Urinary tract dysfunctions after gynecological cancers treatment

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Abstract

Oncological treatment results in a series of major adverse effects, local and systemic, depending on the type of treatment – surgery, radiotherapy (RT), chemotherapy (CT) or a combination of those. Chemotherapy acts mainly systemically, but drugs used during treatment are eliminated through the urinary tract, often unmetabolized, and come in direct contact with the epithelium of the bladder, ureters and urethra. Pelvic radiotherapy, even though targeted at the uterus or cervix, influences the adjacent organs. Radical hysterectomy aims at removing only affected parts of the urogenital tract, but nearby tissues, nerves and blood vessels can be damaged during surgery. They all result in some form of temporary or permanent lower urinary tract dysfunctions. They vary in type and severity and are becoming increasingly more manageable and preventable through recent advancements in targeted chemotherapy, more precise radiotherapy and more selective surgery. More consideration is recently put not only into developing more effective forms of treatment, but also into improving the quality of life for oncological patients during and after therapy. Recent advancements and discoveries in this field are discussed in the following article.

Key words: urinary tract dysfunction, gynecological cancer, chemotherapy, radiotherapy

Introduction

Oncological treatment results in a series of major adverse effects, local and systemic, depending on the type of treatment – surgery, radiotherapy (RT), chemotherapy (CT) or a combination of those. They vary in severity, concern different organs and include the urinary tract complications. An important topic, considering the fact that gynecological cancers rate is high in incidence and mortality worldwide. Chemotherapy acts mainly systemically, but drugs used during treatment are eliminated through the urinary tract, often unmetabolized, and come in direct contact with the epithelium of the bladder, ureters and urethra. Pelvic radiotherapy, even though targeted at the uterus or cervix, influences the adjacent organs. Radical hysterectomy aims at removing only affected parts of the urogenital tract, but nearby tissues, nerves and blood vessels can be damaged during surgery, resulting in temporary or permanent lower urinary tract dysfunctions.

Chemotherapy

The urinary tract, responsible for the elimination of drugs used during chemotherapy, remains in prolonged contact with the toxic agents. Platinum-based antineoplastic family of medications, including carboplatin and cisplatin, are excreted through kidneys partly in unmetabolized form. Kollmannsberger et al. reported a 20%-30% reduction in glomerular filtration rate in testicular cancer patients treated with cisplatin [1].

Acrolein and chloroacetaldehyde, metabolites of cyclophosphamide and ifosfamide, have a strong, local toxic and inflammatory effect on the urothelium, which can result in cystitis [2]. It can manifest itself by pain and burning, accompanied by dysuria, urge incontinence, frequency and nocturia. In severe cases, hemorrhagic cystis can occur [3], with ulcerations and necrosis in the bladder. Its symptoms are similar to ordinary cystitis, with additional hematuria. Luckily, the symptoms can be alleviated by proper hydration and with mesna, known to ease the effects of the chemotherapy on the bladder.

Local adverse effects from the urinary tract are fully reversible, ceasing when the treatment is withheld, and as such do not have a strong negative effect on the quality of life of chemotherapy patients after the treatment ends.

Radiotherapy

Radiotherapy destroys cancer (and healthy) tissues directly, by DNA and cell protein damage, and indirectly, by forming free radicals able to oxidize and ionize key enzymes involved in their metabolism and division. Damage to the urothelium may cause local and regional
inflammation with all its consequences, while destruction to the endothelium and adventitia of blood vessels may result in impaired blood supply, fibrosis and premature degeneration of bladder and urinary tract tissues in the irradiated pelvis.

Pelvic radiotherapy adverse effects (AEs) can be divided into early and late. The latter are usually graded using Radiation Therapy Oncology Group (RTOG) system (Table 1) [4].

<table>
<thead>
<tr>
<th>RTOG system grade</th>
<th>Urinary adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>none</td>
</tr>
<tr>
<td>1</td>
<td>microscopic hematuria</td>
</tr>
<tr>
<td>2</td>
<td>urinary frequency, macroscopic hematuria, teleangiectasia</td>
</tr>
<tr>
<td>3</td>
<td>severe frequency or dysuria, severe generalized teleangiectasia, frequent hematuria, bladder capacity reduced to below 150 cm³</td>
</tr>
<tr>
<td>4</td>
<td>severe hemorrhagic cystitis, bladder capacity reduced to below 100 cm³, necrosis</td>
</tr>
<tr>
<td>5</td>
<td>death</td>
</tr>
</tbody>
</table>

Grade 1 and 2 AEs (minor) are considered mild, occur early and usually require no surgical intervention. They occur when the combined dose of radiation applied higher than 30 Gy and are, in most cases, fully reversible. Grade 3 and 4 (major), however, are qualified as severe, often require repair surgery and have a serious impact on the quality of life for the affected patients. They mostly affect women who also underwent surgery [5] and unfortunately become worse over time.

Cervical cancer

For cervical cancer treatment, a combined dose of 80-90 Gy for external beam radiation therapy (EBRT) and intracervical brachytherapy (BT) is considered an optimal RT regimen [6]. The ureteral orifice and the posterior wall of the bladder are most susceptible to incidental radiation as they lie anteriorly to the cervix. The risk of developing a major urinary tract dysfunction, the most recurrent being fistulas between the bladder and vagina, ureteral strictures and hematuria, is between 1.3% and 14.5%. Minor AEs occur more often – early-onset in 44% of patients, late onset in 9.5% [7–12]. In fact, primary RT for cervical cancer results in more AEs than radical hysterectomy with pelvic lymphadenectomy (RH-PL) [13]. Post-RT ureteral stenosis is also more difficult to manage than intraoperative injury [14, 15]. Repeated stenting remains the best available solution, as the re-plantation of the ureter into the bladder is usually not achievable due to the post-RT ischemia of its distal end. When stenting is not possible or is not accepted by the patient, urostomy, nephrostomy or nephrectomy may be required [16–18].

Endometrial cancer

For endometrial cancer patients, 45-50 Gy radiation dose is considered an optimal therapy, either as EBRT or vaginal BT. The latter was proven in the PORTEC-2 study as resulting in lower AE rate than EBRT while being equally effective [19]. Bladder resides anteriorly to the uterus and as such, it is the most susceptible to incidental irradiation. PORTEC 1 and 2 trials show no evidence of any major urinary AEs after endometrial cancer radiotherapy [19, 20]. Similarly to the cervical cancer treatment, EBRT for endometrial cancer greatly increased the minor urinary AE rate compared to RH-PL only group (30% vs. 8%, p < 0.001) [21].

Urinary tract dysfunctions induced by radiotherapy are more severe, more common and more difficult to treat than AE resulting from any other form of oncological treatment. They also have the highest impact on the quality of life of the patients. Continually improving precision and resolution of the equipment and software used for radiotherapy gives hope for lower amount of radiation affecting the surrounding tissues, thus resulting in fewer and milder adverse effects.

Surgery

Radical hysterectomy (RH) with pelvic lymphadenectomy is the gold standard for surgery in early-stage cervical, endometrial and ovarian cancers. Urinary tract injuries, especially to the bladder and pelvic plexus, depend on the amount and type of nerves that have been damaged [22]. A number of hypotheses had been posed for how sympathetic and parasympathetic nerve balance regulates the function of the bladder, detrusor, sphincter and whole urethra.

The most recent theory, confirmed by Forney and Low et al. states that the destruction of β-adrenergic pathway lowers the plasticity of the bladder, impairing its ability to hold larger volumes of urine. At the same time, obliteration of α-adrenergic axons causes predominance of parasympathetic stimulation leading to higher detrusor activity and relaxation of the internal urethral sphincter. These processes result in high incidence rate of stress incontinence after RH [23, 24]. The key role of
internal urethral sphincter was confirmed by reports finding no difference in urodynamic examinations of women after RH with and without urinary incontinence, apart from the pressure inside the urethra [25]. Other study proves that the severity of the incontinence depends on the extent of the bladder compliance reduction [26], confirming the theory of Forney and Low et al. These phenomena are responsible for late urinary dysfunction, which resolve with no medical intervention within a year in 70% of all cases [27, 28]. Early uterine tract disorders result mainly from general impaired abdomen and pelvic sensation, reduced detrusor activity and lower bladder capacity and are usually not severe [29]. Residual urine volume, used by some to measure early bladder function impairment, has no direct correlation with urinary dysfunction later in life, as proved by Benedetti-Panici et al. [30]. In their report, even though only 15% patients after RH had residual urine volume higher than 30% of their bladder capacity, 76% of patients would develop some kind of bladder dysfunction within the first year after surgery.

A number of reports on nerve-sparing radical hysterectomy (NSRH) show lower uterine tract dysfunction rate and higher quality of life for patients after RH without compromising oncological outcomes [31, 32]. No standardized technique for this type of surgery has been established so far, but as more authors undertake the challenge, uniformity in the approach and even better results could be achieved. Recent study shows that total laparoscopic radical hysterectomy is also yielding promising results, both effective and oncologically safe, while resulting in lower AE rate in the urinary tract, even for advanced stage cervical cancer [33, 34].

Closing remarks

Lower urinary tract dysfunctions as a result of oncological treatment are becoming less and less severe as more focus is put not only into the effectiveness of the therapy, but also the patients’ quality of life. Target chemotherapy, improved resolution of radiotherapy and wider use of novelty surgical procedures, together with better understanding of the mechanisms of urinary tract dysfunctions will help prevent larger percentage of urinary complications of oncological treatment.

References

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