Reports of Practical Oncology and Radiotherapy 25 (2020) 619–624

Available online at www.sciencedirect.com

Reports of Practical Oncology and Radiotherapy

journal homepage: http://www.elsevier.com/locate/rpor

Review

Prostatic irradiation-induced sexual dysfunction: A review and multidisciplinary guide to management in the radical radiotherapy era (Part II on Urological Management)

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ARTICLE INFO

Article history:
Received 27 October 2019
Received in revised form 27 January 2020
Accepted 16 March 2020
Available online 6 May 2020

Keywords:
Prostate cancer
Erectile dysfunction
Ejaculatory dysfunction
Orgasmic dysfunction
Radiation therapy
Sexual Toxicities
PDE-5i
Vacuum erection device
Intracavernosal Injections
Penile Vibratory stimulation
Penile prosthesis

ABSTRACT

Prostate cancer is the most common malignancy in men and the second leading cause of cancer-related death in men. Radiotherapy is a curative option that is administered via external beam radiation, brachytherapy, or in combination. Sexual dysfunction is a common toxicity following radiotherapy, similar to men undergoing radical prostatectomy, but the etiology is different. The pathophysiology of radiation-induced sexual dysfunction is multi-factorial, and the toxicity is a major cause of impaired quality of life among long-term prostate cancer survivors. Management of a patient's sexual function during and after radiotherapy requires multidisciplinary coordination of care between radiation oncology, urology, psychiatry, pharmacy, and dermatology. This review provides a framework for clinicians to better understand prostatic radiotherapy-induced sexual dysfunction diagnosis, evaluation, and a patient-centered approach to toxicity preventive strategies and management.

1. Background

All methods to treat localized prostate cancer with a curative intent have different types and degrees of side effects. Quality of life after individual therapeutic modalities becomes a very important criterion for choosing a method of treatment. Sexual toxicities are common regardless of RT modality employed and increase during each year of follow-up. For example, reported erectile dysfunction (ED) rates increase with time from treatment, with 4% ED rates at one month to 47% at 60 months post-therapy.[1] Another study by Donovan et al. reviewing patient-reported outcomes among 1643 men participating in the Prostate Testing for Cancer and Treatment (ProtecT) randomized controlled trial revealed that radiotherapy negatively effects sexual function peaking at 6 months, followed by some recovery, then stability of a newly established sexual functional status (while maintaining superior preservation of sexual function compared with radical prostatectomy at all time points).[2]

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https://doi.org/10.1016/j.rpor.2020.03.011
1507-1367/

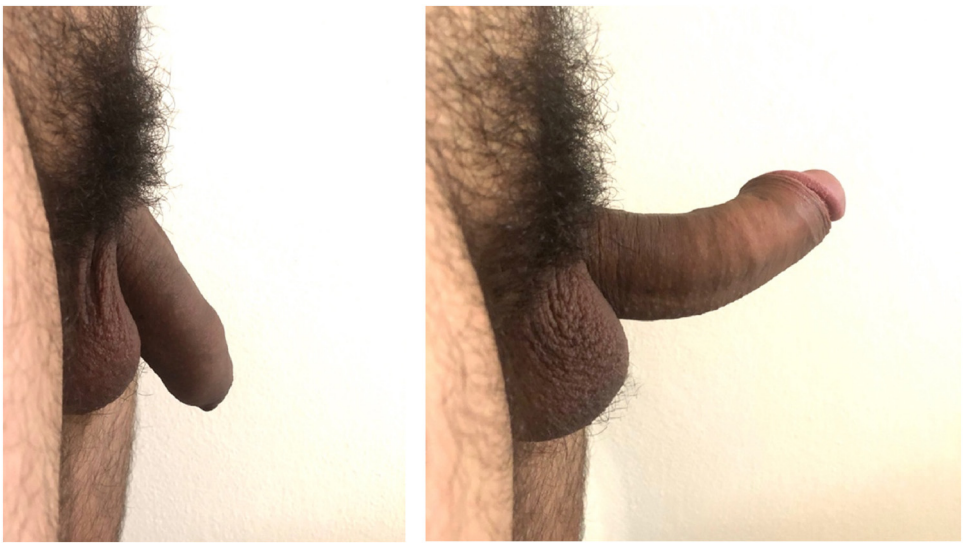

Fig. 1. A,B: A. Is a photograph of an flaccid penis. B. Is a photograph of an erect penis with dorsal curvature caused by localized fibrosis of the tunica albuginea (i.e., Peyronie's disease). Peyronie's disease is characterized by varying degrees of penile deformity (e.g., nodule/plaque, indentation, curvature, shortening, hourglass narrowing) that can result in pain, erectile dysfunction and/or prevent penetrative intercourse. Peyronie's disease, particularly for patients with extreme morphological manifestations, is a psychologically and physically debilitating disorder that is important to identify during a baseline physical examination prior to initiating radiotherapy. While fibrotic nodules and or plaques may be palpable during the flaccid state (A), penile deformities are best visualized while the penis is erect (B).

In Part I of this review series, we emphasized the importance of understanding the natural evolution of sexual toxicities as they are related to prostate irradiation is critical in optimizing management of these toxicities.[60] Herein, we aim to review the management of radiation-induced sexual toxicities improving patient quality of life (QoL) during and after radical radiotherapy of prostate cancer (PCa).

2. Patient evaluation and work-up

Convenient scales for use in the radiotherapeutic practice include the International Index of Erectile Function (IIEF); The Sexual Health Inventory for Men (SHIM), and the Brief Male Sexual Function Inventory (BMSFI).[3–5] These scales were used extensively in the cited studies; however, the BMSFI has fallen out of favor and is not frequently utilized in current clinical trials. Brief symptom scales or questionnaires are available as clinical aids to establish baseline symptoms. Approximately 37-63% of patients have pre-existing comorbidities impacting their sexual function, such as benign prostate hyperplasia/lower urinary tract symptoms (LUTS), hypertension and diabetes. Patients with poor baseline sexual function are at a greater risk for developing worsening sexual dysfunction after irradiation.[6,7] However, the majority of patients with adequate baseline sexual function are expected to retain their function after prostate irradiation. A retrospective analysis of 427 men with the baseline ability to achieve an erection adequate for penetration demonstrated that 74% maintained their baseline erectile function after receiving dose-escalated prostatic irradiation to 86.4 Gy.[8] Interestingly, close to 60% of these patients received neoadjuvant and concurrent androgen deprivation therapy, but on multivariate analysis, only age greater than 65 years ($p < 0.001$, HR = 2.3) and acute GU toxicity ($p < 0.001$, HR = 1.64) were significant predictors of sexual function loss.

2.1. Proper physical examination for sexual medicine

Physical examination of patients with sexual dysfunction should begin with a biref examination of their body habitus and secondary sex characteristics. A brief neurological evaluation of sensation in the lower extremities and deep tendon reflexes should be carried out. A musculoskeletal exam should follow with a focus on eliciting point tenderness or pain to palpation along the vertebral column, particularly in the lumbar-sacral regions, to assess for sciatica or potential PCa extension and/or metastasis. Its important to remember that musculoskeletal pain can lead to avoidance behaviors or phobias, which can manifest clinically as sexual dysfunction.

The patient should be asked to undress from the waist downwards and to cover themselves with a provided examination drape. Testicular size and consistency should be examined for signs of hypogonadism. Penile anatomy should be examined for lesions of the shaft of the penis, suggestive of Peyronie's disease [Fig. 1A,B]. Perineal and penile (glans and shaft) vibratory sensation can be evaluated with a biothesiometer; results should be compared to an age-adjusted nomogram to establish sensory function at baseline and during follow-up assessments. The bulbocavernosus reflex and sphincter tone can then be assessed upon rectal examination. Digital rectal examination should then evaluate the prostate for size, consistency, nodularity, or pain.

3. Medical management

3.1. Phosphodiesterase type 5 inhibitors

Phosphodiesterase type 5 inhibitors (PDE-5i) comprise the first line of treatment for men with ED. Inactivation of PDE-5 maximizes intracellular cGMP, which relaxes smooth muscle, increases blood flow, and helps to obtain and maintain erections. These medications are taken 'on-demand', 30−60 min prior to sexual activity. Tadalafil has a daily dosing option due to a relatively longer half-life of about 18 h, remaining effective up to 36 h after use.[9,10] Tadalafil is also less affected by food and alcohol consumption, comparable to earlier generation PDE-5i. Avanafil (Stendra) is more novel PDE-5i with a more rapid onset of action, and can be taken 15 min prior to sexual activity.

Side effects of PDE-5 include headaches, flushing, visual changes, dyspepsia and myalgias. Additionally, men with extensive cardiac comorbidities must be aware of the contraindication of concomitant use with nitrates. PDE-5i are generally well tolerated, effective, and easy to use, making them excellent first line options.

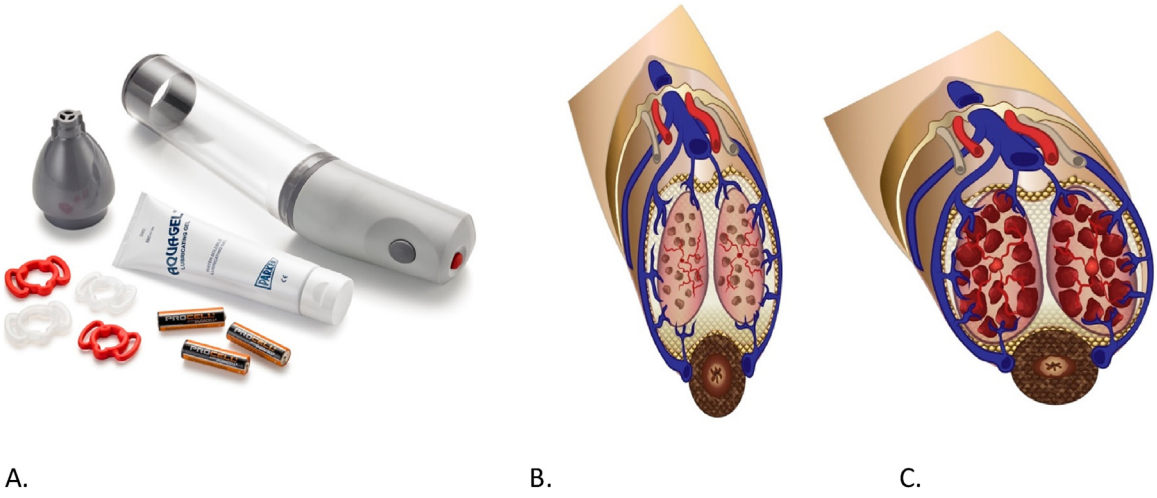

Fig. 2. A–C: A. Is a photograph of a medical grade vacuum device from Gesiva Medical [medical grade vacuum devices comply with the FDA's requirements which include pressure limiters and bio-compatibility testing of core components in order to ensure patient safety]. Medical grade vacuum devices include a vacuum pump (typically housed in the pump handle), a clear plastic cylinder so that the patient can visualize the penis, tension rings and lubricant. Lubricant is used to create a seal between the body and the vacuum device. Tension rings are used to maintain the erection for intercourse. B. Is a flaccid penis prior to use of the vacuum erectile device. C. Is an erect penis after use of the vacuum device.

Multiple animal studies demonstrate that PDE-5i's can have protective effects against ischemia and reperfusion injury in the heart and kidneys.[11] There is also evidence that a single dose can increase erythrocyte superoxide dismutase (SOD), theoretically decreasing superoxide free radicals that contribute to atherosclerosis formation in tumescence-associated vasculature.[12] While the evidence for clinical usage of PDE-5i during radiotherapy for protective effects is minimal, multiple open-label, non-randomized trials have demonstrated improved erectile function in 70–91% of men with varying degrees of ED after external beam radiotherapy (EBRT) or interstitial very low dose radiation (VLDR) brachytherapy.[13–17]

There have been two major studies that have investigated the efficacy of daily sildenafil on mitigating sexual toxicities associated to radiotherapy; both trials found similar results. In a randomized double-blind study,[27] men undergoing prostate irradiation were randomized to daily sildenafil or placebo. Using the IIEF measure of erectile function, the sildenafil group showed significantly better scores at 4 weeks and 6 months, but no difference at 2 years.[18] The largest randomized trial to date entailed 279 men randomized to either sildenafil 50 mg daily or placebo. The intervention was started 3 days prior to radiotherapy and continued for 6 months. Using the IIEF, significantly more men reported 'no/mild' ED in the treatment group at 12 months (73% versus 50%). However, at 24 months there was no difference in ED, but the treatment group still reported higher satisfaction scores; possibly related to the significantly lower incidence of acute sexual dysfunction in this group.[19] Collectively, these results suggest that PDE-5i use during radiotherapy can mitigate acute sexual toxicities.

RTOG 0831 randomized 242 men to 5 mg of daily tadalafil versus placebo during radiotherapy and continued for 24 weeks thereafter. Radiation included both EBRT (63%) and brachytherapy (37%). At 30 weeks and 1-year follow-up, there was no difference noted in erectile function.[20] A criticism of this trial was that the dose of tadalafil was low (i.e., 5 mg) and perhaps insufficient to mitigate acute sexual toxicities. Further, the duration of the trial did not extend into the period where post radiation tissue remodeling occurs towards the development of late sexual toxicities (e.g., fibrotic and atherosclerotic changes). The efficacy of 20 mg therapeutic doses in the radiotherapy setting has not been evaluated.

A randomized, controlled, cross-over study of 43 men evaluated the efficacy of sildenafil after completion adjuvant to radiation therapy. Patients were randomized to attempt sexual activity four times with either sildenafil or placebo, and then switched intervention for another four attempts. IIEF scores were significantly higher when the men were using sildenafil.[21]

3.2. Vacuum erection device

In standard urological practice, medical devices are prescribed to men with refractory ED following PDE-5i monotherapy, or to enhance the erection produced with PDE-5i. Vacuum erection devices (VED) mechanically engorge the corpora and glans with venous blood to produce an erection that is independent of autonomic or sensory neuronal control (that may be compromised to varying degrees with irradiation) [Fig. 2A–C]. The device consists of a clear plastic cylinder with a vacuum seal that is placed around the penile base. A manual or electric pump then produces a negative pressure within the cylinder to pull blood into the phallus.[22] If the patient is unable to maintain the erection after VED-induced erection, an elastic constriction ring may be placed at the base of the penis for up to 30 min to maintain the erection throughout sexual intercourse. Erectile efficacy rates (sufficient for intercourse) using VEDs are as high as 90%, but reported satisfaction ranges from 30 to 70%.[23,24] Notably, drop out rates in this studies are not negligible. Many men report that the devices are cumbersome and the constriction band is uncomfortable, limiting spontaneity. Therefore, VEDs are a good option for patients that have received device education and demonstrate an interest in incorporating the VED in their sexual life.

VEDs have been used for penile rehabilitation after radical prostatectomy, where patients are more likely to develop immediate ED following treatment.[25,26] There are few studies examining VED use during or following radiation therapy. One report indicated that radiotherapy patients were less likely to use a VED compared to patients who had undergone prostatectomy.[27] It is unclear whether this finding is related to decreased need for device usage following radiotherapy in comparison to prostatectomy or decreased knowledge of the device by radiation oncologists.

A recent meta-analysis demonstrated some potential benefit of VEDs during prostatic irradiation.[28] Maintenance of erection requires neurovascular cavernosal reactivity and venous occlusion. Given the inhibition of the pudendo-cavernosal reflex loop during and following radiotherapy, VEDs may be a good option to achieve vascular engorgement and to maintain vascular and ejac-

ulatory ductal patency. Regular erections, even in the absence of intercourse, can help to preserve vascular patency in the cavernosa during periods of psychogenic or iatrogenic impotency. VEDs can enhance the efficacy of PDE-5i by bypassing the need for internal/external stimuli during states of acute neurotoxicity when the neuronal action potentials along autonomic and sensory nerves innervating the penis are diminished.[29,30]

3.3. Intracavernosal injections

Intracavernosal injection (ICI) therapy is an alternative or adjunct to VED use. Patients are provided education and self-injection training prior to home use by a urologist, radiation oncologist, or other trained healthcare professional. Currently available ICI pharmacotherapies include alprostadil, papaverine, and phentolamine. Alprostadil can be administered alone and comes in pre-packaged injector kits (Edex or Caverject). Alprostadil monotherapy injections are metabolized within 60 min. At doses of 10–20 mcg, 70% of patients achieve full erections. Combination formulations with two (e.g. bimix) or three (e.g. trimix) agents offer synergistic effects, with efficacy rates of 80–90%.[31,32] The most common adverse events include injection anxiety (65%), pain at the injection site (11%), hematoma (1.5%), priapism (1–5%).[33,34] Injection anxiety appears to be related to anticipation of injection pain; injection anxiety decreases significantly with the use of ICI from 65% at first injection to 42% at 4 months ($P = 0.003$).[34] Slow dose titration decreases the risk of priapism. Penile pain is a common complaint of alprostadil, which is directly related to the administered dose and is, unfortunately, not mitigated with other agents. Combination formulations can also reduce the discomfort associated with alprostadil if the actual dose of alprostadil is descreased.

3.4. Penile vibratory stimulation

Both anejaculation and anorgasmia/delayed orgasm in the post-irradiation setting are likely affected by diminished efferent nerve responses. There is a paucity of scientific data on post-radiation treatment management for anorgasmia. With the likely cause being reduced activation of reflexes involved in erections and ejaculations, vibratory stimulation devices may be a reasonable option to increase sensation towards reflex activation and orgasm. While there is limited data the use of vibratory stimulation can be a consideration for a man with anorgasmia and could be considered as a future avenue of study. It has been studied in spinal cord injury patients and that data does support the strategy.

Pacinian corpuscles are found in deep and subcutaneous tissues of the penis; vibratory stimulation activates these corpuscles that are buried in the ridges of deep rugae that would otherwise be inaccessible without an erection.[35] Vibratory stimulation of the dorsal and perineal nerve endings (i.e., dorsal and ventral application) appears to have an additive effect on thalamic stimulation. Dorsal nerve afferents can be activated by autonomic visceral pelvic nerve stimulation.[35] Brindley et al. demonstrated that ejaculation could be achieved in men with a completely absent glandi-pudendal reflex via electroejaculation or penile vibratory stimulation.[36] A meta-analysis of 653 trials including 211 men with spinal cord injury treated with penile vibratory stimulation showed that high amplitude vibrations resulted in significantly more ejaculations. All men with an immediate response to this treatment modality had successful ejaculations with vibratory stimuli that were consistent and reproducible 100% of the time, and within 2 min of stimulation.[37] In refractory cases, a retrospective study showed that the use of two vibrators to sandwich the glans penis increased therapeutic efficacy in up to 22% of cases.[38] Warm temperatures (35–45 °C) have independently been shown to increase mechanoreceptor sensitivity; warmth may increase the efficacy of vibratory stimulation.

There are experimental treatment options available as well. Transcutaneous electromyostimulation of the corpus cavernosal smooth muscles is modestly effective in restoring function after cavernosal nerve damage.[39] However, this data has yet to be corroborated in a well-designed clinical trial setting.

3.5. Radiation mitigators

Radiation-induced sexual dysfunction is a late normal tissue radiation toxicity that results from ongoing changes associated with persistent mitotic cell death and regional pro-inflammatory cytokine cascades causing vascular damage, nerve damage, and excessive fibrotic deposition in the extracellular matrix. Radiation mitigators dampen the inflammatory cascade, which reduces toxicity.[40] Transforming growth factor-β has been implicated in the development of radiation-induced fibrosis. Receptor inhibition with antibodies and small molecules has shown prevention or inhibition of radiation-induced fibrosis in preclinical animal models.[41–43] Transforming growth factor-β also plays an important role in tumor survival,[44] therefore further studies are needed to elucidate the optimal timing for TGF-β inhibition so as not to compromise cancer control and efficacy of the radiation treatment.

4. Surgical management

4.1. Penile prosthesis surgery

Penile prostheses, first described in the 1970s, are excellent options for men who have failed or are not interested in the previously discussed options.[45] Prostheses fall into two categories: semi-rigid and inflatable devices. Semi-rigid devices contain two flexible rods placed within the corpora that can be manipulated by the user; directed upwards for intercourse and downwards when not in use. Inflatable devices involve two collapsible cylinders placed within the corpora that are inflated using a pump within the scrotum. Regardless of the type of device implanted, it is important to discuss patient expectations, in regards to penile length, girth and rigidity. Generally, pre-operative demonstration of stretched penile length is a common marker used to predict post-operative penile length. Counseling patients regarding outcomes in the pre-operative setting is associated with higher satisfaction rates.[46,47]

4.2. Semi-rigid prosthesis

A semi-rigid penile prosthesis offers the most straighforard surgical technique for men with erectile dysfunction. Although they remain the most commonly used penile implant worldwide, only 1/10 of implants used in the US are malleable.[48] Implantation is performed most commonly through a peno-scrotal incision, but may be implanted subcoronally or infrapubically. The corporal bodies are isolated and intra-operative measurements are obtained to determine the appropriate cylinder size. Patients may have developed radiotherapy-induced corporal fibrotic changes necessitating dilation and/or secondary incisions to properly place the device. A prosthesis that is too long risks glandular erosion and chronic pain, while a prosthesis that is too short will provide inadequate glandular support making penetration difficult.

4.3. Inflatable penile prosthesis

Inflatable devices are now favored over the semi-rigid devices as they better simulate natural function, allowing length and girth expansion with inflation, as well as flaccidity when desired.[49] The three-piece penile prosthesis or inflatable penile prosthesis (IPP) is

the most common implant in the United States, accounting for up to 90% of all implants.[50]

The AMS/Boston Scientific and Coloplast are the two major manufacturers of penile implants in the United States. The device contains two corporal cylinders, a fluid reservoir, and a pump that resides in the scrotum. The device is operated by squeezing the scrotal pump which cycles saline from the fluid reservoir to the corporal cylinders to increase rigidity until an erection is attained. The user can deflate his prosthesis with a release valve located on the scrotal pump to cycle fluid back to the fluid reservoir and return to a flaccid state.

Inflatable penile implants are very durable with mechanical failure rates of 5% and 30% at 5 and 15 years, respectively.[51] AMS devices are manufactured with an antibiotic coating while Coloplast devices have a hydrophilic bioflex material, which allows device coating of surgeon tailored antibiotic solution. Since the advent of antibiotic coated penile implants, post-operative infection rates have declined significantly to <1%[52,53] with infection and complication rates not influenced by a history of RT.[54] Patients are typically cleared for sexual activity four-six weeks after surgery. Among all treatments for ED, the inflatable penile prosthesis has the highest patient satisfaction,[55] with series reporting 92–100% in patients, and 91–95% satisfaction in female partners[56,57,58] Thus, the IPP is often considered the gold standard in penile prosthesis surgery.

A less commonly used inflatable option is the 2-piece prosthetic. It does not have a reservoir and can be utilized more safely in patients with significant pelvic surgery. The only model available in the United States is the AMS Ambicor 2-piece. Fluid is cycled from a contained-reservoir within the proximal portions of the cylinders. A similar pump to the IPP facilitates transfer of fluid into the inflatable distal section of the cylinders to promote rigidity during erection. Deflation is accomplished by bending the cylinders for approximately 10 s.[59] Currently, 5% of all IPPs are 2-piece devices, which are primarily used for men who are poor candidates for 3-piece devices.[50]

5. Conclusions

PCa is a curable disease; with an increasing survivor population, the secondary goal in PCa management should be to maximize the patient's QoL.

ED is a very commonly addressed problem with good treatments available ranging from oral medications to more advanced treatments such as injection, vacuum erection devices, or penile implants. All have very high success rates in the appropriately selected patient.

Ejaculatory and orgasmic dysfunction are more difficult to manage. Dry ejaculation is caused by scarring of the ejaculatory ducts themselves after radiation, making it more difficult to treat. However, pre-treatment counseling, preventive sexual medicine (e.g., VEDs, PDE5is, vibratory stimulators) and post-treatment referrals to mental health specialists may help to improve understanding, compliance with penile rehabilitation, and lessen adverse impacts on QoL.

Orgasm can also be negatively affected due to peripheral nerve damage or androgen deprivation. Medicines can be partially effective for improving orgasm sensation as can alternative therapies such as vibratory stimulation. Ultimately, more research needs to be performed on ejaculatory and orgasmic function after prostatic on the effects of radiotherapy on ejaculatory and orgasmic in order to improve counseling and optimize management of said sexual toxicities. Collaboration between radiation urologists, local sexual health experts and mental health experts can be an option to improve men's sexual care during and after radiation and to open research opportunities going forward.

Conflict of interest

None declared.

Financial disclosure

Figure 2 was funded by BioFort[SM]

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