

# Erectile Dysfunction Following Radical Prostatectomy

Arthur L. Burnett, MD

## CASE PRESENTATION

**DR BURNETT:** Mr G is a previously healthy 51-year-old man who works as a health program administrator. During a prostate health screening, he was found to have a prostate-specific antigen (PSA) level of 4.2 ng/mL (normal range: 0.0-4.0 ng/mL). On digital rectal examination, the prostate was of average size and without nodules or masses. A urological consultation was recommended.

Mr G underwent a transrectal ultrasound-guided biopsy of the prostate gland. There were no sonographic abnormalities, but the 12-core biopsy established the diagnosis of adenocarcinoma, with a Gleason score of 6 (see TABLE 1 for explanation of Gleason score).<sup>1,2</sup> The cancer involved 80% of a single core from the right base region of the prostate. Because Mr G was judged to have a low risk for metastatic disease, further imaging studies were not indicated. He was counseled regarding management options for his diagnosis of clinically localized prostate cancer.

I saw Mr G for the first time about 5 weeks later for a second opinion. His vital signs were within normal limits. In fact, he appeared quite fit, with a body mass index of 24 ( $\leq 25$  consistent with healthy weight). He stated that he experienced no urinary complaints and his erectile function was fully intact, as evidenced by a score of 25 (range: 0-25) on the Sexual Health Inventory for Men (SHIM).<sup>3</sup> He had never

Erectile dysfunction following radical prostatectomy for clinically localized prostate cancer is a known potential complication of the surgery. Because prostate cancer is diagnosed today more frequently than in the past and because the diagnosis is made in increasingly younger men, there is an urgent need to develop effective interventions that preserve erectile function after surgery. In this presentation, a 51-year-old man with adenocarcinoma of the prostate underwent a bilateral nerve-sparing radical prostatectomy, after which he lost natural erectile function for approximately 9 months. The case highlights the fact that following surgery in which the nerve-sparing radical prostatectomy technique is used, between 60% to 85% of men eventually recover erectile function. This constitutes a dramatic improvement over an earlier era, when postprostatectomy erectile dysfunction was the nearly universal rule. The case also emphasizes that despite expert application of the nerve-sparing prostatectomy technique, early recovery of natural erectile function is uncommon. Many patients experience erectile dysfunction for as long as 2 years after the procedure, requiring the use of erectile aids for sexual activity during this period until natural erections recover. Corrective, cause-specific advances such as neuromodulatory therapy offer valuable adjuncts to this surgery.

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used cigarettes. He was taking nutritional supplements that included saw palmetto, fish oil, and various vitamins. To his knowledge, no one in his family had ever been diagnosed with prostate cancer. We reviewed his clinical presentation and workup, which was consistent with an early stage prostate cancer of intermediate grade. We next discussed applicable management options, including surveillance (watchful waiting); radical prostatectomy; radiation therapy administered by external beam and/or interstitial implants; and cryotherapy (freezing the prostate). We reviewed the advantages and disadvantages of each option.

**DR BURNETT:** Mr G, could you please tell us about your reaction to your di-

agnosis and how you arrived at a decision about your treatment?

**MR G:** I was stunned when first told that I had cancer. I never, ever expected that diagnosis. I thought I was in great physical shape, doing all the right things to live a long, happy life. Before meeting Dr Burnett, I had actually done a considerable amount of study about prostate cancer. I had explored the different

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treatment options and felt certain I should have my prostate removed. Surgery seemed to offer the best chance for a cure, and since I am a young man, I favored a treatment that would give me the best chance for living a lot longer. But the notion that I might lose erectile function was still devastating. Fortunately, my wife was very supportive. I'm not sure how I would have moved forward without her. I recall her saying: "I don't have a relationship with your penis. I have a relationship with you."

**DR BURNETT:** Mr G opted for radical prostatectomy, which was performed successfully 1 year ago. We used a bilateral cavernous nerve-sparing technique at surgery to maximize his likelihood of erection preservation. The final pathology confirmed the presence of organ-confined prostate cancer with negative surgical margins, pelvic lymph nodes, and seminal vesicles, consistent with disease eradication. No adjuvant therapy was indicated. Serial PSA measurements every 3 months since surgery confirmed undetectable levels.

**DR BURNETT:** Mr G, how did you fare with your recovery?

**MR G:** I did great with the surgery. I was back at work within a few weeks. I was continent of urine in 1 month and 27 days! (I am told that this is rather quick for the recovery of continence.) But I was concerned by my lack of erections. I know Dr Burnett explained that erection recovery could take as much as 2 years, but I felt the pressure. The pressure was not from my wife; I had my own pressure as a man. I was the one who really wanted something to be done and done quickly. Most men are that way. By 6 months after the surgery, nothing much was going on. I wanted to know what was happening. I talked to Dr Burnett about the various treatment options. I considered Viagra, but it only helps reliably with at least partial erections to build on, which was not the case for me yet. I decided to begin penile injection therapy. It worked for me, and I knew it wouldn't interfere with my own erections coming back. After 9 months and 16 days, I finally could get an erection

on my own! It is a wonderful thing. (His 12-month postoperative SHIM score was 18.)

**DISCUSSION**

Mr G's case illustrates several key concepts in the current management of prostate cancer. Among solid-organ malignancies, prostate cancer is the most commonly diagnosed tumor and the second-leading cause of cancer-related deaths among men in the United States.<sup>4</sup> Mr G's presentation typifies some of the common dilemmas facing many patients diagnosed today with this disease. Our improved diagnostic capabilities have led to the fact that many prostate cancer patients receive their diagnoses at relatively young ages. In considering the impact of the various treatment approaches on their quality of life, many patients place paramount importance on the possibility of retaining natural erectile function.<sup>5</sup> This matter is frequently important to young men who by age status are more likely to have intact erectile function than older men; however, for all men having normal preoperative erectile function irrespective of age, preservation of this function is understandably important postoperatively.

Although radical prostatectomy has been referred to as the gold standard for definitive cure of early stage prostate cancer, this option has been challenged frequently in recent years, principally over questions related to the degree of functional recovery in many areas. Historically, radical prostatectomy has carried high risks of postoperative complications, including decreased physical capacity for as much as a year after surgery, long-term urinary incontinence in the majority of patients, and permanent erectile dysfunction in almost all men undergoing this procedure. Following a series of anatomical discoveries of the prostate and its surrounding structures about 2 decades ago, changes in the surgical approach permitted the procedure to be performed with significantly improved outcomes.<sup>6</sup> Now after the surgery, expectations are that physical capacity is fully recovered in most patients within

**Table 1.** Explanation of the Gleason Score\*

Aggressiveness Level	Biopsy Incidence, %
Low	2
Gleason 2 (1 + 1)	
Gleason 3 (1 + 2)	
Gleason 4 (2 + 2)	
Intermediate	70
Gleason 5 (2 + 3 - 3 + 2)	
Gleason 6 (3 + 3)	
Intermediate-High	20
Gleason 7 (3 + 4)	
Gleason 7 (4 + 3)	
High	8
Gleason 8 (4 + 4)	
Gleason 9 (4 + 5 - 5 + 4)	
Gleason 10 (5 + 5)	

\*The pathological patterns of prostate cancer range from 1 (almost normal-looking) to 5 (very poorly differentiated). The Gleason system of evaluating prostate cancer is based on this range with grades termed for these 5 specific patterns of cancer-cell architecture. The score refers to the addition of the numbers of the first and second most common patterns. Note that the grouping for "intermediate-high" aggressiveness includes 2 biologically distinct tumors for Gleason 7, with score 4 + 3 = 7 behaving more aggressively than score 3 + 4 = 7.<sup>1,2</sup>

several weeks, return of urinary continence is achieved by more than 95% of patients within a few months, and erection recovery with ability to engage in sexual intercourse is regained by most patients with or without oral phosphodiesterase type 5 (PDE 5) inhibitors within 2 years.<sup>7</sup> It is acknowledged that these expectations reflect results achieved at major academic centers, which may not be representative of the patterns of care experienced by most men treated for localized prostate cancer in the United States.

Regardless of clinical practice setting, the reality of the recovery process after radical prostatectomy today, nonetheless, is that erectile function recovery lags behind other functional recovery in other areas. Patients are understandably concerned about this issue and, following months of erectile dysfunction, become skeptical of reassurances that their potency will return. Current clinical surveys show that among patients eventually recovering erectile function, the quality of erections is frequently inferior to that of those achieved preoperatively.<sup>8</sup> Thus, in addition to whether erections will return after radical prostatectomy, the timing and extent of postoperative erectile function are matters of profound importance to patients.

**Definition and Pathogenesis**

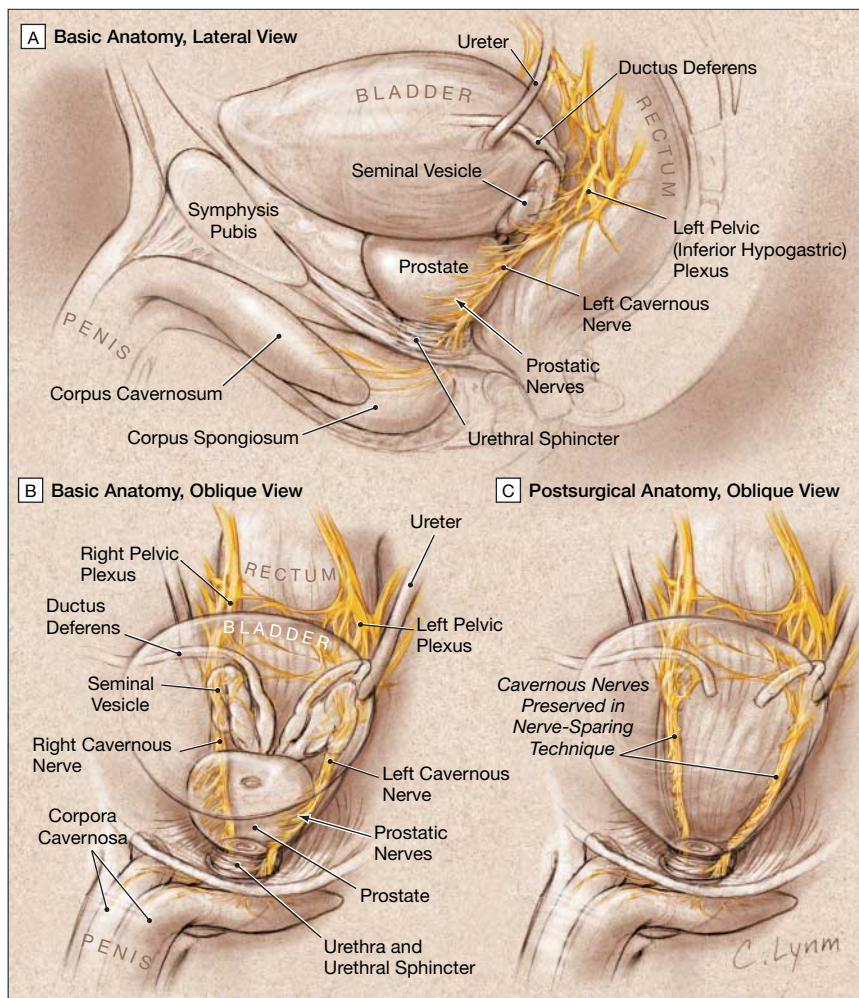
A landmark article by Walsh and Donker<sup>9</sup> in 1982 revealed that the common basis for erectile dysfunction following radical prostatectomy was the severance of the cavernous nerves. These nerves, which mediate autonomic neuroregulatory function, course along the lateral aspects of the prostate and rectum, providing innervation to the proximal penis in the deep pelvis (FIGURE).<sup>9</sup>

This discovery led to modifications of the surgical approach to radical prostatectomy whereby preservation of the cavernous nerves—the so-called nerve-sparing technique—offered many men opportunities to regain erectile function that would have been all but certainly eliminated without such modifications. Under certain circumstances, eg, the finding at surgery of local cancer spread, the nerve-sparing tech-

nique is contraindicated.<sup>10</sup> In the current era of nerve-sparing radical prostatectomy, the rates of erectile function recovery satisfactory for sexual intercourse following the surgery reported at major academic centers performed by highly experienced surgeons range between 60% and 85%, a dramatic improvement over the earlier era.<sup>7,8,11,12</sup> It is acknowledged that contemporary results outside of such centers may differ. For instance, a subset analysis from the cohort study of the Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE), representing 29 academic and community-based sites across the United States, indicated a 75% potency rate in men younger than 65 years after radical prostatectomy.<sup>13</sup> This same database affirmed that other demographic variables including race/ethnicity, education, and relationship status did not affect potency outcomes after the surgery, whereas household income greater than \$30 000 and fewer comorbidities were associated with return to baseline sexual function.<sup>13</sup>

Even when the nerve-sparing surgery is performed with immaculate technique, however, patients do not recover erectile function as quickly as they do urinary continence. In fact, the cavernous nerves are typically functionally inactive for as long as 2 years after surgery, even when nerve-sparing technique is used.<sup>7,8</sup> (In contrast, most men are again continent of urine within 6 months of the surgery.)<sup>7</sup> In a recent series by Walsh and colleagues among preoperatively potent men who underwent prostatectomy using the bilateral nerve-sparing technique, maximal erection recovery was not observed until a mean period of 18 months had elapsed following surgery.<sup>7</sup> A number of explanations have been proposed for this phenomenon of delayed recovery, including mechanically induced nerve stretching that may occur during prostate retraction, thermal damage to nerve tissue caused by electrocoagulative cautery during surgical dissection, ischemic injury to nerve tissue amid attempts to control surgical bleeding, and local inflammatory effects associated with

**Figure.** Schematic of the Cavernous Nerves and Their Preservation During Radical Prostatectomy



A, Lateral view of the male pelvis illustrating the course and distribution of the left cavernous nerve fiber, as part of the left neurovascular bundle within intrapelvic fascia coverings. The cavernous nerve travels from the pelvic plexus proximally to the penis distally, in close anatomical relationship to the seminal vesicle, prostate, striated urethral sphincter, bladder, and rectum. B, Anterosuperior oblique view of the same anatomical structures. C, Anterosuperior oblique view illustrating preservation of the cavernous nerves after bilateral nerve-sparing prostatectomy and bladder neck anastomosis to the urethral stump. The cavernous nerve fibers are preserved by division and clipping of small prostatic nerves alongside the prostate. When non-nerve-sparing surgery is required for cancer eradication either unilaterally or bilaterally, wide excision of periprostatic soft tissue includes the cavernous nerves en bloc with the removed surgical specimen.

surgical trauma.<sup>14</sup> Consistent with current neurobiological concepts of major axonal injury,<sup>15</sup> the injured cavernous nerve fibers undergo a process of Wallerian degeneration, with loss of normal nerve tissue connections to the corpora cavernosa and associated neuroregulatory functions. In addition, the neuropathy induces cavernosal tissue degeneration and atrophy.<sup>16</sup> These complications frequently lead to irretrievable loss of the veno-occlusive function necessary for penile rigidity.<sup>17,18</sup> The fact that erections are eventually recovered in many men who undergo nerve-sparing surgery further supports a neurogenic pathogenesis for the disorder, consistent with the biology of peripheral nerve recovery and regeneration after initial injury.

An issue of major interest is why all men do not achieve recovery when nerve sparing is performed. The most obvious determinant of postoperative erectile dysfunction is preoperative potency status. Some men may experience a decline in erectile function over time, as an age-dependent process.<sup>19</sup> Furthermore, postoperative erectile dysfunction is compounded in some patients by preexisting risk factors that include older age, comorbid disease states (eg, cardiovascular disease, diabetes mellitus), lifestyle factors (eg, cigarette smoking, physical inactivity), and the use of medications such as antihypertensive agents that have erectolytic effects.<sup>19</sup> The impact of these risk factors on patients' eventual outcomes has led to the acknowledgment that rating erection recovery potential after surgery should involve stratification according to relevant risk factors.<sup>8</sup>

#### **Radical Prostatectomy: Current Status**

In recent years, physicians caring for men with prostate cancer have focused on less-invasive prostate surgery. Consequently, in addition to open procedures via retropubic (abdominal) or perineal approaches, laparoscopic procedures with freehand or robotic instrumentation have been developed. Much debate but no consensus about the advantages and disadvantages of the dif-

ferent approaches exist; detailed review of these controversies is beyond the scope of this discussion. Nevertheless, an objective shared by all approaches to the nerve-sparing prostatectomy technique is to maximize the likelihood of erectile function recovery after the surgery. Meaningful determinations of success with different approaches in the future will rely on rigorously designed clinical trials, serial assessments over sufficient periods of time, the use of validated inventories and questionnaires of sexual activity, and the involvement of unbiased outcome assessors.<sup>14</sup>

Several surgical advances may also improve functional outcomes. Optical magnification and avoidance of tissue-destructive energy sources in the vicinity of the cavernous nerves during surgery are widely advocated.<sup>10</sup> Intraoperative nerve stimulation has also been explored with the idea that this technique may assist the surgeon in preserving the cavernous nerves and even predicting a patient's likelihood of erection recovery. The utility of nerve stimulation techniques, however, remains unproven.<sup>20</sup>

#### **Preservation of Erectile Function: Surgery vs Radiation**

With regard to erection preservation following treatment, a pertinent question is how radical prostatectomy compares with other interventions for clinically localized prostate cancer. The growing interest in pelvic radiation, including brachytherapy, as an alternative to surgery can be attributed in part to the supposition that surgery carries a higher risk of erectile dysfunction. Clearly, surgery is associated with an immediate, precipitous loss of erectile function that does not occur when radiation therapy is performed, although with surgery, recovery is possible in many with appropriately extended follow-up. Radiation therapy, by contrast, often results in a steady decline in erectile function to a hardly trivial degree over time.<sup>21-23</sup> As demonstrated recently by the Prostate Cancer Outcomes Study, a retrospective survey of community-based men di-

agnosed and treated without randomization to treatment options for prostate cancer in the mid-1990s, erectile dysfunction rates in radical prostatectomy and external beam radiation therapy groups were similarly considerable (79% and 63%, respectively) at 5 years postintervention.<sup>23</sup> However, whether and how well nerve-sparing surgery was performed remain unclear in this study, and the results may not be representative of the technique's highest level of performance. In another community-based study, which specified performance of nerve-sparing technique at radical prostatectomy, sexual function score was equivalent in men receiving this modification of the surgery and men having undergone pelvic radiation by 2-year follow-up.<sup>24</sup>

#### **Management of Erectile Dysfunction Complications**

Men undergoing radical prostatectomy assign major importance to their resumption of sexual activity postoperatively and are prepared to use erectile aids to be functional.<sup>25-27</sup> The current options, which include both pharmacological and nonpharmacological interventions, are summarized in TABLE 2.<sup>28</sup> Pharmacotherapies include the oral PDE 5 inhibitors (sildenafil, tadalafil, and vardenafil), intraurethral suppositories (alprostadil), and intracavernous injections (alprostadil and vasoactive drug mixtures). Nonpharmacological therapies, which do not rely on the biochemical reactivity of the erectile tissue, include vacuum constriction devices and penile implants (prostheses). With the exception of penile implants, these options are considered "on-demand" therapies requiring repeated administrations when sexual activity is desired.

The treatment algorithm for management of erectile dysfunction after radical prostatectomy generally adheres to stepwise process of care models.<sup>29</sup> With the increased availability of options in the past 2 decades, principles of minimal invasiveness, ease of administration, and cost are important considerations in addition to as-

**Table 2.** Pharmacological and Nonpharmacological Interventions for Erectile Dysfunction

Therapy Treatment Option	Role	Efficacy, %*	Comment
Oral PDE 5 inhibitors	First line	70-80 (nerve sparing) 0-15 (non-nerve-sparing)	Function of "nitric oxide-producing" penile nerves essential; sexual stimulation required
Intraurethral medications (penile suppository)	Second line	20-40	In-office instruction and titration recommended
Intracavernosal injections	Second line	85-90	In-office instruction and titration recommended
Vacuum constriction devices	Second line	90-100	Basic instruction sufficient
Penile implants (malleable and inflatable)	Third line	95-100	Surgical expertise required

Abbreviation: PDE 5, phosphodiesterase type 5.

\*Efficacy refers to percentage range of men having successful sexual intercourse.<sup>28</sup>

sessing levels of reliability, efficacy, and safety, and both patient and partner interest in and preferences for management. In addition, combination therapies have also been described.<sup>30,31</sup>

### Special Management Considerations

A fundamental stipulation in the context of radical prostatectomy-related erectile dysfunction is that men who have undergone nerve-sparing technique should be offered therapies that are not expected to interfere with the potential recovery of spontaneous, natural erectile function. In this light, penile prosthesis surgery would not be considered an option in this select group, at least in the initial 2-year postoperative period, until it becomes evident in some individuals that such recovery is unlikely. For men receiving non-nerve-sparing surgery, all options may be explored and have been shown to be consistently effective with the exception of oral pharmacotherapy.

In considering the role of PDE 5 inhibitors, which currently represent first-line intervention in erectile dysfunction management, the integrity of the cavernous nerves has clear therapeutic implications. These oral medications are well demonstrated to be efficacious in response to the sufficient release of the chemical mediator nitric oxide from cavernous nerve terminations within the erectile tissue.<sup>32</sup> Surgical approaches that

maximize cavernous nerve preservation are associated with the best therapeutic responses to PDE 5 inhibitors.<sup>33-37</sup>

In spite of the overall acceptance and general efficacy of intraurethral and intracavernosal vasoactive drugs and mechanical devices, these options have limitations. Discontinuation rates ranging from 50% to 80% are reported with these treatments, with reasons for dissatisfaction including insufficient response to therapy, unacceptable adverse effects, and a sense that the treatment is "unnatural."<sup>38-40</sup>

### Erection Rehabilitation

The ordeal of immediate and complete sexual loss experienced by many men following prostatectomy has encouraged the development of erection "rehabilitation." This relatively new strategy in clinical management after radical prostatectomy arose from the idea that early induced sexual stimulation and blood flow in the penis may facilitate the return of natural erectile function and resumption of medically unassisted sexual activity. In this respect, an early strategy is intracavernous injection therapy,<sup>41</sup> although its application has not occurred widely, mostly because of patient reluctance to perform needle insertions into the penis on a regular basis. The interest in using oral PDE 5 inhibitors is not surprising, since this therapy is noninvasive, convenient, and highly tolerable. However, while the early, regu-

lar use of PDE 5 inhibitors or other currently available, "on-demand" therapies is widely touted after surgery for purposes of erection rehabilitation, such therapy is mainly empirical. Evidence for its success remains limited.

### Neurogenic Erectile Dysfunction Treatments

The next frontier in the clinical management of erectile dysfunction after radical prostatectomy has centered on strategies that restore nerve function. Recent strategies have included cavernous nerve interposition grafting and neuromodulatory therapy. The former, as a surgical innovation meant to reestablish continuity of the nerve tissue to the penis, may be particularly applicable when nerve tissue has been excised during prostate removal.<sup>42-44</sup> In the modern era of commonly early diagnosed prostate cancer, nerve-sparing technique remains indicated for the majority of surgically treated patients.<sup>45</sup>

Neuromodulatory therapy, comprising both neuroprotective and neurotrophic treatments, represents an exciting, rapidly developing approach to revitalize intact nerves and promote nerve growth. These interventions are applicable with nerve-sparing surgery and would likely benefit even the reconstitution of nerve function after nerve grafting procedures. Therapeutic prospects include neurotrophins, neuroimmunophilin ligands, neuronal cell death inhibitors, nerve guides, tissue engineering/stem cell therapy, electrical stimulation, and even gene therapy. Among these, nonimmunosuppressant neuroimmunophilin ligands, drugs derived from the immunosuppressive agent tacrolimus and shown to possess nerve-sprouting actions, are emerging as promising clinical interventions, as evidenced by an under way multi-institutional phase 2 clinical trial of such therapy in men undergoing bilateral nerve-sparing radical prostatectomy.<sup>46,47</sup>

### CONCLUSION

In summary, Mr G's presentation represents a common scenario for pa-

tients undergoing management for prostate cancer today. In a relatively young man diagnosed with early stage prostate cancer, radical prostatectomy using a nerve-sparing technique eradicated his malignancy. His outcome, including a prolonged latency before the recovery of spontaneous, natural erectile ability, represents a course typical of many patients afterward. His frustration with long-term erectile dysfunction, despite assurances that recovery of erections was likely, is widely observed in this patient population. Although he did eventually recover normal erections, reversible interventions were necessary to allow him to resume sexual activity in the interim. Interventions currently under investigation may hasten the recovery of full erectile ability after prostatectomy.

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