



Urological complications after radiation therapy – nothing ventured, nothing gained: a Narrative Review

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Abstract: Radiation therapy along with chemotherapy and surgery are the three main treatment modalities used in oncology. The main disadvantage of radiotherapy is the fact that it affects both cancer and healthy cells located in the tumour area. As a consequence, different complications develop. A large proportion of cancers treated with radiotherapy are located in the lower abdomen and pelvis, which is why complications often involve the urinary tract. Due to the anatomy of these areas, urological complications occur not only after radiological treatment of urological cancers, but also after treatment of malignancies of the reproductive or digestive system. The most common radiation-induced complications include haemorrhagic cystitis, urethral and ureteral strictures, urinary fistulae, and secondary primary malignancies. Adverse events significantly degrade the quality of life of the patient, and in severe cases can be life threatening to the patient. Because of impaired tissue healing, the treatment of radiation urological complications is a challenge for urologists and often requires complicated reconstruction techniques. Continuous increase in the effectiveness of cancer treatments and the extension of patients' lives, make complications of radiation therapy an increasingly common clinical problem. The aim of this review is to present the pathophysiology, clinical presentation and methods of treatment for radiation-induced urological complications.

Keywords: Radiotherapy; urological complications; pelvic malignancy; radiation cystitis

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Introduction

Radiation therapy along with chemotherapy and surgery are the three main treatment modalities used in oncology (1,2). It is estimated that approximately 50% of patients will receive radiotherapy during the cancer treatment (1-4). It is the most-effective cytotoxic therapy available for the treatment of localized solid malignancies (5-7).

The main disadvantage of radiation therapy is the fact

that it affects both cancer and healthy cells located in the tumour area. Although advances in radiotherapy, such as intensity-modulated radiotherapy (IMRT), conformal radiotherapy (CRT), and high-energy linear accelerators have enabled more accurate delivery of radiation to the tumour and the limitation of surrounding tissue exposition, the effects of this type of therapy on healthy tissues have not been completely eliminated (2,5,7-12). An additional way to reduce complications is the use of so-called radioprotectors.

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These are agents administered prior to or during irradiation to prevent or reduce damage to normal tissue. To date, amifostine is the only clinically used radioprotector, but it can cause various side effects, including hypotension. The use of other compounds in the protection of normal tissues, e.g., melatonin, metformin, nitroxides, shows promising results in preclinical studies (13,14).

The degree of damage to healthy tissues, depends on tissues' radiosensitivity, the size of radiation doses and the irradiated area, the intervals between doses, the method of delivery and the patient's factors such as comorbidities (2,7,11,12). Some of these factors are modifiable, allowing the protection of normal tissues against damage. An example is hyperfractionation, which is the administration of a high total dose of radiation distributed over a large number of small doses per fraction. Normal tissues are more sensitive to fraction size changes than tumours, and with smaller doses per fraction, normal tissues can repair radiation damage more effectively than cancer cells (12).

Complications related to radiotherapy can be divided into acute and late. Acute ones may occur during treatment or within days or weeks after irradiation, while late ones may appear after a few months or even years. Some authors consider 90 days as the threshold between acute and late complications (7,9,10,14-17).

A large proportion of cancers treated with radiotherapy are located in the lower abdomen and pelvis, which is why complications often involve the urinary tract. Due to the anatomy of these areas, urological complications occur after radiological treatment of malignancies of genitourinary and digestive system. The most common pelvic cancers requiring radiotherapy include prostate cancer, rectal cancer and anal cancer in men, and cervical cancer and vulvar cancer in women. Other tumours that cause urological complications after radiation include bladder cancer, ovarian cancer, urethral cancer, endometrial cancer, testicular cancer, and vaginal cancer (7,12,16,18-22).

The aim of this study is to analyse the literature on urological complications after radiotherapy for various cancers, their pathophysiology, clinical presentation and methods of treatment. We present the following article in accordance with the narrative review reporting checklist (available at <http://dx.doi.org/10.21037/tcr-20-2589>).

Evidence acquisition

A narrative review was carried out due to the low quality of the evidence available. A literature search was performed

using the PubMed and Google Scholar electronic databases. The search was limited to English and German articles published until July 2020. Searched terms included: "urological complications", "pelvic radiotherapy", "radiation cystitis", "fistula", "ureteral stricture", "urethral stricture", "second primary cancer", along with free-text, related, derivative, and exploded terms.

Types of complications

Damage caused by radiation therapy most often affects the bladder and ureters (16,23,24). The most common radiation complications include haemorrhagic cystitis, urethral and ureteral strictures, urinary fistulae, and secondary primary malignancies (7,10,18,19,21). Less common are erectile dysfunction, infertility, lower urinary tract dysfunction, bladder fibrosis and necrosis. As a result, chronic kidney disease may develop (7,9,18,21). Radiation-induced urological complications were first reported in 1927 by Dean. He described ulceration of the urinary bladder following the use of radium in a patient with uterine cancer (25).

Grading

Several scales were proposed to assess the severity of acute and late radiological toxicity. The two most commonly used in clinical practice are Radiation Therapy Oncology Group (RTOG)/European Organization for Research and Treatment of Cancer (EORTC) and National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) (Table 1) (26,27). Another scale is LENT-SOMA, which occurs in a separate version for each organ or tissue that may be in the irradiation field. It includes 4 elements, representing the subjective, objective, management and analytical (SOMA) assessment of late effects on normal tissues (LENT). Although comprehensive, it is mainly used in clinical studies (28,29).

Epidemiology

Urological complications after radiotherapy are usually mild and moderate (RTOG grades 1-2) (22,30). Severe (RTOG grades 3-4) occur most frequently after treatment of cervical cancer, prostate cancer and bladder cancer (16,22). The most common late adverse event is radiation cystitis, which occurs in 5–10% of patients undergoing pelvic radiotherapy (16,21,23,24,31,32). The frequency of a given complication depends on the type of cancer. Radiation cystitis occurs

Table 1 Genitourinary complications according to the Radiation Therapy Oncology Group (RTOG)/European Organisation for Research and Treatment of Cancer (EORTC) morbidity scale and the Common Terminology Criteria for Adverse Events (CTCAE) v5.0

Organ/complication	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Genitourinary complications according to the Radiation Therapy Oncology Group (RTOG)/European Organisation for Research and Treatment of Cancer (EORTC) morbidity scoring criteria					
Genitourinary/ bladder acute	Frequency of urination or nocturia twice pretreatment habit/dysuria, urgency not requiring medication	Frequency of urination or nocturia that is less frequent than every hour. Dysuria, urgency, bladder spasm requiring local anaesthetic (e.g., Pyridium)	Frequency with urgency and nocturia hourly or more frequently/dysuria, pelvis pain or bladder spasm requiring regular, frequent narcotic/gross haematuria with/without clot passage	Haematuria requiring transfusion/acute bladder obstruction not secondary to clot passage, ulceration, or necrosis	Death
Genitourinary/ bladder late	Slight epithelial atrophy; minor telangiectasia (microscopic haematuria)	Moderate frequency; generalized telangiectasia; intermittent macroscopic haematuria	Severe frequency and dysuria; severe telangiectasia (often with petechiae). Frequent haematuria; reduction in bladder capacity (<150 cc)	Necrosis/Contracted bladder (capacity <100 cc). Severe haemorrhagic cystitis	Death
Common Terminology Criteria for Adverse Events (CTCAE) v5.0					
Haematuria	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; urinary catheter or bladder irrigation indicated; limiting instrumental ADL	Gross haematuria; transfusion, IV medications, or hospitalization indicated; elective invasive intervention indicated; limiting self-care ADL	Life-threatening consequences; urgent invasive intervention indicated	Death
Cystitis noninfective	Microscopic haematuria; minimal increase in frequency, urgency, dysuria, or nocturia; new onset of incontinence	Moderate haematuria; moderate increase in frequency, urgency, dysuria, nocturia or incontinence; urinary catheter placement or bladder irrigation indicated; limiting instrumental ADL	Gross haematuria; transfusion, IV medications, or hospitalization indicated; elective invasive intervention indicated	Life-threatening consequences; urgent invasive intervention indicated	Death
Urinary fistula	–	Symptomatic, invasive intervention not indicated	Invasive intervention indicated	Life-threatening consequences; urgent invasive intervention indicated	Death
Urinary tract obstruction	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic but no hydronephrosis, sepsis, or renal dysfunction; urethral dilation, urinary or suprapubic catheter indicated	Altered organ function (e.g., hydronephrosis or renal dysfunction); invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death

ADL, activities of daily living; IV, intravenous.

most frequently after prostate, bladder and cervical cancer treatment, ureteral stenosis after cervical radiotherapy, and urethral stenosis after brachytherapy of prostate cancer (6,12,22,33). The latency period between the end of treatment and the onset of complications may be up to 30 years, and the risk of developing adverse events increases with time (22,33,34).

The incidence of urological complications depends on the method of treatment for prostate cancer. In the case of external beam radiotherapy, the incidence of adverse events was 20–43%, 7–19% and 5–13% for RTOG grade 1, 2, 3, respectively, after 10 years. The most common complication is radiation cystitis (35–40). In the case of brachytherapy, the incidence of adverse events was 36%, 24%, 6.2% and 0.1% for RTOG grade 1, 2, 3 and 4, respectively, with follow-up of up to 5 years. The most common complications of brachytherapy include haematuria, obstructive or irritating urinary tract symptoms and urethral stricture (41,42).

Late urological complications following radiation therapy for bladder cancer were reported in 18–27% patients for RTOG grade 2 and in 6–17% patients for RTOG grade 3 or higher, with a median follow-up of 29–76 months (43–46).

After radiation therapy for cervical cancer, late complications occur in 7–9.8% patients for RTOG 1–2 and in 1.3–14.5% patients for RTOG 3–4 after 3 years. The most common adverse events include radiation cystitis, ureteral stenosis and vesicovaginal fistula (47–53).

The incidence of mild to moderate (RTOG grade 1–2) adverse events after radiotherapy for endometrial cancer is 11–17% (54–57). There were no serious (RTOG grade 3–4) complications with a median follow-up of 52 and 68 months, except for one series of cases in which ureteric stenosis was described in 6% of patients (54–56,58).

Late severe urological complications after irradiation of colorectal cancer occur in 2–4% of patients (59).

Radiation cystitis

Radiation cystitis is one of the most common complications of radiation therapy (19,60). It occurs in 5% to 10% of patients undergoing pelvic irradiation and most often complicate treatment for prostate, bladder or cervical cancer (12,21,23,24,31). Acute radiation cystitis is common and usually self-limiting (24,32). Chronic haemorrhagic cystitis is a rare, progressive and irreversible condition that can occur up to 20 years after irradiation, and its treatment is a challenge to modern medicine (24,61–63). Both forms of cystitis significantly affect patients' quality of life and can

lead to life-threatening situations (24,30). Complications of radiation therapy constitute up to 7% of emergency admissions to the urology department (19).

Pathophysiology

Among all the organs of the urinary system, urinary bladder is the most sensitive to radiation (12,64). The exact mechanism of radiation cystitis is unknown, but 3 phases of this process are commonly distinguished: an acute phase, self-limiting, occurring up to 6 weeks after radiation therapy; a latent phase, asymptomatic, dose-dependent, lasting months or years; and a chronic and irreversible late phase (61,64–67).

Acute radiation cystitis is caused by damage to the bladder mucosa and it is characterized by hyperaemia, mucosal oedema and inflammation. The physiological urothelial barrier is impaired, which leads to secondary damage to deeper tissues through contact with urine and the spread of inflammation (61,65,68).

A feature of late damage is obliterative endarteritis (12,69). Tissues become hypovascular, hypocellular and hypoxic (so-called “three-H tissue”) (30,32,70). Hypoxia leads to necrosis of the mucosa, which is manifested by bleeding and necrosis of the detrusor muscle, which promotes fistula formation to adjacent organs (12,68,70,71). Ischemia also stimulates progressive fibrosis of the bladder wall, which, when severe, may lead to a decrease in bladder capacity and, as a consequence, to urinary incontinence (12,65,69). Telangiectasia also develops, and the dilated vessels are fragile and can be a source of bleeding and pain (32,64,65,69–71).

Clinical presentation

Acute radiation cystitis occurs during or shortly after irradiation. It manifests as dysuria and increased frequency and urgency to urinate. It is characterized by self-limiting course and usually lasts up to 3 months (32).

The main symptom of chronic radiation cystitis is haematuria of varying severity—from mild haematuria to severe life-threatening haemorrhage leading to hypovolemic shock (32,64,72,73). Haematuria with clot formation may cause urinary retention (32,64). Other ailments include lower urinary tract symptoms such as nocturia, urgency, dysuria, frequency and urinary incontinence. In addition, patients may complain of suprapubic pain and fatigue (21,31,62,64–69,72,74).

Among the risk factors for chronic radiation cystitis, in addition to the previously mentioned radiation-related factors, are the comorbidities e.g., diabetes and hypertension, previous unrelated abdominal surgery, stage of the cancer, as well as other cancer treatment methods such as chemotherapy or surgery along with postoperative complications (32,65).

Diagnosis

Symptoms of chronic radiation cystitis are nonspecific, therefore other causes of haematuria, such as urinary tract infection, urolithiasis, anti-thrombotic agents, coagulopathies or malignancy, should be excluded. Laboratory investigations including full blood count, blood urea, serum creatinine and coagulation profile should be performed. General urine analysis and urine culture are the basis for the diagnosis of urinary tract infections, while urine cytology is a tool used in the diagnosis of high-grade urothelial tumours. Possible fistulas should be sought during the physical examination. In the next stage, the urinary tract should be assessed: upper, by ultrasonography or urography, and lower by means of cystoscopy. In addition, endoscopic examination allows the collection of samples for histopathological examination, which allows confirmation of the diagnosis and exclusion of the tumour process. During the biopsy, one should remember about impaired healing of the irradiated bladder wall and the risk of perforation. Urodynamic tests can help assess cystometric capacity, sphincter function, detrusor compliance, or the presence of vesicoureteral reflux.

Management

With the development of medicine, more and more therapeutic options are available to treat radiation cystitis. Part of the therapy is effective only for a short time and they cause various side effects. In addition, currently there are no standardized guidelines describing the algorithm for the management of radiation cystitis, which results, among others, from the lack of quality randomized studies.

Management methods can be divided into intravesical, systemic, ablative, hyperbaric oxygen and surgical techniques.

Currently, the type of treatment depends on the experience of the urologist, the availability of the method in the hospital, the severity of bleeding and the general condition of the patient. Patients with mild bleeding may

only require conservative management, and in the case of massive bleeding, more aggressive management such as cystectomy may be necessary. In addition, comorbidities may disqualify the patient from general anaesthesia necessary for surgery or formalin instillation. Renal failure may limit the use of aluminium.

In general, treatment begins with stabilizing the general condition and conservative management. In the absence of effectiveness, minimally invasive methods such as intravesical instillations or endoscopic treatment are used. Surgical options should only be considered as a last resort (*Figure 1*).

Acute radiation cystitis

Because of the self-limiting nature, treatment of acute radiation cystitis is symptomatic. Anticholinergic drugs (e.g., oxybutynin) are mainly used. Alternatively, phenazopyridine or flavoxate may be prescribed (32,65).

Chronic radiation cystitis

Initial management

Initial management depends on the severity of the haematuria and the general condition of the patient. In the case of hypovolemic shock, intravenous fluid resuscitation and blood transfusion are necessary (30-32,69,70,72). If possible, anticoagulants and ASA should be discontinued, and coagulation disorders should be corrected (30,75,76). The procedure to remove clots involves the introduction of a large (at least 22 Ch) transurethral catheter, copious bladder washout followed by intermittent or continuous irrigation of the bladder with saline (18,30,32,70,72-74,77,78). Irrigation should continue until the urine is clear (32,64). Leaving blood clots may cause urethral obstruction, urinary retention, and consequent perforation of the bladder (31,64,69). Sometimes clot removal requires cystoscopy (64,73). Most patients respond to conservative treatment, and in the absence of efficacy, alternative treatment options are needed (32,70).

Intravesical instillations

Bladder therapy is usually carried out using aluminium or formalin. Due to insufficient data, other methods cannot be recommended as routine management of chronic radiation cystitis. These include the use of placental extract (79),

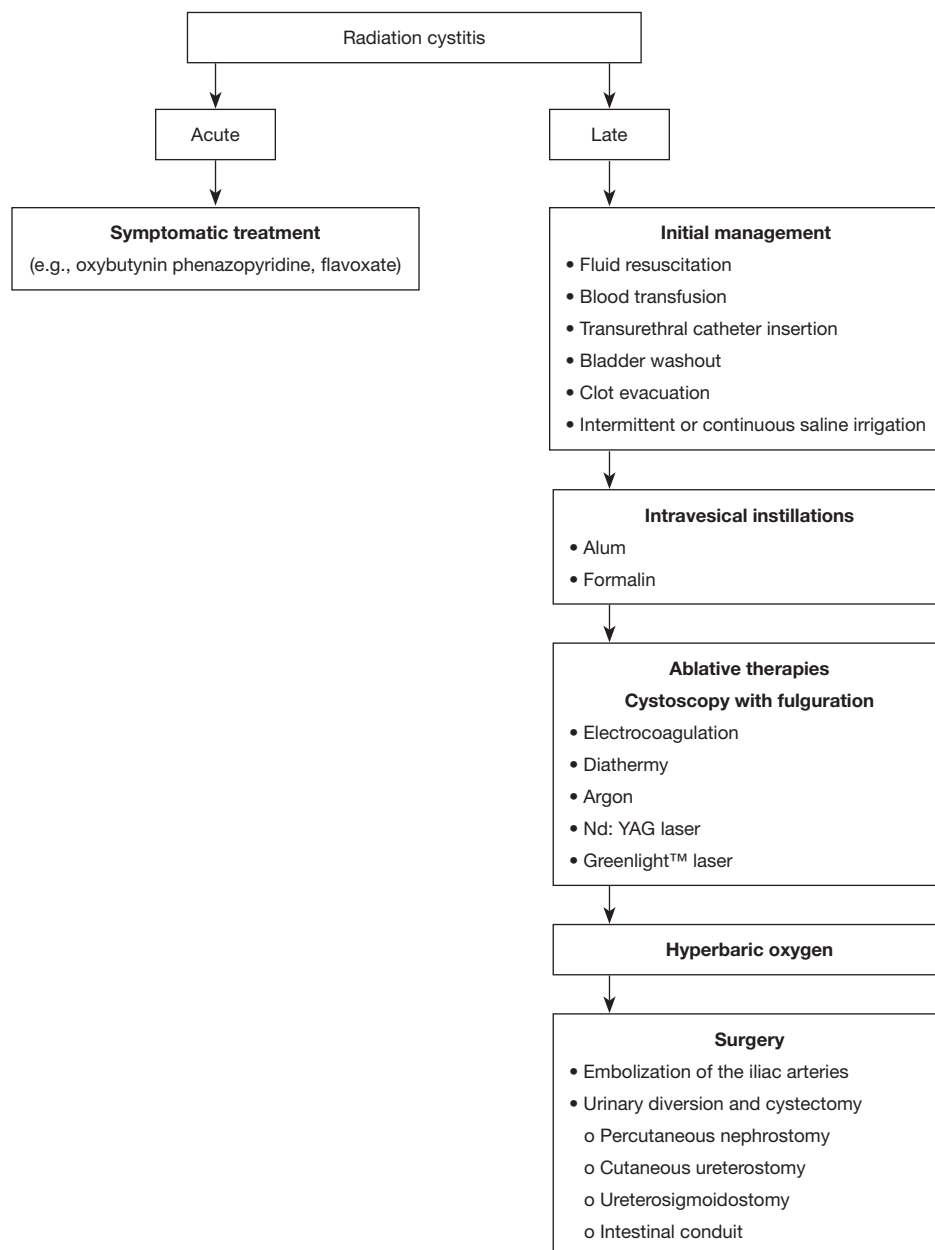


Figure 1 Management of radiation cystitis.

prostaglandins (80-82), silver nitrate (83-86), epsilon aminocaproic acid (87), hyaluronic acid (88), recombinant factor VII (89,90), dexamethasone (91), tacrolimus (92,93).

Alum

Alum is a solution of aluminium ammonium sulphate or aluminium potassium sulphate. As an astringent, it causes protein precipitation on urothelium surfaces and in

interstitial spaces. A decrease in capillary permeability and vasoconstriction occurs, which in effect leads to stopping bleeding (94). In the event of heavy bleeding, clot formation and recurrence of haematuria may occur (95). Typically, an infusion of 1% alum solution (50 g alum dissolved in a 5-liter bag of sterile water) is used at a rate of 200–300 mL/h (78,96). The procedure can be performed under local anaesthesia. The response rate ranges from 50% to

100% (52,77,78,94-100). Adverse events include suprapubic pain and bladder spasms that respond to treatment with analgesics and/or antispasmodics (77,96). Urinary tract infection develops less often (96). Patients with impaired renal function are at risk of developing encephalopathy and acidosis, therefore monitoring of serum alum levels is recommended (95,97,100). Due to the favourable toxicity profile, alum infusions are recommended as first-line treatment in the event of ineffective conservative treatment (32,72).

Formalin

Formalin is a formaldehyde solution. The mechanism of its action is the precipitation of cellular proteins in the mucosa as well as occlusion and fixation of telangiectasia and small capillaries, which leads to stopping of haemorrhage. It causes protein hydrolysis and coagulation of the superficial tissues of the bladder mucosa (78,101). The intravesical instillation of formalin causes severe suprapubic pain, so it is performed under general or regional anaesthesia (101-103). Prior to initiation of therapy, vesicoureteral reflux and bladder perforation should be excluded by cystography (104,105). In patients with reflux, ureteric orifices should be sealed with a balloon to prevent damage to the ureters and kidneys (105-107). Formalin concentrations used are 1–10%, however, maximum dilution is preferred because formalin toxicity increases with higher concentration (103,105,108). The instillation time should not exceed 15 minutes (103). After the bladder is completely empty, the saline irrigation should be continued. The effectiveness of treatment ranges from 70% to 90% (101,103-105,108-111). However, this method is highly toxic. Adverse events include severe bladder spasm, ureter obstruction, hydronephrosis, and renal failure. Bladder wall fibrosis can lead to a decrease in its capacity and an increased frequency of urination. Formal reflux into the upper urinary tract leads to bilateral pyonephrosis with lethal sepsis (102,103,105,108,109,112). Due to the high toxicity, formalin instillation should be used as a last resort before surgery, in the case of less invasive methods being ineffective (32,64,66,102,104).

Systemic therapies

Systemic therapies are non-invasive, and treatment does not require hospitalization. However, the evidence for systemic therapies is of low quality and therefore cannot be recommended as routine management of chronic radiation cystitis. The general principle of their operation

is to strengthen the protective polysaccharide layer of urothelium (32,72,75,113). The compounds proposed in systemic therapy include pentosan polysulfate (114-116), WF10 (117,118), conjugated oestrogen (119), tranexamic acid (120).

Pentosan polysulfate

Pentosan polysulphate is a synthetic polysaccharide sulphate that creates a protective coating on the bladder wall reducing the permeability and inflammatory response of urothelium. It is used sublingually at a dose of 100 mg 3 times a day. No adverse events were observed (114-116).

WF10

WF10 is diluted tetrachlorodecaoxide that induces natural immunity and counteracts the inflammatory process associated with submucosal endarteritis. It was used intravenously at a dose of 0.5 mL/kg, diluted in 250 mL 5% dextrose and administered over 2 hours. The therapy was continued every day for 5 consecutive days, every 3 weeks for 2–4 cycles. Complete response was 74–88%. No adverse events were observed (117,118).

Hyperbaric oxygen

Hyperbaric oxygen therapy involves the administration of 100% oxygen at a higher than atmospheric pressure in a special chamber. This allows maximum haemoglobin saturation and better oxygen diffusion in the tissues. Neoangiogenesis is stimulated and fibroblasts are activated and proliferated. New vessels provide oxygen to ischemic tissue, facilitating tissue reepithelialisation and healing (71,74,121-123). Various hyperbaric oxygen therapy regimens are used. Generally, 100% oxygen is administered at a 1.5–2.5 atmospheric pressure for 45–120 minutes, which gives additional time for compression and decompression. To reduce the risk of oxygen toxicity, a 5-minute “air gap” can be introduced every half hour. The therapy takes place every day and usually includes 20–40 sessions (32,67,124). Complete resolution of haematuria occurs in 34–96% of patients (23,63,121,122,124-136). This method of treatment avoids surgical treatment and at the same time has no negative effect on the bladder wall, which occurs when using, for example, formalin. Adverse events are rare and include ear and sinus barotrauma, convulsions caused by toxic oxygen, and claustrophobia (71,121,125,128,132,133). The disadvantages of this method include the limited availability and nuisance caused by daily sessions and a long

period of treatment (72). Hyperbaric oxygen therapy may be an alternative to surgery in the event of resistance to conventional therapy (32).

Ablative therapies

In the case of resistance to intravesical instillations, cystoscopy with fulguration of bleeding points is recommended (62). Treatment is performed under general or spinal anaesthesia with electrocoagulation, diathermy, argon, Nd: YAG laser or Greenlight™ potassium-titanyl-phosphate laser (137-142). Argon and the Greenlight™ laser have a more favourable safety profile due to the smaller penetration depth compared to the Nd: YAG laser (138-140). Fulguration cystoscopy has a high efficiency, ranging from 75% to 100% (137-142). Adverse events associated with this procedure include bladder perforation and/or fistula formation (137-139,142).

Other intravesical therapies

Other intravesical therapies include transurethral placement of a large balloon in the bladder (hydrodistension) (143,144), and botulinum toxin A injections into the bladder wall (145). Due to insufficient data, these methods are not recommended as routine management of chronic radiation cystitis (32,72,113).

Surgical interventions

Surgical treatment should be treated as a last resort in the case of resistance to other forms of therapy, because it is associated with high morbidity and mortality rates. It includes selective embolization of the internal iliac arteries, urinary drainage and cystectomy.

Embolization

Embolization of the iliac arteries is characterized by high efficiency reaching 100%. Complications of the therapy include necrosis of the skin, bladder, gluteal muscles, rectum, lumbosacral plexus or sciatic nerve palsy. The most common complication is gluteal pain secondary to obstruction of the upper gluteal artery. With the introduction of new embolization particles and superselective embolization, the rate of complications has decreased (146-151).

Urinary diversion and cystectomy

Urinary drainage methods include percutaneous

nephrostomy, cutaneous ureterostomy, ureterosigmoidostomy, and intestinal conduit formation (152-155). The transverse colon conduit is the preferred method because the transverse colon, unlike the small intestine, is not in the irradiation area (153). Complications associated with urinary diversion include pyocystitis, haemorrhage, pain and neoplastic transformation (156,157). Due to the high rate of adverse events exceeding 50%, simultaneous cystectomy should be considered (156,158). However, it should be remembered that cystectomy is associated with a high risk of perioperative complications and mortality. In addition, many patients with refractory radiation cystitis are elderly with many comorbidities, which may need to be considered for qualification for surgery (159,160).

Urinary fistulae

Urinary fistulae are rare complications of radiation therapy but are considered potentially severe and the most difficult to treat (19,161). They can occupy the entire urinary system, as well as the gastrointestinal tract or reproductive organs, and can occur up to 20–30 years after treatment (161-163). Vesicovaginal fistulae develop in 1–10% of patients undergoing pelvic radiotherapy (31,162,164). Up to 3% of patients treated with radiation for prostate cancer develop fistulae, and the most common are rectourethral and rectovesical (161,165-169).

Pathophysiology

As previously described, radiation causes endarteritis and, consequently, hypoxia, necrosis and fibrosis (167,170). The accumulation of collagen in the mucosa of the ureters and the bladder leads to a loss of compliance and a subsequent increase in wall tension (31). Together with tissue necrosis caused by hypoxia, these changes lead to fistula formation (12,16,68,70,71,161,165,171). Radiotherapy-related fistulae are usually large and multiple and are most often located within the bladder trigone, since this region usually receives the highest dose of radiation (165,172).

Localisation

Urinary fistulae can potentially develop throughout the entire urinary tract, the lower digestive tract and the reproductive system. The most common are vesicovaginal fistula in women and rectourethral fistula in men (31).

Both sexes also develop fistulae between the urinary tract and the gastrointestinal tract, which most often occupy the colon (e.g., enterovesical) (161,170,173). Rare radiation fistulas include vesicocutaneous, ureteroarterial and prostatosymphyseal (19,167,174-177).

Clinical presentation

Urinary fistula can be asymptomatic and accidentally detected. Symptoms depend on the location of the fistula. Vesicovaginal fistula is manifested by urine leakage from the vagina, recurrent urinary tract infections and dermatitis of the genital area (31,162,178). In the case of fistulae between the urinary tract and the gastrointestinal tract (enterovesical, rectourethral), patients complain of pneumaturia, fecaluria, recurrent urinary tract infections, haematuria, lower urinary tract symptoms (frequency, urgency), as well as pain in the suprapubic area (165,174,179-181). Skin fistulae manifest themselves as urine leakage onto the body surface (167,176). Recurrent urinary tract infections in the course of fistulae are associated with the risk of developing sepsis (167,179).

Diagnosis

Diagnosis of fistulae begins with physical examination, including gynaecological examination in women. A general urine test and urine culture are performed. The basis for diagnosis is imaging tests that allow visualization of the fistula canal, its size, as well as assessment of adjacent tissues and detection of accompanying pathologies (e.g., bladder neck stenosis) and planning of surgical treatment. The most commonly used are retrograde urethrography, voiding cystourethrography, intravenous urography, barium ingot, cystoscopy, and ultrasound. The methylene blue test, in which the dye is introduced into the bladder or rectum is also helpful. Cystoscopy is the preferred examination, during which the guidewire can be passed through the canal and the material for histopathological examination can be taken. Computed tomography and magnetic resonance imaging are considered the most sensitive imaging tests in fistula diagnostics.

Management

In the case of radiation urinary fistulae, conservative treatment is ineffective and the basis for treatment is surgery (178,182-184). The type of surgery depends on the location and extent of the fistula. Due to ischemia of surrounding

tissues, postoperative healing may be impaired, therefore, in order to restore the function of the genitourinary system or gastrointestinal tract, complicated reconstruction techniques are often necessary (161,167,185). The basis of surgical management is to ensure adequate nutrition of the tissue surrounding the fistula (161). Treatment is associated with a high percentage of failures and relapses (7).

Vesicovaginal fistula

The treatment of vesicovaginal fistulae can be carried out transvaginal or transabdominal using a variety of surgical techniques (161). In the presence of fistulae within the other pelvic organs or if additional urological procedures are required, transabdominal approach is preferred. Combined transvaginal and transabdominal access may be used in severe and recurrent cases (162,178). Regardless of surgical approach, the most important element is to provide blood supply and nutrition to the ischemic and fibrotic tissue surrounding the fistula. For this purpose, omental and peritoneal flaps or labial fat are used during fistula repair (16,161,186-188). The effectiveness of treatment ranges from 40% to 100% (189-191). In case the surgery is ineffective or technically impossible, urine drainage is recommended (7,162,178).

Rectourethral fistula

Treatment of the rectourethral fistula begins with intestinal and urinary diversion to reduce inflammation in the fistula and surrounding tissues prior to surgery and therefore reduce the risk of sepsis (19,165,192). The type of surgery depends on the general condition of the patient, life expectancy, local anatomy, as well as whether the return of urinary and gastrointestinal tract function is expected. Ultimately, the goal is to close the fistula and restore bladder and bowel function. Transperineal access is preferred as it allows greater urethral and rectal exposure. Abdominal access is less common (192-195). Due to ischemia of the tissues surrounding the fistula, to allow healing, a graft from the buccal mucosa or vascularized lobe is placed in the plane between the urethra and the rectum. The most commonly used lobe is the gracilis muscle, the less common are omentum, gluteus maximus muscle, abdominal rectus muscle and dartos (165,169,182,183,193,196-198). During surgery, due to tissue fibrosis, there is a risk of damage to adjacent structures such as the external urethral sphincter and the external anal sphincter (7,161,193). The effectiveness of therapy reaches 84% (193). In cases that do not suggest a return to the function of the urinary and

gastrointestinal tract, cystoprostatectomy and proctectomy with subsequent urinary and intestinal diversion are used (9,19,165,192).

Ureteral stricture

Ureteral stricture is a rare but serious complication of radiation therapy. Diagnosis is often late, and treatment is complicated (199,200). The overall incidence of stenosis is 0.4–2.7% (21,201). Strictures most often occur after radiotherapy for cervical cancer and are diagnosed in 3.3% of patients within 25 years after the end of cancer treatment (22,33). The average latency period is 16.8 years (21). Less often they are a complication of prostate cancer irradiation, with an incidence of 1–2.7% (75,202,203). Ureteral stricture is most often located 4–6 cm proximal to the ureteric orifice, because of its proximity to the area exposed to the greatest radiation (21,33,60). Due to the fact that stenosis can occur even 20 years after the end of treatment, young patients are at increased risk of developing this complication (33).

Pathophysiology

Changes in the ureters caused by radiation are the same as in the urinary bladder. Endarteritis and ischemia occur, which induces tissue fibrosis. Impaired tissue healing leads to atrophy and contraction in the ureter and, as a result, ureter stenosis develops (12,20,204).

Clinical presentation

Symptoms depend on the extent to which the ureter is narrowed and whether the stenosis is one or both sides (20). Most cases are asymptomatic and accidentally diagnosed (60,199,205). The only manifestation may be hydronephrosis or impaired renal function in laboratory tests. Flank pain is a rare symptom (60,205). Long-term, unrecognized ureteral stricture carries the risk of the development of vesicoureteral reflux and recurrent upper urinary tract infections complicated by life-threatening urosepsis (18,20,21,205). As a result, there may be a progressive loss of kidney function with the development of hypertension (21,60,206).

Diagnosis

During diagnostics, laboratory tests may show elevated

creatinine and urea nitrogen. Imaging tests include contrast studies, computed tomography and MAG3 renography, which allow to assess the degree of ureter stenosis and function of the affected kidney. Cancer recurrence should always be excluded. In the case of tumour recurrence, stenosis usually appears within 5 years. If differentiation is not possible based on imaging tests, a biopsy is required (18,33,205,207,208).

Management

The management of ureteral strictures should be initiated by ensuring free urine flow by means of a percutaneous nephrostomy or ureteral catheters, which prevents upper urinary tract infections and deterioration of kidney function (18,21,60,75). Further management depends on the patient's general condition, comorbidities, age, prognosis, location and length of stenosis, the presence of other radiation complications and the patient's preferences (20,21). Therapy options include minimally invasive procedures, reconstructive techniques, surgical urinary diversion or permanent drainage using nephrostomy or ureteral stents (16,19–21,60). The effectiveness of treatment reaches 67% (Figure 2) (16).

Minimally invasive treatment is an alternative to open surgery and include the use of a balloon, catheter dilatation and holmium laser endoureterotomy (205).

The method of choice for the treatment of ureteral stricture is surgery involving reconstruction or urinary diversion that provide long-term results (21). In rare cases, when stenosis is very short, end-to-end anastomosis may be used (20,21). Distal defects can be treated with resection and Psoas hitch or Boari flap ureterocystoneostomy (7,16,21,75,206,209,210). The use of an omental flap has been described to improve healing by providing blood and nutrition (210). Alternatively, the ureter can be anastomosed to a contralateral ureter by transureteroureterostomy (21,211). For long stenoses, the ureter is reconstructed using the small intestine segment, large intestine segment or the appendix (16,20,21,212–214). If the capacity of the bladder is small, urine drainage with ileal, jejunal or transverse colonic conduit is performed (16,19,21,75). The ileum segment is most commonly used, but the condition for successful surgery is the selection of the segment of the intestine that was not in the irradiation field (7,21,212).

In patients whose general condition does not allow surgery or who do not want to undergo surgery,

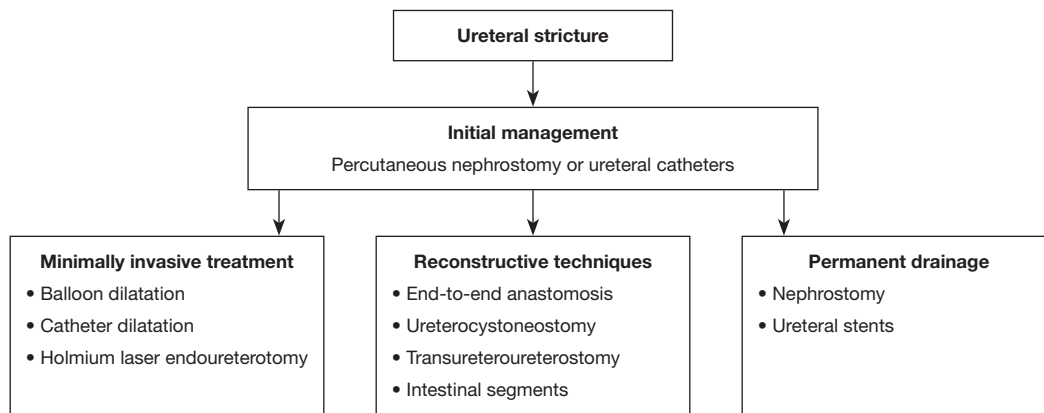


Figure 2 Management of ureteral stricture.

nephrostomy is created or stents are introduced, but these procedures are associated with a high risk of complications (19-21,207).

Urethral stricture

Urethral stricture is a serious complication that can lead to voiding dysfunction and, as a consequence, damage to the upper urinary tract (215). Most often, the narrowing is caused by radiation therapy for prostate cancer (6,12). At the same time, it is the most common long-term side effect of this type of prostate cancer therapy (6). To date, only one case of urethral stricture has been reported among women after radiation therapy for cervical cancer (216).

The overall incidence of urethral strictures after radiotherapy for prostate cancer is 2.2%, of which 1.5% after external beam radiotherapy, 1.9% after brachytherapy, and 4.9% after combination therapy (6,217,218). They are usually observed within 1–3 years after treatment (215,217,219,220). More than 90% of strictures are located in the bulbomembranous urethra, but this phenomenon remains unclear because this area receives a lower dose of radiation than the prostate urethra (6,215,217,220,221). The median stenosis length is between 1 and 3.5 cm (215,222-224).

The most important risk factor for developing urethral stricture is total radiation dose (202,218,220,225). Therefore, the combination of brachytherapy and external beam radiation therapy significantly increases the incidence of stenosis (217,218,226). Other risk factors include previous transurethral resection of the prostate, patient's age and comorbidities such as hypertension and

diabetes (221,225-228).

Pathophysiology

The processes leading to the development of urethral stricture are the same as in radiation cystitis and ureteral stricture. Endarteritis develops, followed by hypoxia and tissue necrosis, and collagen deposition stimulation. As a result, atrophy, contraction and fibrosis occur, which causes urethral stenosis (12,217,229).

Clinical presentation

The main complaints of urethral stricture are lower urinary tract symptoms, both irritant and obstructive. Other symptoms include recurrent urinary tract infections, haematuria, and bladder stones. They worsen the patient's quality of life and, if left untreated, can lead to damage to the upper urinary tract (215,217,230-232).

Diagnosis

Diagnostics include anamnesis, physical examination, laboratory tests such as estimation of kidney function, urinalysis and urine culture. In the differentiation with local tumour recurrence, serum prostate-specific antigen level assessment is used. Urodynamic examination allows the measurement of urinary bladder capacity and postvoid residual urine volume. Radiological studies such as retrograde urethrography and voiding cystourethrography are recommended to delineate the length, location, severity and complexity of the stenosis. The next stage of diagnostics

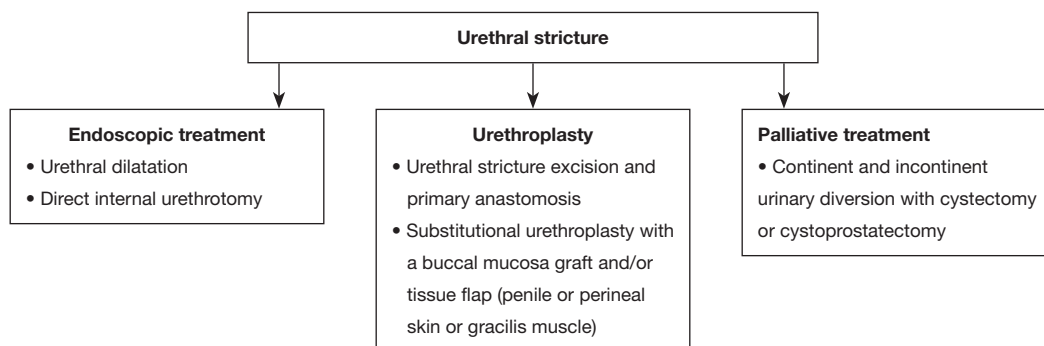


Figure 3 Management of urethral stricture.

is urethrocytoscopy, which, in addition to visualizing the location of the stenosis, allows to assess the function of the external sphincter.

Management

Treatment of urethral stricture is difficult and associated with a high risk of complications and recurrences, which is caused by impaired healing of ischemic and fibrotic tissues and the close proximity of the sphincter. Management methods include endoscopic techniques, open surgery and palliative procedures. The choice of treatment depends on the patient's general condition, features of stenosis, sphincter and bladder function, and patient preferences (Figure 3) (6,9,75,215,218,233,234).

Endoscopic treatment such as urethral dilatation and direct internal urethrotomy are minimally invasive but are associated with a high (over 50%) risk of recurrence (19,191,215,221,235). Repetition of procedures leads to lengthening of the stenosis, exacerbation of periurethral fibrosis, delaying and complicating subsequent urethroplasty (236). Therefore, the method is recommended for patients who are unable or unwilling to undergo surgery (6,219,237-239).

Urethroplasty is the basis of surgical treatment. Urethral stricture excision and primary anastomosis is the treatment of choice for short stenoses (less than 2–3 cm), and the rate of effectiveness is 70–97% (215,219,222,223,230,233,240-243). For longer stenoses, substitutional urethroplasty with a buccal mucosa graft and/or tissue flap (penile or perineal skin or gracilis muscle) is used (215,219,240). The effectiveness of the procedure is 70–83% (222,224,230,241,244). Both procedures are associated with a risk of urinary incontinence, which occurs in 7–40%

of patients after excision and primary anastomosis, and in 10.5–44% after urethroplasty using a buccal mucosa graft (6,222-224,230,242,245). In this case, artificial sphincter implantation is used (215,224,230,244).

Palliative methods are reserved for patients who, due to their general condition, do not qualify for surgery or whose repeated attempts to repair the stenosis have been unsuccessful. The management includes continent and incontinent urinary diversion with cystectomy or cystoprostatectomy (6,19,159,215,219,233,238,246).

Secondary primary cancer

Radiation-induced second primary tumours are a rare and late adverse event that occurs after a long latency period (more than 5 years after radiotherapy) in regions exposed to radiation. They have a different histological type from the primary tumour and are neither a recurrence nor a metastasis (247-252). Carcinogenesis is caused by the accumulation of mutagenic genetic changes caused by radiation (12,249).

The risk of developing secondary primary tumours after irradiation of pelvic malignancies is slightly higher (250,253-261). Some studies have reported an increased risk of developing bladder cancer (253,254,256,260-265). For the treatment of prostate cancer and rectal cancer, the results are inconclusive (255,266-271).

An interesting relationship that has been observed is a reduction in the risk of developing prostate cancer in patients undergoing radiotherapy for rectal cancer (254,255,266,267,272,273). Probably the simultaneous irradiation of the prostate can prevent or delay the development of prostate cancer (255,266,272). In addition, the dissipated dose of radiation for the testicles can lead to

a decrease in testosterone, which limits the development of prostate tumour (274,275).

However, due to the described risk of developing secondary cancers, even after 40 years from the end of treatment, long-term follow-up of patients undergoing radiation therapy is important (253).

Conclusions

In conclusion, radiotherapy is one of the main methods of treating patients suffering from cancer. Despite its high effectiveness, it causes damage to adjacent healthy tissues, which is associated with the development of complications. Due to the pelvic anatomy, irradiation of gastrointestinal and genitourinary cancers is often associated with side effects from the urinary tract. Adverse events significantly degrade the patient's quality of life, and in severe cases can be life threatening to the patient. Because of impaired tissue healing, the treatment of radiation urological complications is a challenge for urologists and often requires complicated reconstruction techniques. Maintaining renal function and improving the patient's quality of life are the main therapeutic goals. Unfortunately, there are currently no general recommendations and the available treatment methods are associated with a high percentage of relapses and complications. Therefore, further high-quality research is needed to better understand the pathophysiology of tissue radiation damage, to discover and evaluate the effectiveness of new therapeutic options. This will allow for the development of an effective therapeutic path and international recommendations.

Due to the continuous increase in the effectiveness of cancer treatments and the extension of patients' lives, complications of radiation therapy are becoming an increasingly important clinical problem. The time from the end of treatment to the appearance of adverse events may be up to several years, so monitoring and early detection are important. Observation after oncological treatment allows not only to detect recurrence of the neoplastic disease, but also to diagnose complications related to the treatment method, including radiotherapy. During regular follow-up visits with the help of laboratory tests (serum and urine tests), imaging and endoscopic examinations, it is possible to monitor and early detect radiation complications. Due to the fact that urological complications of radiotherapy also complicate non-urological pelvic cancers, these patients should be

considered for regular urological care.

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Footnote

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