considering the effect of bladder and urethra function, the occurrence of lumbo-sacral spine injuries and the consequent nerve plexus lesions cannot be neglected. Pudendal and coccygeal nerves are of fundamental importance for filling and voiding activities. Neurogenic sphincter-detrusor dysfunction can be an additional cause of the observed reactions.

There are also other predisposing factors, especially previous pelvic surgery and inflammatory processes. In these cases chronic postradiation complications occur 10-15% more often [18]. The prognosis depends on the patient's health and presence of chronic diseases, e.g. diabetes.

The effect of combined preventive treatment of the bladder and urethra on the lower urinary tract is unknown so far. Functional disorders do not recover spontaneously, unless they are minimal and patients know how to reduce the intensity and duration interval.

Presence of such diverse disturbances in previously healthy women can not be explained only by the analysis of urodynamic records and parameters.

Conclusions

The obtained results allow us to conclude that voiding disorders after combined radiotherapy and surgery are frequent and mainly apply to the detrusor muscle with the domination of functional disturbances.

It seems that early quantitative and qualitative changes *do not* depend on combined therapy with the standard dose pattern.

The presence of functional disorders after oncological treatment should be considered in the planning of prevention and treatment. Urinary incontinence and other iatrogenic urogynecological symptoms restricts patients' activity, the quality of their lives and are the cause of patient discomfort.

Many patients suffering from lower urinary tract pathologies pose a therapeutic problem. Possible causes are lack of information on urinary system physiology and available treatment options.

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