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# Post-Irradiation Bladder Syndrome After Radiotherapy of Malignant Neoplasm of Small Pelvis Organs: An Observational, Non-Interventional Clinical Study Assessing VESicare®/Solifenacin Treatment Results

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**Background:** Radiotherapy is explicitly indicated as one of the excluding factors in diagnosing overactive bladder syndrome (OAB). Nevertheless, symptoms of OAB such as urgent episodes, incontinence, pollakiuria, and nocturia, which are consequences of irradiation, led us to test the effectiveness of VESicare®/Solifenacin in patients demonstrating these symptoms after radiation therapy of small pelvis organs due to malignant neoplasm.


**Material/Methods:** We conducted an observatory clinical study including 300 consecutive patients with symptoms of post-irradiation bladder; 271 of those patients completed the study. The observation time was 6 months and consisted of 3 consecutive visits taking place at 12-week intervals. We used VESicare® at a dose of 5 mg a day. Every sixth patient was examined urodynamically at the beginning and at the end of the observation period, with an in-flow speed of 50 ml/s.

**Results:** We noticed improvement and decline in the average number of episodes a day in the following parameters: number of micturitions a day (–36%,  $P < 0.01$ ), nocturia (–50%,  $P < 0.01$ ), urgent episodes (–41%,  $P < 0.03$ ), and episodes of incontinence (–43%,  $P < 0.01$ ). The patients' quality of life improved. The average maximal cystometric volume increased by 34 ml (21%,  $p < 0.01$ ), average bladder volume of "first desire" increased by 42 ml (49%,  $P < 0.01$ ), and average detrusor muscle pressure at maximal cystometric volume diminished by 9 cmH<sub>2</sub>O (–36%,  $P < 0.03$ ).

**Conclusions:** The substance is well-tolerated. Solifenacin administered long-term to patients with symptoms of OAB after radiotherapy of a malignant neoplasm of the small pelvis organs has a daily impact in decreasing number of urgent episodes, incontinence, pollakiuria, and nocturia.

**MeSH Keywords:** **Muscarinic Antagonists • Urinary Bladder Neoplasms • Urodynamics**

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## Background

Modern treatment of malignant neoplasms is based on an approach that combines surgery, radiotherapy, and chemotherapy, achieving better results in curability and survival rate. Every oncological procedure has its own characteristic adverse symptoms rate which affects patient quality of life, and the severity of those adverse reactions is higher when the therapy is more complex. The biological effect of radiation therapy on human tissues takes place over time. Whole-body effects of late irradiation reaction may be more likely when the lifetime of a patient is longer and the irradiation dose is higher.

In Poland, about 5000 radical radiotherapies for malignant neoplasm of small pelvis organs are performed every year. The irradiation area, apart from the involved organ, also includes healthy organs and tissues. Despite more sophisticated planning methods, a significant number of patients have morphological and functional changes in healthy organs after radiotherapy, which leads to functional restrictions, infections, and pain.

For the early post-irradiation reaction, one recognizes the effect that occurs during the procedure and 3 months after its completion. However, late post-irradiation reaction symptoms occur more than 3 months after the completion of radiation therapy. Early reactions are often transitory. Regarding the early post-irradiation reaction involving the urinary bladder, the symptoms are “para-inflammatory”, with pollakiuria, dysuria, nocturia, hematuria, and pain complaints. Ulceration and necrosis of the bladder wall are very rare. In this stage, about 68% of patients require treatment [1]. In late post-irradiation reaction, in addition to the symptoms described above, there may also be atrophic lesions of epithelium, telangiectasias, ulceration of mucosa, necrosis, fibrosis of the bladder wall with its volume depletion, and fistulas. Those lesions most frequently occur 2 to 6 years after the treatment and affect 2% to 13% of patients, requiring differentiation with persistent or recurrent neoplastic process [2].

Lesions arising in the detrusor muscle, which are innervated parasympathetically from the S2–S4 spinal cord level and are controlled by the supraspinal micturition center, significantly affect patient quality of life. Muscarinic receptors (M3 and M2) and cholinergic receptors stimulation of the urinary bladder smooth muscles contracts the detrusor, and blocking of those receptors leads to muscle relaxation [3]. Anticholinergic drugs decrease the stimulation of afferent fibers A and C, leading to reductions in the number of detrusor muscle contractions and increased bladder volume. New-generation drugs such as solifenacin, darifenacin, and fesoterodine are competitive receptors antagonists, which means that blocking of muscarinic receptors takes place during bladder filling and the effect

diminishes during micturition, thus reducing the probability of urine retention after micturition [4]. Solifenacin has organ-specific affinity to the bladder. It is particularly selective to muscarinic receptors M3 and, to a lesser degree, to M2. The half-life time of this substance is 45–68 hours [5,6].

According to the definition provided by the International Continence Society, radiotherapy is explicitly indicated as one of the excluding factors in diagnosing overactive bladder syndrome (OAB), as well as infections, lithiasis, and active neoplastic processes of the bladder [7]. Nevertheless, symptoms of OAB such as urgent episodes, incontinence, pollakiuria, and nocturia, which are consequences of irradiation, led us to assess the effectiveness of modern pharmacological substances in so-called post-irradiation bladder.

## Material and Methods

In the period from May 2011 to February 2013, an observatory clinical study was conducted including 300 consecutive patients who were referred to the Urological Outpatients Department in Oncology Center Cracow Branch with symptoms of OAB after radiotherapy of malignant neoplasm of small pelvis organs. Of these 300 patients, 271 (90%) finished the observation period. Eighty-five percent (230 patients) were females with gynecological carcinomas of the uterine cervix, endometrium, and ovaries, 10% (27 patients) had bladder carcinoma, 3% (8 patients) had prostate carcinoma, and 2% (6 patients) had carcinoma of the rectum.

The average age was 46 years, 92% (249 patients) were females and 8% (22 patients) were males. Demographic data are shown in Table 1.

Demographic data are described in Table 1; however, at the time of study entry the following were free of the cancer: 45% (104) of patients with gynecological disease, 37% (10) with bladder cancer, and 50% (3) with rectum cancer. Among the 8 patients with prostate cancer, 38% (3) had characteristics of biochemical recurrence, and 13% (1) had features of clinical progression.

One of the aims of this study was to evaluate the effectiveness of solifenacin in patients with lower urinary tract symptoms after radiation therapy for various cancers.

All patients completed the radiotherapy. The average time elapsed from the completion of radiation therapy was 38 months. Most frequently (78% of cases), teloradiotherapy with brachytherapy was conducted. As a supplementary therapy after surgery, a XTR 44–50 Gy/22–25 fr with brachytherapy PDR 21 Gy/20 h/0.5 cm from the surface of the applicator

**Table 1.** Study group – demographic data.

Gender	Number	Gynecological cancer patients	Bladder cancer patients	Rectum cancer patients	Prostate cancer patients
Women	249	230	17	2	–
Men	22	–	10	4	8
Total	271	230	27	6	8

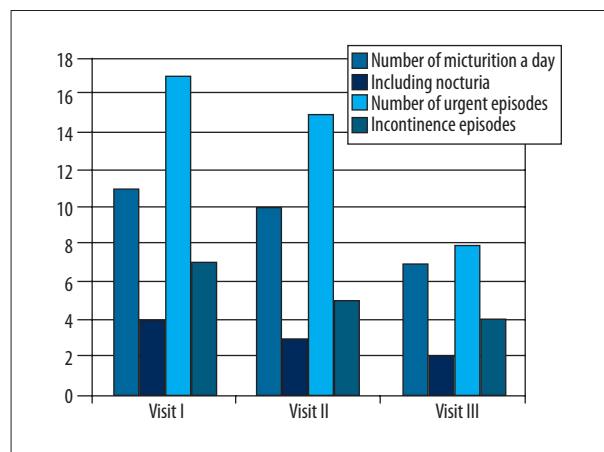
**Table 2.** Average number of episodes a day.

Feature	Visit I	Visit II	Visit III	Percentage reduction of feature, p
Number of micturition a day	11	10	7	–36%, p<0.01
Including nocturia	4	3	2	–50%, p<0.01
Number of urgent episodes	17	15	8	–53%, p<0.03
Incontinence episodes	7	5	4	–43%, p<0.01

was performed, and only brachytherapy in the above-mentioned treatment was conducted. In patients who did not undergo surgery, a XTR 50 Gy/25 fr with brachytherapy 2×20 Gy or 13.3 Gy was conducted. The total dosage of irradiation in cases of bladder cancer was 20–50 Gy, 65–72 Gy for prostate cancer, and 20–45 Gy for rectum cancer.

Exclusion criteria were: urinary tract infections, post-micturition retention over 50 ml, glaucoma, severe gastro-intestinal disturbance, severe renal or hepatic failure, vesical fistula, and use of muscarinic drugs within 6 months prior to enrollment.

Every patient was examined and evaluated during 3 consecutive visits taking place at 12-week intervals. We used the APPL-VES-001 questionnaire, taking into consideration IPSS scale, micturition diary, and the KHQ life quality scale with subjective patient evaluation. These data were collected during every visit based on the data provided by the patient regarding the 3 days preceding the visit. Every patient who was not excluded was qualified to the treatment with VESIcare® at a dose of 5 mg a day for 6 months. Every sixth patient was examined urodynamically with the use of a Medtronic Duet II device at the beginning and at the end of the observation period, with an inflow speed of 50 ml/s. Use of sanitary pads was reported by 71% of patients, and 13% were performing pelvis floor muscle exercises before the examination. None of the patients reported use of behavioral training or electrostimulation. Past use of oxybutynin was reported by 49% of patients, and 4% had used tolterodine. The most important reason for interruption of previous treatment was lack of effectiveness in 78% of cases and poor tolerance in 27% of cases.



**Figure 1.** Average number of episodes a day.

## Results

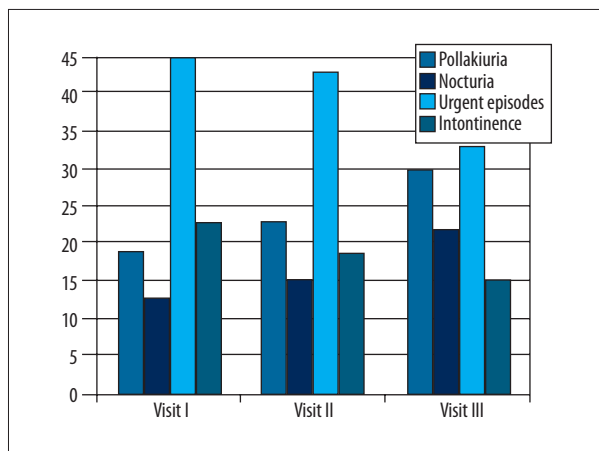
The data collected during this study are presented in the form of tables and Figures. Data were calculated as a quantitative and percentage average based on the questions included in the questionnaire regarding particular symptoms of OAB syndrome. Patients were asked to take into account only the 3 days preceding the qualification visit (I) and the 2 control visits (II and III) scheduled every 12 weeks.

### Average number of episodes a day

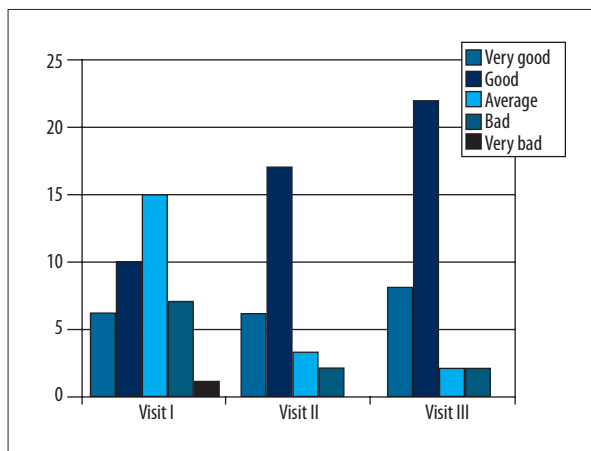
The collected data indicated a significant improvement in patient evaluation of every estimated feature (Table 2, Figure 1). Especially important is the significant improvement in number of micturitions and urgent episodes in the second trimester of

**Table 3.** Which syndrome of overactive bladder is most troublesome for the patient after radiotherapy?

Feature	Visit I	Visit II	Visit III
Pollakiuria	19% (52 p.)	23% (62 p.)	30% (81 p.)
Nocturia	13% (35 p.)	15% (41 p.)	22% (60 p.)
Urgent episodes	45% (122 p.)	43% (117 p.)	33% (89 p.)
Incontinence	23% (62 p.)	19% (51 p.)	15% (41 p.)



**Figure 2.** Which symptom of overactive bladder is most troublesome for you after radiotherapy?



**Figure 3.** How would you describe your present condition?

**Table 4.** How would you describe your present condition?

Feature	Visit I	Visit II	Visit III
Very good	6% (16 p.)	6% (16 p.)	8% (22 p.)
Good	10% (27 p.)	17% (47 p.)	22% (60 p.)
Average	62% (168 p.)	72% (195 p.)	66% (179 p.)
Bad	15% (41 p.)	3% (8 p.)	2% (5 p.)
Very bad	7% (19 p.)	2% (5 p.)	2% (5 p.)

treatment; the average number of urgent episodes diminished by 53% and incontinence by 43% (all statistically significant).

**Which syndrome of OAB is most troublesome for the patient after radiotherapy?**

During the observation and treatment periods, we noticed a change in patient perception of symptoms of OAB after radiotherapy and gradual reevaluation of those features (Table 3, Figure 2). Initially, the most troublesome symptoms during treatment (urgent episodes and incontinence, described by 68% of patients) were significantly diminished. Some patients from this group described different symptoms that affected their quality of life: pollakiuria 30% and nocturia 22%.

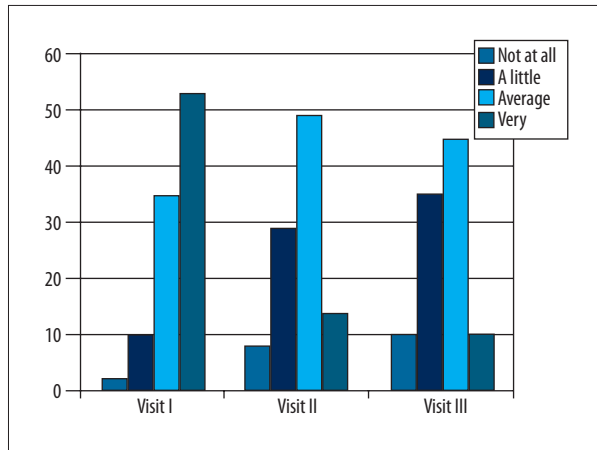
In cases of urgent episodes, the most significant improvement took place in the second trimester of treatment.

**How would you describe your present condition?**

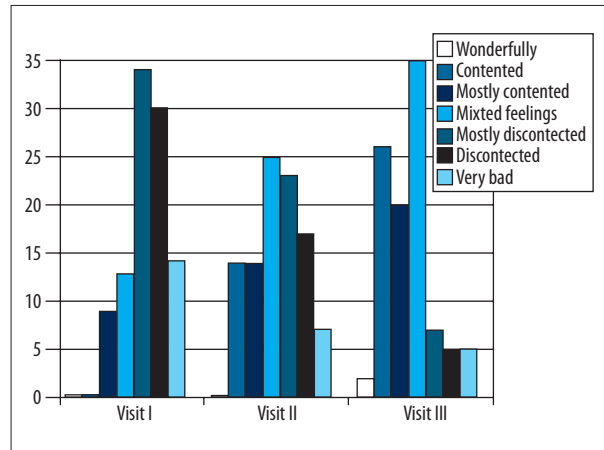
Our attention was drawn to significant change in the 22% of patients describing their general condition as bad and very bad. After treatment, only 4% of patients described their status as before. The proportion of patients describing their status as good increased significantly from 10% to 22% (Table 4, Figure 3).

**Table 5.** How, in your opinion, problems with bladder affect your life quality?

Feature	Visit I	Visit II	Visit III
Not at all	2% (5 p.)	8% (22 p.)	10% (27 p.)
A little	10% (27 p.)	29% (78 p.)	35% (95 p.)
Average	35% (95 p.)	49% (133 p.)	45% (122 p.)
Very	53% (144 p.)	14% (38 p.)	10% (27 p.)



**Figure 4.** How do problems with bladder affect your quality of life?



**Figure 5.** How would you feel if the current bladder problems persisted?

**Table 6.** How would you feel if the current problems with bladder persisted?

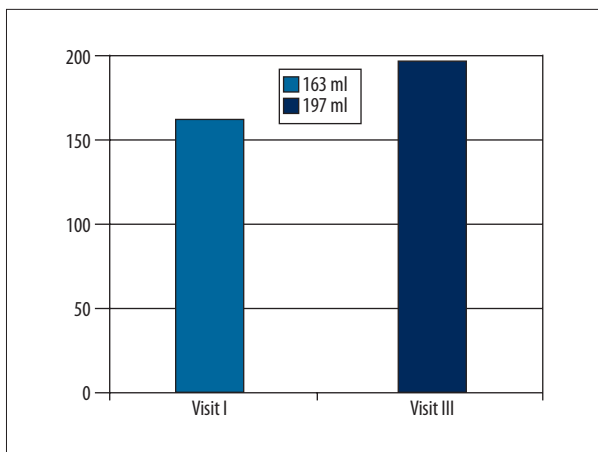
Feature	Visit I	Visit II	Visit III
Wonderfully	0%	0%	2% (5 p.)
Contented	0%	14% (38 p.)	26% (70 p.)
Moslty contented	9% (25 p.)	14% (38 p.)	20% (54 p.)
wMixed feelings	13% (35 p.)	25% (67 p.)	35% (95 p.)
Moslty discontented	34% (92 p.)	23% (62 p.)	7% (19 p.)
Discontented	30% (81 p.)	17% (47 p.)	5% (14 p.)
Very bad	14% (38 p.)	7% (19 p.)	5% (14 p.)

**In your opinion, how do bladder problems affect your quality of life?**

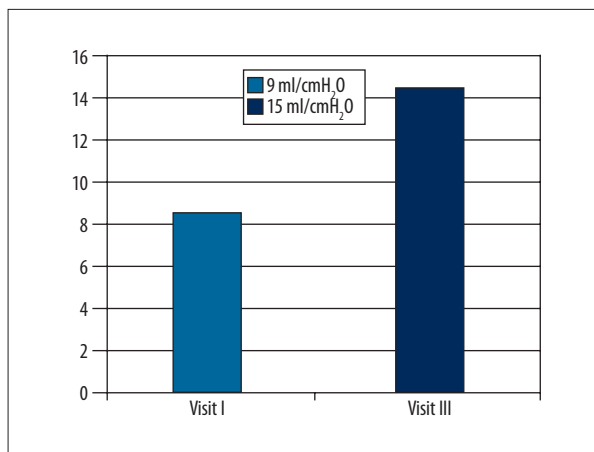
As many as 88% of patients during the first visit reported that bladder problems affected their quality of life to a moderate or high degree. After a 6-month period of treatment, a diminished influence of bladder problems affecting quality of life was observed in each group (Table 5, Figure 4). In the group that chose the answer “very”, the number of patients decreased 5-fold (from 53% to 10%).

**How would you feel if the current problems with your bladder persisted?**

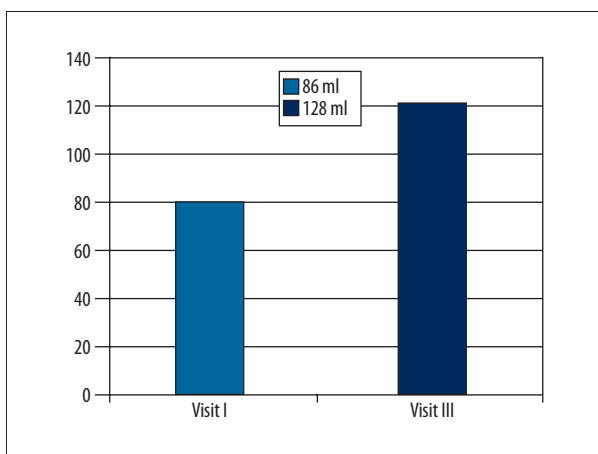
This question reflects the individual subjective evaluation of the impact on the future quality of life. Patients choosing answers: “very bad”, “discontented”, and “mostly discontented” accounted for 78% of all the patients during visit I. During visit III, this number decreased to 17%. The group choosing the answers: “wonderful”, “contented”, or “mostly contented” rose from 9% to 48% (Table 6, Figure 5).



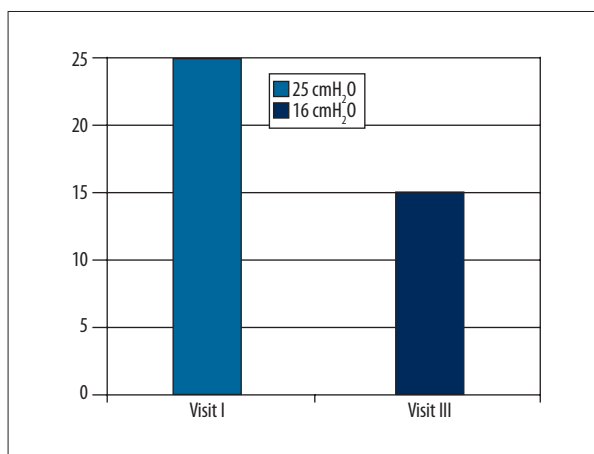
**Figure 6.** Average maximal cystometric volume during visits I and III,  $p < 0.01$ .



**Figure 8.** Average bladder compliance  $\Delta V(\text{ml})/\Delta P_{\text{det}}(\text{cmH}_2\text{O})$  during visits I and III,  $P < 0.9$ .



**Figure 7.** Average bladder volume of "first desire" during visits I and III,  $p < 0.01$ .



**Figure 9.** Average detrusor muscle pressure (cmH<sub>2</sub>O) at maximal cystometric volume – visits I and III,  $P < 0.03$ .

Every sixth patient underwent cystometry after visits I and III. The results are presented below in the form of a Figure. After a 6-month period of treatment, we noticed an increase in average maximal cystometric volume by 34 ml, which is an average increase of 21% ( $P < 0.01$ ) (Figure 6).

Pharmacological treatment with 5 mg solifenacin in the 6-month period increased the volume of "first desire" average from 86 ml to 128 ml, which is an improvement of 49% (42 ml) and is statistically significant ( $P < 0.01$ ) (Figure 7).

Post-irradiation bladder is characterized by very low elasticity of the bladder wall because of a change in its structure, which will be further discussed. The 6-month treatment period with solifenacin caused an increase in average compliance of 6 ml/cmH<sub>2</sub>O (67%), but this change was not statistically significant (Figure 8).

Average detrusor muscle pressure with maximal volume was decreased by 9 cmH<sub>2</sub>O (36%), with a statistical significance level of  $P < 0.03$  (Figure 9).

According to urodynamic percentage of the weakest response observed in patients with bladder cancer, we detected an increase in average cystometric maximal volume of 12 ml, average "first desire" volume of 17 ml, and average compliance of 2 ml/cmH<sub>2</sub>O. This is probably due to changes in the wall of the bladder, including scarring from surgery, TURBT, transurethral resection of bladder tumor, a residue of infiltration, or radiotherapy. Despite this, subjective assessment by patients with bladder cancer did not differ from that in the other groups.

In the entire group, 85% (230 people) rated the therapy as well-tolerated; 12% (33 persons) reported feeling of dryness in the mouth, 4% (12 people) reported somnolence and dysgeusia, and 3% (9) reported nausea and constipation. Treatment was interrupted by 29 patients: 4% (12) because of poor tolerance, and the

rest due to scheduling problems. The cause of discontinuation in 0.8% (2) was due to poor tolerance, in 2.4% (6) it was due to a strong feeling of dryness in the mouth, and in 1.6% (4) discontinuation was due to drowsiness, altered taste, or blurred vision.

## Discussion

Numerous studies have evaluated the impact of muscarinic receptors antagonists on symptoms of OAB. In each of those studies, radiotherapy was one of the exclusion criteria of measuring the effectiveness of relieving OAB symptoms. Our literature search failed to find any study that evaluated the effect of those substances on symptoms of post-irradiation bladder. In oncology and in radiotherapy, we have several adverse symptoms classification systems. Those systems are not unified and do not classify complication features in case of a particular therapy, which makes objective evaluation difficult. The most common system in use is the SOMA/LENT (*Subjective Objective Management and Analytic Scale/Late Effect of Normal Tissue*) toxicity system, created in 1995 [8]. The morphological changes occurring in tissues depend on the dose and the method of radiotherapy. In oncological radiotherapy, 2 radiation techniques are used, very often combined – teleradiotherapy and brachytherapy – and the overall dose is summarized. When the summarized dose of radiation of the small pelvic organs is lower than 60 Gy, the complication rate is only 2–3%. When the dose increases to 80 Gy, the complication rate is elevated to 11–28%, and in this group there are patients with bladder fistulas [9]. Ionizing radiation damages healthy cells and tissues by 2 mechanisms: direct disruption of DNA chains (20–30% of damages) and indirect disruption (70–80% of damages), which is the result of hydrolysis and the effect of free radicals and peroxides on DNA chains. The most sensitive cells are those in the G2 and M phase of division, and the most resistant are those in the S phase. Tissues with high  $\alpha/\beta$  index (fast-proliferating) more commonly manifest early reaction. Tissues with low  $\alpha/\beta$  index (slow-proliferating) manifest late reaction. In animal models, researchers demonstrated that urothelium has a low proliferating activity and is sensitive to radiation. In basal and intermediate cells, cellular junctions and polysaccharide layer are damaged, which directly affects hypertonic urine and bacteria in submucosal layers of the bladder. Up to 12 months after radiotherapy, changes in endothelial vessels of the bladder arise (edema and fibrosis), which leads to disturbance in blood supply to the detrusor muscle. Destruction and replacement with fibroblasts affect the compliance and volume of the bladder [10].

We found no data in the literature on the influence of solifenacin in patients with post-irradiation bladder. The data obtained in the present study demonstrate the positive effect of solifenacin on quality of life by reducing the symptoms of post-irradiation bladder.

During a 6-month treatment period, we achieved a decrease in average number of micturitions a day from 11 to 7 (–36%), number of urgent episodes from 17 to 8 (–41%), nocturia from 4 to 2 (–50%), and episodes of incontinence from 7 to 4 (–43%). In patients after radiotherapy, the improvement in objective and subjective parameters occurred mostly in the second trimester of treatment, which suggests the importance of long-term and periodical intake of this medicine. The urodynamic evaluation confirmed the effect of this treatment on function of accumulation of urine. The following parameters significantly improved: maximal cystometric volume ( $P<0.01$ ), volume of “first desire” ( $P<0.01$ ), and detrusor muscle pressure at maximal cystometric volume ( $P<0.03$ ). Bladder compliance rose by 67%, but without statistical significance. The above-mentioned objective data are reflected in the subjective patient evaluation. During observation and treatment, the perception of post-irradiation bladder symptoms changed and were gradually reevaluated by patients. At the beginning, 68% considered urgent episodes and incontinence as the most troublesome symptoms; by the end of study, those symptoms lost such significance. Some patients from this group indicated different symptoms as most affecting their quality of life: pollakiuria 30% and nocturia 22%. Our attention was drawn to the significant change in perception of life quality as “bad” and “very bad”; overall, 22% during the first visit and 4% during the third visit. The proportion of patients describing their overall status as good significantly increased, from 10% to 22%.

In the entire group, 85% rated the therapy as well-tolerated. Only 4.8% (12) interrupted participation because of poor tolerance. The cause of discontinuation was a strong feeling of dryness in the mouth in 0.8% (2), drowsiness and altered taste in 2.4% (6), and blurred vision in 1.6% (4).

The remaining 17 patients did not complete observation because of different reasons.

Solifenacin has well-documented effectiveness in treatment of patients with OAB. Two open multicentric clinical phase III trials – VOLT (*VESicare Open-Label Trial*) and VERSUS (*VESicare Efficacy and Research Study*) [11] – have documented the efficiency and safety of using this drug. A 12-week treatment significantly reduced the number of urgent episodes, episodes of incontinence and nocturia, and improved quality of life. The VERSUS study proved the advantage of solifenacin in the above-mentioned aspects over tolterodine, as well as in quality of life. The study showed males presenting symptoms of OAB when the subvesical clinical obstruction was excluded. The study enrolled 444 males with no cases of acute urine obstruction, and a positive influence on the whole examined population of 2666 patients was reported.

## Conclusions

1. Long-term administration of solifenacin to patients with symptoms of OAB after radiotherapy of malignant neoplasm of small pelvis organs has a daily impact in decreasing

number of urgent episodes, episodes of incontinence, polakiuria, and nocturia.

2. The quality of life was improved after treatment.

3. The substance is well-tolerated.

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