SEQUELAE OF PROSTATE CANCER THERAPY: AVOIDANCE STRATEGIES AND MANAGEMENT OPTIONS

EDITED BY: Clemens Mathias Rosenbaum, Luis Alex Kluth and Felix Campos-Juanatey

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SEQUELAE OF PROSTATE CANCER THERAPY: AVOIDANCE STRATEGIES AND MANAGEMENT OPTIONS

Topic Editors:
Clemens Mathias Rosenbaum, Asklepios Klinik Barmbek, Germany
Luis Alex Kluth, University Hospital Frankfurt, Germany
Felix Campos-Juanatey, Marqués de Valdecilla University Hospital, Spain

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EDITORIAL
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Editorial: Sequelae of Prostate Cancer Therapy: Avoidance Strategies and Management Options

Clemens M. Rosenbaum[1†], Felix Campos-Juanatey[2†] and Luis A. Kluth[3†] for the Trauma Reconstructive Urology Working Party of the European Association of Urology Young Academic*

[1] Department of Urology, Asklepios Hospital Barmbek, Hamburg, Germany, [2] Department of Urology, Marqués de Valdecilla University Hospital, Santander, Spain, [3] Department of Urology, University Hospital Frankfurt, Goethe University Frankfurt, Frankfurt, Germany

Keywords: urinary incontinence, prostate neoplasia, erectile dysfunction, urethral stricture, radiation, prostatectomy, focal therapy

Editorial on the Research Topic

Sequelae of Prostate Cancer Therapy: Avoidance Strategies and Management Options

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Cozzarini Cesare,
San Raffaele Hospital (IRCCS), Italy

****Correspondence:***
Clemens M. Rosenbaum
c.rosenbaum@asklepios.com

†Member of the Trauma and Reconstructive Urology Working Party of the European Association of Urology (EAU) Young Academic Urologists (YAU)

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Prostate cancer is the most common malignancy among men in the Western world (1). More than 80% of patients with clinically localized prostate cancer will undergo definite treatment (2). Most common treatment options are radical prostatectomy and radiotherapy, focal therapies such as high-intensity focused ultrasound (HIFU) or cryoablation being increasingly used. All of them come along with different patterns of early and late side effects (3). Given excellent survival rates at 10 years (4), urologists have to face a relevant number of patients who present with one of these prostate cancer treatment related sequelae.

The goal of our Research Topic "Sequelae of Prostate Cancer Therapy: Avoidance Strategies and Management Options" was therefore to provide readers, researchers and physicians a comprehensive overview of strategies to prevent consequences of prostate cancer therapies and future perspectives of management of sequelae of prostate cancer treatments.

One of the most common side effects of prostate cancer treatment is urinary incontinence (5). Prostatectomy has worse effects on urinary incontinence compared to radiation therapy (5). Rahnama'i et al. illustrate the current knowledge of how to avoid urinary incontinence during radical prostatectomy. Besides surgical factors, patient characteristics as higher body mass index, older age, pre-existing lower urinary tract symptoms, neurological disease and functional bladder changes, have been identified to negatively impact continence (6). Lately, sarcopenia, defined as low skeletal muscle volume, has been increasingly recognized as a potential risk factor for worse outcome in oncologic patients. However, Angerer et al. were able to show that it has no influence on post-prostatectomy continence rates. As treatment of post-prostatectomy caused urinary incontinence, the artificial urinary sphincter has been considered the gold standard for several decades. Rahnama'i et al. demonstrated in their review several alternative surgical procedures that challenge the artificial urinary sphincter (6).

Another common consequence of prostate cancer treatment is erectile dysfunction (5). Sparing neurovascular bundles during surgery is the most important factor to maintain erectile function. Besides nerve-sparing surgery, methods for penile rehabilitation after radical prostatectomy and radiation therapy are focus of current research. Nicolai et al. give an overview about pathophysiology and treatment of erectile dysfunction following

radical prostatectomy. In addition, Schoentgen et al. are able to show in their systematic review, that sexual rehabilitation prior to radical prostatectomy may result in better erectile recovery.

For both urinary incontinence and erectile dysfunction, tissue engineering could help to overcome the current borders of treatment. Autologous stem cell transplantation is one of the most promising approaches. Adamowicz et al. describe a tissue engineering approach, mode of vascular and neuro-regeneration and stem cell safety. They are able to illustrate the unquestionable potential of tissue engineering to improve outcome of prostate cancer treatment related sequelae (Adamowicz et al.).

Furthermore, bladder outlet obstruction is a common problem not only after radical prostatectomy but also after radiation therapy.

The review "Contemporary Management of Vesico-Urethral Anastomotic Stenosis After Radical Prostatectomy" gives an overview about pathophysiology and treatment of vesicourethral anastomotic stenosis. The authors demonstrate endourological procedures should still remain as an initial treatment. However, in refractory stenoses, open or robotic reconstruction is a viable option with high success rates (Rosenbaum et al.). In contrast to vesicourethral anastomotic stenosis after radical prostatectomy, radiation induced membranous urethral strictures may occur years after therapy. Waterloos et al. illustrate that management of radiation induced urethral strictures can be challenging. Poor vascularized tissue and the proximity of the sphincter can impair functional outcomes (Waterloos et al.).

Devasted bladder outlet or radiogenic chronic cystitis are rare complications after prostate cancer treatments, but can have a huge impact on quality of life. Hoeh et al. provide an overview about treatment options in these patients, in which urinary diversion may also be discussed as a definite treatment.

Most of the aforementioned problems result of surgery or radiation. Focal therapy aims to selectively treat the part of the prostate that harbors significant prostate cancer while preserving the rest of the gland. Aim of this therapeutic approach is to retain the oncological benefit of active treatment while minimizing side-effects. Most common complications of focal therapy are urinary tract infections, acute urinary retention, dysuria and haematuria, however, urinary incontinence is rare. In the salvage setting, after external beam radiation therapy, focal therapy has a significantly higher rate of severe complications. Rakauskas et al. give a comprehensive overview.

Finally, all type of treatment inherit the risk of recurrence. After radical prostatectomy, the role and timing of radiation therapy remains highly controversial (7–9). Zattoni et al. give a comprehensive overview about the currently ongoing discussion. Still, about 40% of patients develop biochemical recurrence within 10 years after primary therapy (10). Limited sensitivity and specificity of conventional imaging methods, such as computed tomography and magnetic resonance imaging has led to efforts in developing better modalities. Lately PSMA-PET/CT has been introduced as such. Initially promising results have been confirmed. Leitsmann et al. are able to demonstrate that mesorectal lymph node metastases detected by PSMA-PET/CT seem to be a relevant localization of tumor recurrence after active therapy. They may serve as index lesion in the treatment of recurrent prostate cancer.

Prostate Cancer remains one of the major parts of Urology. Primary treatment of prostate cancer and management of recurrences is one side of the coin, while the other side is dealing treatment of sequalae of initial or recurrent treatment.

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REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. *CA Cancer J Clin.* (2020) 70:7–30. doi: 10.3322/caac.21590
2. Gray PJ, Lin CC, Cooperberg MR, Jemal A, Efstathiou JA. Temporal trends and the impact of race, insurance, and socioeconomic status in the management of localized prostate cancer. *Eur Urol.* (2017) 71:729–37. doi: 10.1016/j.eururo.2016.08.047
3. Nam RK, Cheung P, Herschorn S, Saskin R, Su J, Klotz LH, et al. Incidence of complications other than urinary incontinence or erectile dysfunction after radical prostatectomy or radiotherapy for prostate cancer: a population-based cohort study. *Lancet Oncol.* (2014) 15:223–31. doi: 10.1016/S1470-2045(13)70606-5
4. Hamdy FC, Donovan JL, Lane JA, Mason M, Metcalfe C, Holding P, et al. 10-Year outcomes after monitoring, surgery, or radiotherapy for localized prostate cancer. *N Engl J Med.* (2016) 375:1415–24. doi: 10.1056/NEJMoa1606220
5. Donovan JL, Hamdy FC, Lane JA, Mason M, Metcalfe C, Walsh E, et al. Patient-reported outcomes after monitoring, surgery, or radiotherapy for prostate cancer. *N Engl J Med.* (2016) 375:1425–37. doi: 10.1056/NEJMoa1606221
6. Heesakkers J, Farag F, Bauer RM, Sandhu J, De Ridder D, Stenzl A. Pathophysiology and contributing factors in postprostatectomy incontinence: a review. *Eur Urol.* (2017) 71:936–44. doi: 10.1016/j.eururo.2016.09.031
7. Tilki D, Chen MH, Wu J, Huland H, Graefen M, Wiegel T, et al. Adjuvant versus early salvage radiation therapy for men at high risk for recurrence following radical prostatectomy for prostate cancer and the risk of death. *J Clin Oncol.* (2021) 39:2284–93. doi: 10.1200/JCO.20.03714
8. Parker CC, Clarke NW, Cook AD, Kynaston HG, Petersen PM, Catton C, et al. Timing of radiotherapy after radical prostatectomy (RADICALS-RT): a randomised, controlled phase 3 trial. *Lancet.* (2020) 396:1413–21. doi: 10.1016/S0140-6736(20)31553-1

9. Vale CL, Fisher D, Kneebone A, Parker C, Pearse M, Richaud P, et al. Adjuvant or early salvage radiotherapy for the treatment of localised and locally advanced prostate cancer: a prospectively planned systematic review and meta-analysis of aggregate data. *Lancet.* (2020) 396:1422–31. doi: 10.1016/S0140-6736(20)31952-8
10. Roehl KA, Han M, Ramos CG, Antenor JA, Catalona WJ. Cancer progression and survival rates following anatomical radical retropubic prostatectomy in 3,478 consecutive patients: long-term results. *J Urol.* (2004) 172:910–4. doi: 10.1097/01.ju.0000134888.22332.bb

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MINI REVIEW
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Contemporary Management of Vesico-Urethral Anastomotic Stenosis After Radical Prostatectomy

Clemens M. Rosenbaum[1†], *Margit Fisch*[2] *and Malte W. Vetterlein*[2*†]
for the Trauma and Reconstructive Urology Working Party of the European Association of Urology Young Academic Urologists

[1] Department of Urology, Asklepios Klinik Barmbek, Hamburg, Germany, [2] Department of Urology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

Vesico-urethral anastomotic stenosis is a well-known sequela after radical prostatectomy for prostate cancer and has significant impact on quality of life. This review aims to summarize contemporary therapeutical approaches and to give an overview of the available evidence regarding endoscopic interventions and open reconstruction. Initial treatment may include dilation, incision or transurethral resection. In treatment-refractory stenoses, open reconstruction via an abdominal (retropubic), transperineal or combined abdominoperineal approach is a viable option with high success rates. All of the open surgical procedures are generally accompanied by a high risk of developing *de novo* incontinence and patients may need further interventions. In such cases, subsequent artificial urinary sphincter implantation is the most common treatment option with the best available evidence.

Keywords: prostatic neoplasms, urethral obstruction, transurethral resection, transurethral incision, urethral reconstruction

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Edited by:
Andreas Becker, Goethe University Frankfurt, Germany

Reviewed by:
Francisco E. Martins, University of Lisbon, Portugal
Ignacio Puche Sanz, Virgen de las Nieves University Hospital, Spain

***Correspondence:**
Malte W. Vetterlein
m.vetterlein@uke.de

[†]*Member of the Trauma and Reconstructive Urology Working Party of the European Association of Urology (EAU) Young Academic Urologists (YAU)*

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INTRODUCTION

Prostate cancer (PCa) represents the most frequent, solid malignant tumor among men in the Western hemisphere (1) and more than 80% of patients with localized PCa opt for definite treatment (2). Besides radiotherapy, one of the most common treatment option is radical prostatectomy (RP). Urinary incontinence and erectile dysfunction represent well-known and well-described treatment-related adverse events (3). Another common mid- to long-term complication after PCa treatment is bladder outlet obstruction (BOO) (4, 5). Given the relatively high overall and cancer-specific survival at 10 years (90% and 99%, respectively) (6), there is a relevant proportion of patients at risk of such long-term sequelae.

We believe it is important to emphasize that the term "urethral stricture" should be exclusively restricted to those parts of the urethra, which are surrounded by corpus spongiosum. This excludes the prostatic urethra at the outset (7). Moreover, it seems inevitable to us to distinguish between a bladder neck contracture (BNC) after surgical procedures for benign prostatic hyperplasia and VUAS after RP (7). It is a known fact, that etiology, anatomy, recurrence rates, and functional outcomes differ significantly between BNC and VUAS (8). BOO after PCa treatment includes radiation-induced bulbomembranous urethral stricture (9) as well as VUAS after RP (10). The following comprehensive narrative review aims to provide a contemporary summary of the epidemiology, etiology, preoperative evaluation, and treatment strategies for VUAS.

EPIDEMIOLOGY

Evaluating the existing literature on VUAS, it is of utmost importance to keep in mind that VUAS is mainly defined as a condition resulting in a surgical procedure based on a patient's complaint. To the very best of our knowledge, there are no prospective studies available, which analyzed urethral patency after RP by any standardized diagnostic procedure. Thus, in most studies, any surgical procedure is considered as the diagnosis of VUAS. This may translate into a certain underestimation of the true VUAS incidence. In 2007, an analysis of the Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) database provided a detailed insight into epidemiology of BOO related to prior PCa therapy. Overall obstruction rate among all treatment modalities was 5.2% at a median follow-up of 2.7 years. Highest prevalence of BOO occurred in patients after RP (8.4%) (11). Remarkably, BOO rates in patients treated with RP and adjuvant or salvage radiotherapy were lower (2.7%).

Generally, it appears that VUAS incidence has declined over the years. **Table 1** summarizes the evidence on VUAS incidence over the last two decades (5, 11–18). Of note, VUAS after robot-assisted laparoscopic RP seem to be less common as compared to open RP (∼1.3 vs. 3.6%, respectively) (5, 14, 17, 19). These data suggest that not only the refinement of surgical techniques over time, but also (robotic or open) RP in experienced surgical hands and in high-volume centers will result in lower VUAS rates. Notably, VUAS rates in men who had to undergo salvage RP after failed radiotherapy is significantly higher (22–40%). However, this evidence originates from small case series (20, 21). Beyond VUAS, salvage therapies come along with a much higher risk of urinary incontinence, rectal injury and urorectal fistulae (22).

ETIOLOGY

Preoperative known measurable risk factors for the development of VUAS are obesity, smoking, diabetes, and hypertension (12). These factors may result in decreased microvasculature, possibly leading to prolonged healing of the vesico-urethral anastomosis. Transurethral resection of the prostate prior to RP and a large prostatic volume have been proven as risk factors of VUAS as well (12, 23). Intraoperative risk factors for VUAS are extensive blood loss, mismatch, and tension on the anastomosis (12, 24) whereas running sutures of the anastomosis as well as robot-assisted compared to open procedures are supposed to lower the risk (5, 17, 25). In general, VUAS occurs within the first 6 months after surgery. The incidence of VUAS significantly decreases 2 years after RP (11).

DIAGNOSTIC WORKUP

Preoperative workup of VUAS should always include the medical history, previous procedures, and an evaluation of length and location of the stenosis (26). Clinical presentation usually includes obstructive symptoms such as a weak stream, hesitancy, and post-void residual urine. Moreover, patients who underwent adjuvant or salvage radiotherapy after RP often present with urgency and frequency symptoms with or without urinary incontinence.

If there is any surgical treatment planned, a prostate-specific antigen test should be performed to rule out PCa recurrence. Diagnosis of recurrent PCa would lead to different treatment strategies. Uroflowmetry and post-void residual urine measurement should objectify obstructive symptoms.

Radiologic investigation represents another important part of the diagnostic workflow. Combined retrograde urethrography (RUG) and voiding cystourethrography (VCUG) gives valuable information about the status of the anterior and posterior urethra. Moreover, combination of RUG and VCUG reveals a "funneled" VUAS (27). This "funneled" VUAS may impair the exact identification of VUAS location and length. As the anastomosis during RP is performed by connecting bladder neck and membranous urethra, the funneled area can be part of the VUAS. This may result in involving the membranous urethra and therefore the external urethral sphincter. Therefore, another integral part of the diagnostic workflow is a cystoscopy. Stenotic involvement of the external sphincter can be evaluated more precisely compared to isolated radiographic evaluation and urethral diameter can be adequately assessed. Given that incontinence rates are twice as high in patients with a VUAS compared to those without VUAS (5), pad test and evaluation of patient-reported outcome measurements (PROMs) should be performed prior to any surgical intervention to assess the baseline continence status.

TREATMENT

Endoscopic Procedures

Treatment algorithms for VUAS should usually commence with endoscopic therapy (**Figure 1**). Whereas, the European Association of Urology (EAU) guideline on urological trauma suggests dilation or transurethral incision (28), the American Urological Association (AUA) recommends a treatment decision at the surgeon's discretion (dilation, incision, or resection) (29). The most comprehensive recommendation regarding the sequential treatment of patients with VUAS is provided by a collaboration of the Société Internationale D'Urologie (SIU) and the International Consultation on Urological Diseases (ICUD) (30). A priori, patients are stratified according to continence status. In incontinent patients, the guidelines differentiate between a completely obliterated urethra with the recommendation to perform suprapubic cystostomy followed by open reconstruction as a first line strategy. In incontinent patient with residual urethral patency, transurethral incision with or without continuous intermittent catheterization is recommended. For continent patients, the SIU/ICUD guideline recommends dilation or incision as a first line therapy (30). It is important to mention that all of such recommendations are based on data with low level of evidence.

If the membranous urethra is involved, most authors favor dilation as a first line therapy (27), which may already lead to reasonable success rates (31).

Success rates after primary incision or resection range between 37 and 69%. This rate may increase up to 91% after numerous

TABLE 1 | Incidence of vesico-urethral anastomotic stenosis after radical prostatectomy as reported in the last two decades.

First author	Year of publication	Number of patients	Study design	Follow-up	VUAS incidence
Open retropubic prostatectomy					
Borboroglu et al. (12)	2000	467	Single-center	mean: 54 months	11%
Hu et al. (13)	2003	2,292	Multicenter	N/A	26%
Elliott et al. (11)	2007	3,310	Multicenter	median: 32 months	8.4%
Erickson et al. (14)	2009	4,132	Single-center	median: 44 months	2.5%
Carlsson et al. (15)	2010	458	Single-center	median: 30 months	4.5%
Gillitzer et al. (16)	2010	2,052	Single-center	median: 52 months	5.5%
Breyer et al. (17)	2010	695	Single-center	median: N/A; ≥ 12 months in all patients	2.6%
Modig et al. (5)	2019	942	Multicenter	mean: 24 months	3.6%
Laparoscopic robot-assisted prostatectomy					
Carlsson et al. (15)	2010	1,253	Single-center	median: 19 months	0.2%
Breyer et al. (17)	2010	293	Single-center	median: N/A; ≥ 12 months in all patients	1.4%
Parihar et al. (18)	2014	930	Single-center	mean: 23 months	1.6%

VUAS, vesico-urethral anastomotic stenosis.

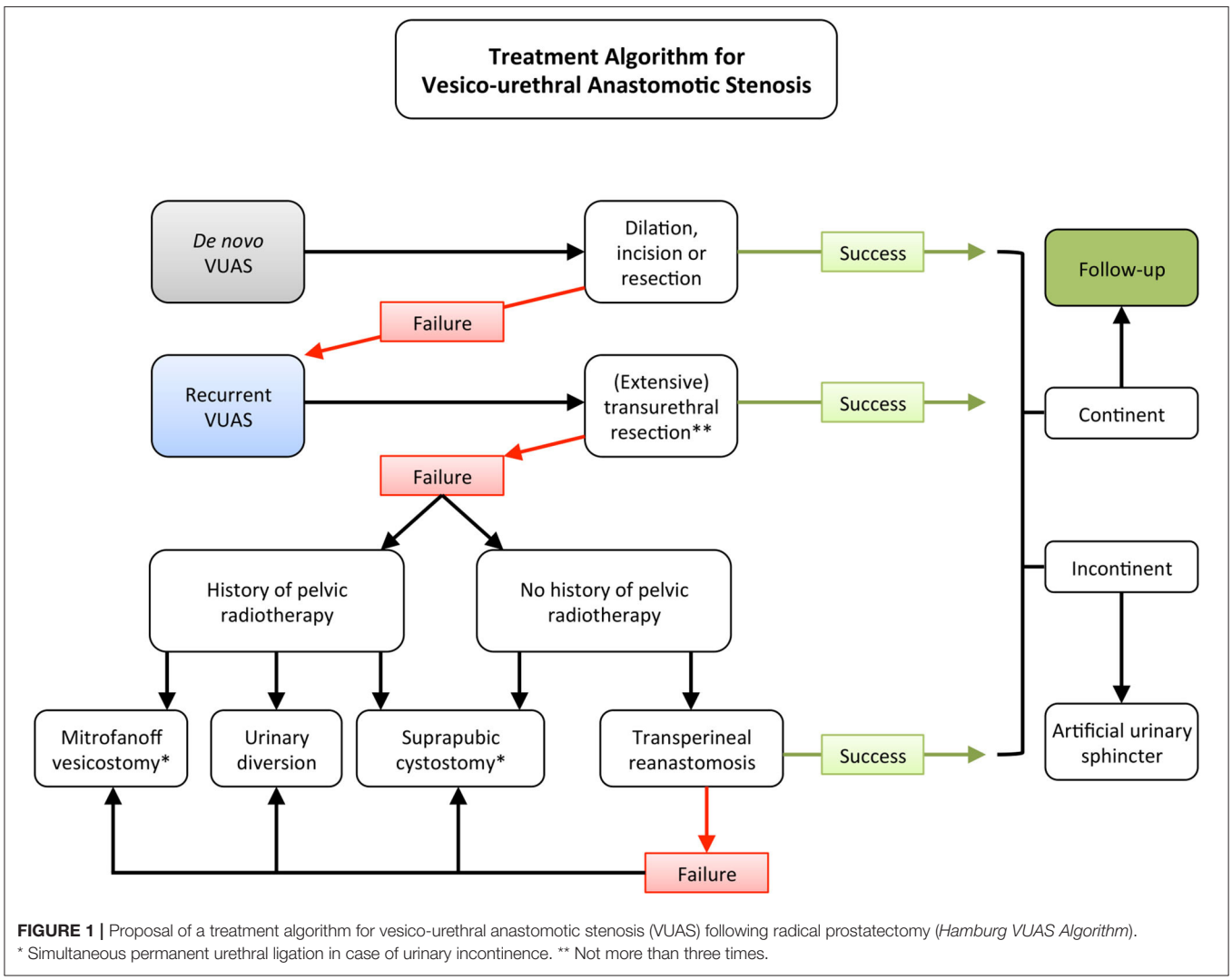

FIGURE 1 | Proposal of a treatment algorithm for vesico-urethral anastomotic stenosis (VUAS) following radical prostatectomy (*Hamburg VUAS Algorithm*).
* Simultaneous permanent urethral ligation in case of urinary incontinence. ** Not more than three times.

sequential surgical procedures (8, 10, 32). There are only two publications to exclusively report on endoscopic treatment of VUAS and most of the published series do not distinguish between a BNC after surgery for benign prostatic hyperplasia and VUAS after RP. **Table 2** summarizes the results from those two studies (10, 32).

Transurethral incision of the VUAS is usually performed at two sites. It should be emphasized that incision at the six o'clock position should be avoided. After RP, there is usually only a thin tissue plane between the vesico-urethral anastomosis and the rectum. Therefore, incision at this location would be prone to fistula formation or rectal injury (24). There is no high-level evidence on whether the incision should be performed by (hot or cold) knife or by laser (holmium or thulium). However, there is one publication suggesting a certain superiority of the holmium laser incision over cold knife incision (32). Injection of triamcinolone or mitomycin in addition to incision for recurrent VUAS has been described with success rates of 83–89% (33, 34). In this context, potential serious adverse events such as osteitis pubis, bladder necrosis, or rectourethral fistula with eventual need of cystectomy and supravesical diversion should be kept in mind and the risks and benefits should be adequately weighed (35). Another effort to treat recurrent VUAS has been made by using the UroLume stent (36). However, long-term follow-up has lowered initial expectations (37).

As mentioned above, the SIU/ICUD guidelines base treatment recommendations on a patient's continence status (30). The association of VUAS with incontinence is not uncommon (5). One possible explanation is that extensive fibrosis may involve the external sphincter, described as funneling by some authors (27). However, data about incontinence after endoscopic surgery for VUAS are rare. Pfalzgraf et al. have reported on postoperative *de novo* incontinence after endoscopic approaches in almost one third of patients. Incision resulted in higher incontinence rates as compared to resection (31 vs. 12%, respectively), whereas no difference was observed for previously irradiated vs. non-irradiated or primary vs. repeatedly treated patients (10).

Open Surgical Reconstruction

All endoscopic therapies inherit the risk of recurrence. Therefore, there is a non-negligible number of patients with recurrent VUAS. In those patients, transurethral therapy should not be continued and open surgical reconstruction should be discussed with the patient (**Figure 1**). We generally opt for open reconstruction in case of treatment failure after three previously failed transurethral procedures. Treatment choices should be patient-centered. Therefore, bladder drainage by permanent catheterization (transurethral or suprapubic) may be one option, especially for frail and very old patients. However, in most cases it is worth considering an open reconstruction of the VUAS. In very complex situations, urinary diversion may be another option but should be regarded as a last resort.

Different approaches have been discussed for open reconstruction: the abdominal (retropubic), the (trans)perineal, and the combined abdominoperineal approach (27, 38–43). For all of these approaches, results have been generally satisfying. **Table 3** gives an overview about the latest published evidence.

Lately, robotic reconstruction of VUAS has been added to the surgical armamentarium. In a recent case series of 12 patients including seven patients with BNC and five patients with VUAS, treatment success was 75%. *De novo* incontinence has been observed in 18% of patients (44).

When using the open retropubic approach, the bladder neck is accessed via an abdominal midline incision. VUAS scar tissue is excised and a reanastomosis is established similarly to primary vesico-urethral anastomosis during RP (41). Primary success rate can be as high as 60%. If further endoscopic therapies are performed for recurrences, overall success rate may raise up to 95% (41).

The transperineal approach inherits several advantages over the abdominal approach: First, adhesiolysis and surgical obstacles due to extensive scarred tissue in the previously operated field may be avoided. It can be difficult to identify surgical planes. Scar tissue resection can be challenging. Second, urethral mobilization to achieve a tension-free anastomosis can be difficult by the

TABLE 2 | Endoscopic treatment of vesico-urethral anastomotic stenosis after radical prostatectomy.

First author	Overall treatment success; *n* (%)	Treatment success in patients with no previous endoscopic treatment; *n* (%)	Treatment success in patients with ≥ 1 previous endoscopic treatment; *n* (%)
		Holmium laser incision	
LaBossiere et al. (32)	89/162 (55%)	48/70 (69%)	41/92 (45%)
Pfalzgraf et al. (10)	N/A	N/A	N/A
		Cold knife incision	
LaBossiere et al. (32)	5/15 (33%)	2/8 (25%)	3/7 (43%)
Pfalzgraf et al. (10)	19/36 (53%)	N/A	N/A
		Transurethral resection	
LaBossiere et al. (32)	26/64 (41%)	14/36 (39%)	12/28 (43%)
Pfalzgraf et al. (10)	25/67 (37%)	N/A	N/A
		Dilation	
LaBossiere et al. (32)	6/46 (13%)	0/17 (0%)	6/29 (21%)
Pfalzgraf et al. (10)	N/A	N/A	N/A

TABLE 3 | Open surgical reconstruction of recurrent vesico-urethral anastomotic stenosis after radical prostatectomy.

First author	Year	Number of patients	Follow-up	Treatment success	Comment
			Abdominal approach		
Pfalzgraf et al. (41)	2011	20	median: 59 months	60%	95% treatment success after secondary endoscopy
			Abdominoperineal approach		
Theodoros et al. (38)	2000	6	mean: 24 months	83%	Simultaneous AUS implantation in all patients Simultaneous bladder augmentation in three patients
Elliott et al. (39)	2006	10	median: 24 months	70%	50% treatment success in irradiated patients
			Perineal approach		
Reiss et al. (42)	2014	15	mean: 21 months	93%	100% treatment success after secondary endoscopy
Schüttfort et al. (43)	2017	23	mean: 45 months	87%	100% treatment success after secondary endoscopy

AUS, artificial urinary sphincter.

retropubic approach and may be facilitated by transperineal access (42). However, the transperineal approach can be very challenging (27). It seems mandatory that this procedure is performed in experienced centers.

For transperineal reanastomosis the patient is exposed in an exaggerated lithotomy position. A transperineal half-moon incision should be performed and the urethra should be dissected under digital-rectal examination. A complete exposition of the urethra and anastomotic area should be obtained. Scar tissue should be completely excised, beginning from the urethral lumen until healthy tissue is reached. A transurethral catheter allows for better orientation and identification of the distal end of the healthy urethra. Wide mobilization of urethra and bladder should be performed to guarantee a tension-free anastomosis (42). By some authors, a separation of the crura and sometimes even an inferior wedge pubectomy is recommended as the mobilization is generally done very far forward into the anterior triangle of the perineum (27). A dorsal spatulation of the anterior urethra should be performed and reanastomosis should be sutured by single knots under direct vision control. We propose inserting an 18 F transurethral catheter postoperatively (42). As recently shown, transperineal reanastomosis may result in success rates of up to 90% (43).

In previously irradiated patients, we would advise against performing a transperineal reanastomosis (**Figure 1**). One treatment option in those patients is to perform a continent vesicostomy (Mitrofanoff) with reasonable success rates (45). In patients with urinary incontinence, perineal ligation of the bladder neck should be performed simultaneously. However, in irradiated patients, bladder neck ligation can be challenging and success rates are lower compared to non-irradiated patients undergoing continent vesicostomy. Therefore, urinary diversion represents a reliable treatment option in this subgroup of patients (46).

Continence rates after open retropubic or robotic reanastomosis range between 18 and 31% in preoperatively continent patients (41, 44). After transperineal reanastomosis, almost all patients remain incontinent (43). It is therefore mandatory to counsel patients prior to reanastomosis about the possible necessity of a subsequent artificial urinary sphincter (AUS) implantation. A simultaneous reanastomosis and AUS placement is possible, but a two-staged procedure minimizes the risk of infection (31, 38). Additionally, staged procedures maintain the option of further endoscopic therapy in case of early VUAS recurrence. Ultimately, the stressed urethra is prone to revascularization. Urethral atrophy after cuff placement during AUS is therefore more unlikely. AUS placement should be performed 3–6 months after reanastomosis as completion of wound healing after this time period is very likely.

FUTURE DIRECTIONS

In the light of 90% overall and 99% cancer-specific survival at 10 years of follow-up (6), there is a need to better classify VUAS severity and complexity. That said, treatment options ought to be tailored more precisely. A superior classification system could possibly be achieved by including magnetic resonance tomography (MRI) into the diagnostic workup. As of today, combined urethrography represents the standard diagnostic procedure. In some cases, a "funneled" VUAS can be detected (27). However, the relation to the external sphincter, the exact length of the stenosis, and severity of fibrosis surrounding the stenosis cannot be predicted precisely. As a standard diagnostic tool for prostate cancer, MRI could help to better understand the pathophysiology of VUAS and the aforementioned factors. Whereas, there is no relevant data on MRI in the context of VUAS, MRI compared to standard radiographic assessment showed a better predictive capacity regarding the length of stenosis in obliterated posterior urethral strictures (47, 48). Moreover, in traumatic bulbar urethral strictures, MRI appears more precise in anticipating the degree of spongiofibrosis, concomitant fistula, and stricture length compared to conventional diagnostic tools (49). A novel VUAS classification should—among others—possibly include stenosis grading and etiological aspects. Taken together, a VUAS classification system would have important implications for both patients and urologists to improve treatment choices and predict surgical outcomes. Furthermore, an accepted grading system could aid in choosing the optimal treatment option, as previous attempts to predict urethral patency after VUAS treatment have failed (10). As of now, the type of endoscopic treatment as well as the decision to move on to open reconstruction is mostly

based on surgeon preference and institutional experience. There is a crucial need for prospective, multi-institutional randomized studies with a well-selected patient population.

CONCLUSIONS

VUAS is one of the most common complications after RP. Fortunately, incidence has declined over the last decades and was reported at ∼2% in recent series. VUAS usually occurs within the first 2 years after RP. Endoscopic treatment should usually be performed as a first line therapy, and most patients can be treated successfully. However, some patients develop recurrent VUAS. In those, reconstructive surgery should be considered. Reanastomosis, if performed by an abdominal, a perineal or a robotic-assisted laparoscopic approach, can result in high success rates. All types of VUAS therapy inherit the risk of *de novo* incontinence, which may be as high as 31 and 100% after endoscopic and open reconstruction, respectively. In these cases, AUS implantation can be regarded the most common treatment option with the best evidence available.

AUTHOR CONTRIBUTIONS

CR: conceptualization, methodology, investigation, writing - original draft, and project administration. MF: writing - review, editing, and supervision. MV: conceptualization, methodology, investigation, and writing - original draft. All authors contributed to the article and approved the submitted version.

REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. *CA Cancer J Clin*. (2020) 70:7–30. doi: 10.3322/caac.21590
2. Gray PJ, Lin CC, Cooperberg MR, Jemal A, Efstathiou JA. Temporal trends and the impact of race, insurance, and socioeconomic status in the management of localized prostate cancer. *Eur Urol*. (2017) 71:729–37. doi: 10.1016/j.eururo.2016.08.047
3. Potosky AL, Davis WW, Hoffman RM, Stanford JL, Stephenson RA, Penson DF, et al. Five-year outcomes after prostatectomy or radiotherapy for prostate cancer: the prostate cancer outcomes study. *J Natl Cancer Inst*. (2004) 96:1358–67. doi: 10.1093/jnci/djh259
4. Nam RK, Cheung P, Herschorn S, Saskin R, Su J, Klotz LH, et al. Incidence of complications other than urinary incontinence or erectile dysfunction after radical prostatectomy or radiotherapy for prostate cancer: a population-based cohort study. *Lancet Oncol*. (2014) 15:223–31. doi: 10.1016/S1470-2045(13)70606-5
5. Modig KK, Godtman RA, Bjartell A, Carlsson S, Haglind E, Hugosson J, et al. Vesicourethral anastomotic stenosis after open or robot-assisted laparoscopic retropubic prostatectomy-results from the laparoscopic prostatectomy robot open trial. *Eur Urol Focus*. (2019). doi: 10.1016/j.euf.2019.10.012. [Epub ahead of print].
6. Hamdy FC, Donovan JL, Lane JA, Mason M, Metcalfe C, Holding P, et al. 10-year outcomes after monitoring, surgery, or radiotherapy for localized prostate cancer. *N Engl J Med*. (2016) 375:1415–24. doi: 10.1056/NEJMoa1606220
7. Latini JM, McAninch JW, Brandes SB, Chung JY, Rosenstein D. SIU/ICUD consultation on urethral strictures: epidemiology, etiology, anatomy, and nomenclature of urethral stenoses, strictures, and pelvic fracture urethral disruption injuries. *Urology*. (2014) 83:S1–7. doi: 10.1016/j.urology.2013.09.009
8. Kranz J, Reiss PC, Salomon G, Steffens J, Fisch M, Rosenbaum CM. Differences in recurrence rate and *de novo* incontinence after endoscopic treatment of vesicourethral stenosis and bladder neck stenosis. *Front Surg*. (2017) 4:44. doi: 10.3389/fsurg.2017.00044
9. Vetterlein MW, Kluth LA, Zumstein V, Meyer CP, Ludwig TA, Soave A, et al. Buccal mucosal graft urethroplasty for radiation-induced urethral strictures: an evaluation using the extended Urethral Stricture Surgery Patient-Reported Outcome Measure (USS PROM). *World J Urol*. (2020) 38:2863–72. doi: 10.1007/s00345-020-03102-5
10. Pfalzgraf D, Worst T, Kranz J, Steffens J, Salomon G, Fisch M, et al. Vesico-urethral anastomotic stenosis following radical prostatectomy: a multi-institutional outcome analysis with a focus on endoscopic approach, surgical sequence, and the impact of radiation therapy. *World J Urol*. (2020). doi: 10.1007/s00345-020-03157-4. [Epub ahead of print].
11. Elliott SP, Meng MV, Elkin EP, McAninch JW, Duchane J, Carroll PR, et al. Incidence of urethral stricture after primary treatment for prostate cancer: data From CaPSURE. *J Urol*. (2007) 178:529–34. doi: 10.1016/j.juro.2007.03.126
12. Borboroglu PG, Sands JP, Roberts JL, Amling CL. Risk factors for vesicourethral anastomotic stricture after radical prostatectomy. *Urology*. (2000) 56:96–100. doi: 10.1016/s0090-4295(00)00556-2
13. Hu JC, Gold KF, Pashos CL, Mehta SS, Litwin MS. Role of surgeon volume in radical prostatectomy outcomes. *J Clin Oncol*. (2003) 21:401–5. doi: 10.1200/JCO.2003.05.169
14. Erickson BA, Meeks JJ, Roehl KA, Gonzalez CM, Catalona WJ. Bladder neck contracture after retropubic radical prostatectomy: incidence and risk factors from a large single-surgeon experience. *BJU Int*. (2009) 104:1615–9. doi: 10.1111/j.1464-410X.2009.08700.x
15. Carlsson S, Nilsson AE, Schumacher MC, Jonsson MN, Volz DS, Steineck G, et al. Surgery-related complications in 1253 robot-assisted and 485 open retropubic radical prostatectomies at the Karolinska University Hospital, Sweden. *Urology*. (2010) 75:1092–7. doi: 10.1016/j.urology.2009.09.075
16. Gillitzer R, Thomas C, Wiesner C, Jones J, Schmidt F, Hampel C, et al. Single center comparison of anastomotic strictures after radical perineal and radical retropubic prostatectomy. *Urology*. (2010) 76:417–22. doi: 10.1016/j.urology.2009.10.009
17. Breyer BN, Davis CB, Cowan JE, Kane CJ, Carroll PR. Incidence of bladder neck contracture after robot-assisted laparoscopic and open radical prostatectomy. *BJU Int*. (2010) 106:1734–8. doi: 10.1111/j.1464-410X.2010.09333.x
18. Parihar JS, Ha YS, Kim IY. Bladder neck contracture-incidence and management following contemporary robot assisted radical prostatectomy technique. *Prostate Int*. (2014) 2:12–8. doi: 10.12954/PI.13034
19. Webb DR, Sethi K, Gee K. An analysis of the causes of bladder neck contracture after open and robot-assisted laparoscopic radical prostatectomy. *BJU Int*. (2009) 103:957–63. doi: 10.1111/j.1464-410X.2008.08278.x
20. Ward JF, Sebo TJ, Blute ML, Zincke H. Salvage surgery for radiorecurrent prostate cancer: contemporary outcomes. *J Urol*. (2005) 173:1156–60. doi: 10.1097/01.ju.0000155534.54711.60
21. Corcoran NM, Godoy G, Studd RC, Casey RG, Hurtado-Coll A, Tyldesley S, et al. Salvage prostatectomy post-definitive radiation therapy: The Vancouver experience. *Can Urol Assoc J*. (2013) 7:87–92. doi: 10.5489/cuaj.11056
22. Heidenreich A, Richter S, Thuer D, Pfister D. Prognostic parameters, complications, and oncologic and functional outcome of salvage radical prostatectomy for locally recurrent prostate cancer after 21st-century radiotherapy. *Eur Urol*. (2010) 57:437–43. doi: 10.1016/j.eururo.2009.02.041
23. Moul JW, Mooneyhan RM, Kao TC, McLeod DG, Cruess DF. Preoperative and operative factors to predict incontinence, impotence and stricture after radical prostatectomy. *Prostate Cancer Prostatic Dis*. (1998) 1:242–9. doi: 10.1038/sj.pcan.4500248
24. Browne BM, Vanni AJ. Management of urethral stricture and bladder neck contracture following primary and salvage treatment of prostate cancer. *Curr Urol Rep*. (2017) 18:76. doi: 10.1007/s11934-017-0729-0

25. Albisinni S, Aoun F, Peltier A, van Velthoven R. The single-knot running vesicourethral anastomosis after minimally invasive prostatectomy: review of the technique and its modifications, tips, and pitfalls. *Prostate Cancer*. (2016) 2016:1481727. doi: 10.1155/2016/1481727
26. Vetterlein MW, Rosenbaum CM, Fisch M. Surgical reconstruction of posterior urethral complications following prostate cancer treatments. In: Martins FE, Kulkarni SB, Köhler TS, editors. *Textbook of Male Genitourethral Reconstruction*. Cham: Springer International Publishing (2020). p. 303–17. doi: 10.1007/978-3-030-21447-0_25
27. Mundy AR, Andrich DE. Posterior urethral complications of the treatment of prostate cancer. *BJU Int*. (2012) 110:304–25. doi: 10.1111/j.1464-410X.2011.10864.x
28. Summerton DJ, Kitrey ND, Lumen N, Serafetinidis E, Djakovic N, European Association of U. EAU guidelines on iatrogenic trauma. *Eur Urol*. (2012) 62:628–39. doi: 10.1016/j.eururo.2012.05.058
29. Wessells H, Angermeier KW, Elliott S, Gonzalez CM, Kodama R, Peterson AC, et al. Male urethral stricture: American urological association guideline. *J Urol*. (2017) 197:182–90. doi: 10.1016/j.juro.2016.07.087
30. Herschorn S, Elliott S, Coburn M, Wessells H, Zinman L. SIU/ICUD consultation on urethral strictures: posterior urethral stenosis after treatment of prostate cancer. *Urology*. (2014) 83:S59–70. doi: 10.1016/j.urology.2013.08.036
31. Anger JT, Raj GV, Delvecchio FC, Webster GD. Anastomotic contracture and incontinence after radical prostatectomy: a graded approach to management. *J Urol*. (2005) 173:1143–6. doi: 10.1097/01.ju.0000155624.48337.a5
32. LaBossiere JR, Cheung D, Rourke K. Endoscopic treatment of vesicourethral stenosis after radical prostatectomy: outcomes and predictors of success. *J Urol*. (2016) 195:1495–500. doi: 10.1016/j.juro.2015.12.073
33. Eltahawy E, Gur U, Virasoro R, Schlossberg SM, Jordan GH. Management of recurrent anastomotic stenosis following radical prostatectomy using holmium laser and steroid injection. *BJU Int*. (2008) 102:796–8. doi: 10.1111/j.1464-410X.2008.07919.x
34. Vanni AJ, Zinman LN, Buckley JC. Radial urethrotomy and intralesional mitomycin C for the management of recurrent bladder neck contractures. *J Urol*. (2011) 186:156–60. doi: 10.1016/j.juro.2011.03.019
35. Redshaw JD, Broghammer JA, Smith TG, Voelzke BB, Erickson BA, McClung CD, et al. Intralesional injection of mitomycin C at transurethral incision of bladder neck contracture may offer limited benefit: TURNS study group. *J Urol*. (2015) 193:587–92. doi: 10.1016/j.juro.2014.08.104
36. Elliott DS, Boone TB. Combined stent and artificial urinary sphincter for management of severe recurrent bladder neck contracture and stress incontinence after prostatectomy: a long-term evaluation. *J Urol*. (2001) 165:413–5. doi: 10.1097/00005392-200102000-00014
37. Anger J. Management of recalcitrant bladder neck contracture after radical prostatectomy for prostate cancer. UroLume stent. *J Urol*. (2011) 185:391–2. doi: 10.1016/j.juro.2010.11.022
38. Theodoros C, Katsifotis C, Stournaras P, Moutzouris G, Katsoulis A, Floratos D. Abdomino-perineal repair of recurrent and complex bladder neck-prostatic urethra contractures. *Eur Urol*. (2000) 38:734–40. doi: 10.1159/000020371
39. Elliott SP, McAninch JW, Chi T, Doyle SM, Master VA. Management of severe urethral complications of prostate cancer therapy. *J Urol*. (2006) 176:2508–13. doi: 10.1016/j.juro.2006.07.152
40. Simonato A, Gregori A, Lissiani A, Carmignani G. Two-stage transperineal management of posterior urethral strictures or bladder neck contractures associated with urinary incontinence after prostate surgery and endoscopic treatment failures. *Eur Urol*. (2007) 52:1499–504. doi: 10.1016/j.eururo.2007.03.053
41. Pfalzgraf D, Beuke M, Isbarn H, Reiss CP, Meyer-Moldenhauer WH, Dahlem R, et al. Open retropubic reanastomosis for highly recurrent and complex bladder neck stenosis. *J Urol*. (2011) 186:1944–7. doi: 10.1016/j.juro.2011.07.040
42. Reiss CP, Pfalzgraf D, Kluth LA, Soave A, Fisch M, Dahlem R. Transperineal reanastomosis for the treatment for highly recurrent anastomotic strictures as a last option before urinary diversion. *World J Urol*. (2014) 32:1185–90. doi: 10.1007/s00345-013-1180-6
43. Schuettfort VM, Dahlem R, Kluth L, Pfalzgraf D, Rosenbaum C, Ludwig T, et al. Transperineal reanastomosis for treatment of highly recurrent anastomotic strictures after radical retropubic prostatectomy: extended follow-up. *World J Urol*. (2017) 35:1885–90. doi: 10.1007/s00345-017-2067-8
44. Kirshenbaum EJ, Zhao LC, Myers JB, Elliott SP, Vanni AJ, Baradaran N, et al. Patency and incontinence rates after robotic bladder neck reconstruction for vesicourethral anastomotic stenosis and recalcitrant bladder neck contractures: the trauma and urologic reconstructive network of surgeons experience. *Urology*. (2018) 118:227–33. doi: 10.1016/j.urology.2018.05.007
45. Spahn M, Kocot A, Loeser A, Kneitz B, Riedmiller H. Last resort in devastated bladder outlet: bladder neck closure and continent vesicostomy–long-term results and comparison of different techniques. *Urology*. (2010) 75:1185–92. doi: 10.1016/j.urology.2009.11.070
46. Riedmiller H, Kocot A. The devastated bladder outlet: treatment options. *Curr Opin Urol*. (2015) 25:352–6. doi: 10.1097/MOU.0000000000000185
47. Oh MM, Jin MH, Sung DJ, Yoon DK, Kim JJ, Moon du G. Magnetic resonance urethrography to assess obliterative posterior urethral stricture: comparison to conventional retrograde urethrography with voiding cystourethrography. *J Urol*. (2010) 183:603–7. doi: 10.1016/j.juro.2009.10.016
48. Sung DJ, Kim YH, Cho SB, Oh YW, Lee NJ, Kim JH, et al. Obliterative urethral stricture: MR urethrography versus conventional retrograde urethrography with voiding cystourethrography. *Radiology*. (2006) 240:842–8. doi: 10.1148/radiol.2403050590
49. Horiguchi A, Edo H, Soga S, Azuma R, Shinchi M, Ojima K, et al. Magnetic resonance imaging findings of traumatic bulbar urethral stricture help estimate repair complexity. *Urology*. (2020) 135:146–53. doi: 10.1016/j.urology.2019.09.036

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Impact of Sarcopenia on Functional and Oncological Outcomes After Radical Prostatectomy

Markus Angerer[1,2]*, *Georg Salomon*[1], *Dirk Beyersdorff*[3], *Margit Fisch*[2], *Markus Graefen*[1] *and Clemens M. Rosenbaum*[4]

[1] Martini-Klinik Prostate Cancer Center, University Hospital Hamburg-Eppendorf, Hamburg, Germany, [2] Department of Urology, University Hospital Hamburg-Eppendorf, Hamburg, Germany, [3] Department of Radiology, Interventional Radiology and Nuclear Medicine, University Hospital Hamburg-Eppendorf, Hamburg, Germany, [4] Department of Urology, Asklepios Hospital Barmbek, Hamburg, Germany

Introduction and Objectives: Knowledge about the significance of sarcopenia (muscle loss) in prostate cancer (PCa) patients is limited. The aim of this study was to determine the influence of skeletal muscle index (SMI) on early functional and pathological outcome in patients undergoing radical prostatectomy (RP).

Materials and Methods: One hundred randomly chosen patients who received RP between November 2016 and April 2017 at Martini-Klinik (Hamburg, Germany) were retrospectively assessed. SMI (skeletal muscle mass cross-sectional area at L3/m^2) was measured by preoperative staging computed tomography scans at L3 level. Cox regression analysis was applied to determine the impact of SMI on post-operative outcome. Follow-up was 12 months. Continence was defined as no more than one safety pad per day.

Results: Mean age of the cohort was 63.6 years. Mean SMI was 54.06 cm^2/m^2 (range, 40.65–74.58 cm^2/m^2). Of the patients, 41.4% had pT2, 28.7% had pT3a, and 29.9% had pT3b or pT4 PCa. SMI revealed to be without significant correlation on tumor stage. Follow-up data of 55 patients were available for early functional outcome analysis. SMI showed no significant influence on erectile function in multivariable Cox regression analysis. In multivariable Cox regression analysis, SMI turned out to have no influence on continence rates 6 weeks after surgery.

Conclusion: The present study shows that patients undergoing RP have a wide range of SMI. Unlike in other urological malignancies, there was no significant impact of SMI on early functional outcome and pathological outcome. A larger cohort is needed to confirm these results.

Keywords: prostate cancer, sarcopenia, radical prostatectomy, oncological outcome, functional outcome

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***Correspondence:**
Markus Angerer
markusangererhh@gmail.com

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INTRODUCTION

Prostate cancer (PCa) is the most common cancer and the third most common cause of cancer death among men in the western world (1). According to the German health report in corporation with the Robert-Koch-Institute, ∼49,000 cases of PCa are reported per annum; the incidence is 120 in all age classes in Germany (2).

Radical prostatectomy (RP), brachytherapy (BT), and the advanced technique of radiation using intensity-modulated radiation therapy (IMRT) are the three most common treatment procedures for localized prostate cancer. All techniques show no significant contrariness in overall survival (3, 4). RP embodies one of the most often used treatment option in localized prostate cancer, mainly implemented as either retropubic open RP or laparoscopic/robot-assisted RP (5).

The most recognized risk factors for developing PCa are increasing age, ethnic origin, and family history (6). The familiar predisposition suggests an inherited genetic component to PCa (7, 8). Preoperative prostate-specific antigen (PSA), pathological stage, Gleason score, and surgical margins status predicted BCR after RP (9).

"Sarcopenia is a progressive and generalized skeletal muscle disorder that is associated with increased likelihood of adverse outcomes including falls, fractures, physical disability, and mortality" as defined by the European Working Group on Sarcopenia in Older People (EWGSOP) (10). Sarcopenia is increasingly recognized as a risk factor for a worse performance especially in patients suffering from a malignant tumor disease (11). Lately, the presence of sarcopenia has been identified as a "prognostic marker of disease recurrence, cancer-specific mortality (CCM), and all-cause mortality (ACM)" in patients with not particularly urological malignancies but also, e.g., gynecological and gastrointestinal cancer diseases (12–15).

The definition of sarcopenia is based on the skeletal muscle index (SMI). The muscle volume can reproducibly be measured by computed tomography (CT) or magnetic resonance imaging (MRI) (10).

Among others, potential risk factors of perioperative complications are BMI >30 and Charlson comorbidity index (CCI) ≥ 1 (16). Performance status and comorbidity are generally subjective and difficult to define. The American Association of Anesthesiologists (ASA) score, the Eastern Cooperative Oncology Group (ECOG) performance status, and CCI are commonly calculated prognostic factors for analyzing post-operative outcomes. Yet, they have been doubted to identify those patients at highest risk of perioperative morbidity and mortality, despite the successfully recognition of all status (14, 17). Sarcopenic patients have been demonstrating a higher rate of perioperative complications (18–21).

This resulted to proclaim sarcopenia as an important acknowledging factor in treatment planning, decision-making, and gaining information regarding patients peri- and post-operative outcome (17).

In men diagnosed with prostate cancer, little is known about the role of sarcopenia influencing the functional and oncological outcome. One study concluded that sarcopenia does not predict the oncological outcome after RP (22). Another study that investigated men undergoing radiotherapy for PCa identified a significant impact of skeletal muscle reduction on non-cancer mortality (23).

We hypothesized that sarcopenia may be correlate with a higher complication rate and worse oncological outcome in men undergoing RP. Consequently, we examined the association between sarcopenia and perioperative as well as oncological outcome in men undergoing RP (17).

Abbreviations: PCa, prostate cancer; RP, radical prostatectomy; IMRT, intensity modulated radiotherapy, BT, brachytherapy; EWGSOP, European Working Group on Sarcopenia in Older People; ACM, all-cause mortality; CCM, cancer-specific mortality; MRI, magnetic resonance imaging; CCI, Charlson comorbidity index; ECOG, Eastern Cooperative Oncology Group; ASA, American Association of Anesthesiologists; SMI, skeletal muscle index; OS, overall survival; CT, computed tomography; HU, Hounsfield unit; BMI, body mass index; HR, hazard ratio; CI, confidence interval.

MATERIALS AND METHODS

We retrospectively analyzed 100 patients who were treated with RP, either open retropubic RP or laparoscopic, robot-assisted RP at a high-volume center (Martini-Klinik Prostate Cancer Center, Hamburg-Eppendorf, Germany) between November 2016 and April 2017. RP was only performed consistently by eight highly trained surgeons performing RRP and robot-assisted RP regularly.

We have identified the patients randomly within our database. Staging CT scans were obtained by patients with intermediate- and high-risk PCa defined by D'Amico as a clinical T stage $\geq$cT2c, a Gleason score ≥ 8, or a PSA >20 ng/ml (24).

CT images were obtained from the patients preoperative CT scans of the abdomen or pelvis. Included were only patients with sufficient quality of CT images. Patients' informed consent for data collection was obtained. The cross-sectional area of all skeletal muscle at third lumbar vertebrae 3 (L3) has a high correlation to the body's general muscle volume (18). Lumbal SMI is calculated by the cross-sectional area of all skeletal muscle at L3 by height squared (m^2) and reported as cm^2/m^2. Clinical, blood sample results, and oncological data were collected from the hospitals' documenting program, Soarian, and Martini Data Registry.

A single axial image at the level of L3 was selected, and the cross-sectional area of all skeletal muscle at L3 was measured after identifying the muscle-specific attenuation thresholds (−29–150 HU). For the measurement, musculus rectus abdominus; internal, external, and lateral musculus obliquus abdominis; musculus psoas; musculus quadratus lumborum; and musculus erector spinae were included. Axial CT images at L3 vertebra depicting patient without sarcopenia are shown in **Figures 1A,B** as compared to patients with different BMIs and significantly different SMI shown in **Figures 1C,D**. The radiologist program Centricty Viewer GE was used for image analysis. Image analysis was performed by the same investigator who was unaware about the patients' cancer-specific data.

Clinical and pathological data were collected. Clinical data are include information on age, clinical TNM classification (clinical tumor and lymph node stage), preoperative PSA, continence by the number of pad usage per day, as well as preoperative androgen deprivation therapy. Pathological data collected included prostate biopsy Gleason score, pathological specimen Gleason score, pathological TN classification (pathological tumor and lymph node stage), and surgical margin status.

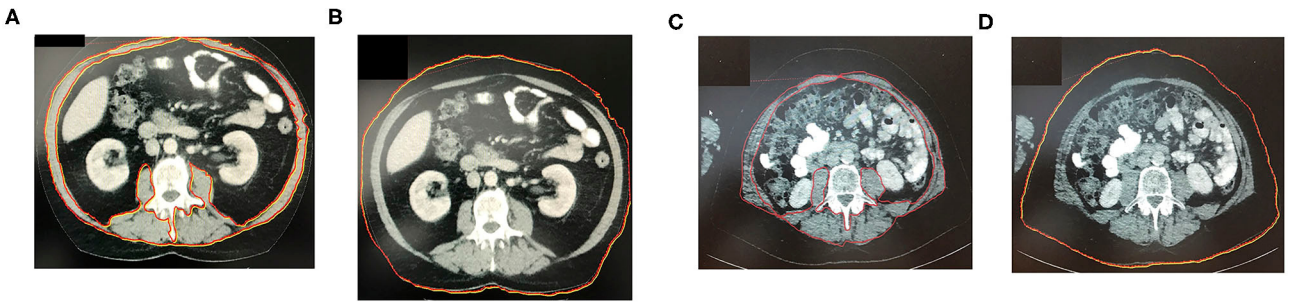

FIGURE 1 | (A,B) Axial CT-image at L3 vertebra depicting patient without sarcopenia. **(C,D)** Axial CT-image at L3 vertebra depicting patient with BMI and significantly different SMI (sarcopenic patient). The red marked area represents the cross-sectional area of all skeletal muscle at L3 including the rectus abdominus; internal, external, and lateral obliques; psoas; quadratus lumborum; and erector spinae muscles. The red marked line in the image represents patients abdominal circumference.

Taking into consideration the EWGSOP definition of sarcopenia, SMI was based on sex- and BMI-specific cutoffs for men <43 cm^2/m^2 (BMI <25) and <53 cm^2/m^2 (BMI >25) to classify patients as sarcopenic vs. non-sarcopenic (25).

Urine continence was defined not to use more than 1 safety Pad per Day.

Statistical Analysis

Clinical and pathological variables were compared between the sarcopenic and non-sarcopenic patients. Age, BMI (in kg/m^2), pathological tumor and lymph node stage, pathological surgical margin status, PSA, and Gleason score are taken into account for comparison of the two groups. Continuous features were summarized with medians and interquartile ranges (IQRs). Categorical features were summarized with frequency counts and percentages and compared using the chi-square test. The primary interest was to evaluate the functional and oncological outcome.

Logistic regression analysis was used to estimate the oncological outcome and biochemical recurrence (BCR). BCR was defined as PSA value >0.2 ng/ml after RP. Urine continence was assessed by univariable and multivariable Cox proportional hazards regression models and summarized with hazards ratios (HRs) and 95% confidence intervals (95% CIs).

Furthermore, statistically significant prognosticators on univariable analysis were also analyzed in multivariable models. A $p < 0.05$ was considered to be statistically significant.

For follow-up assessment, patients were evaluated for urinary continence and erectile function (EF) after 6 weeks and 12 months after RP. Patient-reported outcomes were registered by standardized Martini–Klinik questionnaires (5).

RESULTS

We included for the first analysis 99 patients from our database who fulfilled the inclusion criteria. All of them were operated between November 2016 and April 2017. One patient was excluded due to missing data.

SMI measurements of all 99 patients were conducted based on SMI definition; 26 patients (26.3%) were classified as sarcopenic. Descriptive pathological and perioperative characteristics are shown in **Table 1**.

Overall, sarcopenic patients were older than non-sarcopenic patients (mean age, 68.0 vs. 64 years, $p = 0.02$). There was no difference between sarcopenic and non-sarcopenic patients in local and lymphonodal pathologic stage or Gleason score. There was no significant difference between sarcopenic and non-sarcopenic patients regarding nerve-sparring surgery (84.9 vs. 88.5%, $p = 0.91$).

In addition, there was no significant difference in urine continence at 1 year after surgery between sarcopenic and non-sarcopenic patients in multivariable logistic regression analysis [odd's ratio (OR), 1.05; 95% confidence interval (CI), 0.96–1.16; $p = 0.26$].

Results are shown in **Table 2**.

In Cox regression analysis, the incidence of BCR did not differ significantly 1 year after surgery between sarcopenic and non-sarcopenic patients [hazard ratio (HR), 0.97; 95% CI, 0.3–3.08; $p = 0.953$].

DISCUSSION

Sarcopenia represents "a response to both nutrient deprivation and systemic stress, resulting in critical anatomic and functional deficits" (17). Sarcopenia is a major public health issue. Using the definition with highest prevalence estimates, the number of individuals with sarcopenia would rise from 19,740 million in 2016 to 32,338 million in 2045 only in Europe, corresponding to an increase from 20.2 to 22.3% (26).

In this current study, we examined the association between sarcopenia and functional and oncological outcome after RP. Our hypothesis that sarcopenia significantly effects functional and oncologic outcome in men undergoing RP could not be proven.

We noted several findings of interest. First, we determined that in this cohort of patients with RP, 26.3% of patients were classified as sarcopenic preoperatively. The median age of sarcopenic patients was significantly older.

The correlation between BMI and outcome after RP has been investigated often in past. An increase in BMI

TABLE 1 | Descriptive pathologic and perioperative characteristics of PCa patients that underwent RP between November 2016 and April 2017.

Characteristics	Overall	Non-sarcopenic patients	Sarcopenic patients	*p*-value
No. of patients, *n* (%)	99	73 (73.7)	26 (26.3)	
Age at RP (years), median	65 (59–68.7)	64 (57–67)	68 (61–71)	0.02
Prostate volume (ml), median	39 (30–47.5)	38 (28–48)	41 (33–46)	0.19
SMI (cm^2/m^2), median	54 (49.4–58.6)	57 (53–61)	50 (46–50)	<0.001
Nerve-sparing (%), *n*				
Yes	85	62 (84.9)	23 (88.5)	0.91
No	14	11 (15.1)	3 (11.5)	
pT-Stadium (%), *n*				0.81
pT2	42	32 (43.8)	10 (38.5)	
pT3/4	57	41 (56.2)	16 (61.5)	
pN-Status (%), *n*				0.29
Nx/N0	66	46 (63)	20 (67.9)	
N+	33	27 (37)	6 (23.1)	
Gleason (%), *n*				0.35
3 + 3/3 + 4	40	27 (37)	13 (50)	
4 + 4/>4 + 4	59	46 (63)	13 (50)	

TABLE 2 | Urine continence at 1 year after RP.

Characteristics	Odd's ratio	95% CI	*p*-value
Age at RP	1.05	0.95–1.17	0.31
Prostate volume	1.02	0.98–1.06	0.4
Nerve-sparing			
Yes	Reference		
No	0.38	0.03–3.35	0.4
pT-Stadium			
pT2	Reference		
pT3a	0.53	0.1–2.46	0.43
pT3b/pT4a	1.99	0.35–10.92	0.42
SMI	1.05	0.96–1.16	0.26

showed a significant increase risk of peri- and post-operative complications; prolonged operative time, increased blood loss, increased open conversions, longer hospitalization, and higher positive surgical margin rate (27). BMI has known associations with diabetes, coronary artery disease, and hypertension (27). Obesity also has a significant impact on mortality in cancer patients (24). Freedland et al. concluded that elevated BMI has been associated with biochemical failure after radical prostatectomy, due to inferior surgery, which caused a higher rate of positive surgical margin. Also in their cohort, obese men after RP showed worse outcomes, suggesting that obesity may be associated with a biologically more aggressive form of prostate cancer (28–30). Still, it remains controversial regarding the effect on BCR (22).

As mentioned before, McDonald et al. assessed in their study the cross-sectional area at the L4–5 level after radiotherapy for localized prostate cancer retrospective of 653 men (23). They were concluding that sarcopenia significantly increased risk of non-cancer mortality after radiotherapy. Analyzing their cohort, the conclusion is due to the fact that cross-sectional area of all total skeletal muscle was measured at L4–5 and relatively few patients. Furthermore, this study had muscle L4–5 values below the sarcopenic threshold.

Mason et al. published in June 2018 the association between sarcopenia and oncological outcome after RP in a cohort of totally 698 patients and 310 patients identified as sarcopenic (22). They concluded that sarcopenia has no significant association with either perioperative complications or oncological outcome after RP. This study showed a representative number of patients classified sarcopenic (55.6%). Furthermore, there were no significant differences in clinical T or N stage or biopsy Gleason score.

Two different cohort of men with prostate cancer showed contradictory associations of sarcopenia. This may be because of the different populations or different cancer-specific criteria. Patients for RP selected by urologists favoring patients younger in age with a longer life expectancy and reduced comorbidities.

Our data reveal that SMI has neither significant influence on pathological outcome nor on BCR rates after RP.

Furthermore, SMI had no impact on post-operative urine continence in our cohort. These results may suggest that sarcopenia is not a prognostic marker for functional and oncological outcome after RP.

In our study, we acknowledge several limitations to this study. First, we cannot rule out a bias due to random selection of included patients. Not all patients between the period of November 2016 and April 2017 who underwent RP have been selected for analysis and follow-up. Exclusion was caused by missing CT scans, either not readable, poor quality for analysis or missing import; or low-risk PCa patients accordingly to D'Amico classification, which have not received a preoperative CT staging. Another major limitation is that our cohort only figured 99 patients. Therefore, additional subanalyses of risk classifications are necessary. SMI was only measured by preoperative scans. The

change in SMI is not considered. Ha et al. showed a significant change in sarcopenia and SMI 1 year after radical cystectomy and might be an effective marker for oncological outcome (31). Another limitation of this study is the time of follow-up after RP, which limits the statement of sarcopenia effecting BCR. The results currently show the 12 months questionnaire feedback. The effect of BCR cannot safely be clarified; hence, the follow-up time must be prolonged. We are continuing to assess follow-up data.

Nevertheless, little is known about the association of sarcopenia on functional and oncological outcome after RP. Our study presents that sarcopenia is not significantly associated with influencing the oncological outcome, urine continence, or BCR after RP.

CONCLUSION

Sarcopenia was not significantly associated with worse functional and oncological outcome after RP. In addition, sarcopenia has no significant effect on BCR. Thus, sarcopenia is not a prognostic marker for patients with prostate cancer after RP.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethikkommission Hamburg. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

MA was responsible for conceiving the presented idea, designed the study, developed the theory, and performed the computations, literature research, data collection, writing of the manuscript with the help of CR, CT image analysis, and statistical calculations. GS contributed with literature research, investigated, and supervised the findings of this work, helped with manuscript correction and revision. DB contributed with the help of CT image analysis and providing the software, also helped with manuscript correction and revision. MF contributed with the help of manuscript correction and revision. MG contributed with literature, verified the analytical methods, helped with manuscript correction and revision. CR contributed with planning and supervision of the work, helped with statistical calculations, manuscript correction and revision. All authors discussed the results and contributed to the final manuscript.

REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. *CA Cancer J Clin.* (2020) 70:7–30. doi: 10.3322/caac.21590
2. Rohde V, Katalinic A, Wasem J, Aidelsburger P. *Gesundheitsberichterstattung des Bundes Heft 36 Prostataerkrankungen*. Arnhem: Robert Koch Institut; Statistisches Bundesamt (2007).
3. Hayashi N, Yokomizo Y, Osaka K, Makiyama K, Nakaigawa N, Yao M, et al. Ten year outcomes of treatment for localized prostate cancer in a single institution; comparison of radical prostatectomy vs radiation therapy–prospensity score matching analysis. *J Urol.* (2016) 195:2477–84. doi: 10.1016/j.juro.2016.02.2882
4. Mottet N, Bellmunt J, Briers E, Bolla M, Bourke L, Cornford P, et al. EAU–ESTRO–ESUR–SIOG guidelines on prostate cancer. In: *Presented at the EAU Annual Congress Amsterdam 2020*. Berlin: EAU Guidelines Office (2020).
5. Haese A, Knipper S, Isbarn H, Heinzer H, Tilki D, Salomon G, et al. A comparative study of robot-assisted and open radical prostatectomy in 10 790 men treated by highly trained surgeons for both procedures. *BJU Int.* (2019) 123:1031–40. doi: 10.1111/bju.14760
6. Key T. Risk factors for prostate cancer. *Cancer Surv.* (1995) 23:63–77.
7. Lichtenstein P, Holm NV, Verkasalo PK, Iliadou A, Kaprio J, Koskenvuo M. Environmental and heritable factors in the causation of cancer–analyses of cohorts of twins from Sweden, Denmark, and Finland. *N Engl J Med.* (2000) 343:78–85. doi: 10.1056/NEJM200007133430201
8. Oh SJ, Mandel P, Chun FKH, Tennstedt P, Peine S, Hohenhorst JL, et al. AB0/Rhesus blood group does not influence clinicopathological tumor characteristics or oncological outcome in patients undergoing radical prostatectomy. *Front Surg.* (2017) 4:75. doi: 10.3389/fsurg.2017.00075
9. Ouzzane A, Koenig P, Ballereau C, Zini L, Ghoneim T, Maladry F, et al. Oncologic outcomes after radical prostatectomy: French validation of the D'Amico Risk Group classification. *Prog Urol.* (2010) 20:1206–12. doi: 10.1016/j.purol.2010.05.015
10. Cruz-Jentoft AJ, Bahat G, Bauer J, Boirie Y, Bruyere O, Cederholm T, et al. Sarcopenia: revised European consensus on definition and diagnosis. *Age Ageing.* (2019) 48:16–31. doi: 10.1093/ageing/afz046
11. Joglekar S, Nau PN, Mezhir JJ. The impact of sarcopenia on survival and complications in surgical oncology: a review of the current literature. *J Surg Oncol.* (2015) 112:503–9. doi: 10.1002/jso.24025
12. Pinsky PF, Kramer BS, Reding D, Buys S. Reported family history of cancer in the prostate, lung, colorectal, and ovarian cancer screening trial. *Am J Epidemiol.* (2003) 157:792–9. doi: 10.1093/aje/kwg043
13. Del Fabbro E, Parsons H, Warneke CL, Pulivarthi K, Litton JK, Dev R, et al. The relationship between body composition and response to neoadjuvant chemotherapy in women with operable breast cancer. *Oncologist.* (2012) 17:1240–5. doi: 10.1634/theoncologist.2012-0169
14. Peng P, Hyder O, Firoozmand A, Kneuertz P, Schulick RD, Huang D, et al. Impact of sarcopenia on outcomes following resection of pancreatic adenocarcinoma. *J Gastrointest Surg.* (2012) 16:1478–86. doi: 10.1007/s11605-012-1923-5
15. Hamaguchi Y, Kaido T, Okumura S, Fujimoto Y, Ogawa K, Mori A, et al. Impact of quality as well as quantity of skeletal muscle on outcomes after liver transplantation. *Liver Transpl.* (2014) 20:1413–9. doi: 10.1002/lt.23970
16. Liu X, Liu L, Chang K, Ye D, Zheng Y, Yao X. Risk factors of perioperative complications in patients undergoing radical retropubic prostatectomy: a ten-year experience. *J Huazhong Univ Sci Technol.* (2017) 37:379–83. doi: 10.1007/s11596-017-1743-7
17. Psutka SP, Carrasco A, Schmit GD, Moynagh MR, Boorjian SA, Frank I, et al. Sarcopenia in patients with bladder cancer undergoing radical cystectomy impact on cancer-specific and all-cause mortality. *Cancer.* (2014) 120:2910–8. doi: 10.1002/cncr.28798
18. Shen W, Punyanitya M, Wang Z, Gallagher D, St.-Onge MP, Albu J, et al. Total body skeletal muscle and adipose tissue volumes: estimation from a single abdominal cross-sectional image. *J Appl Physiol.* (2004) 97:2333–8. doi: 10.1152/japplphysiol.00744.2004

19. Tan BH, Birdsell LA, Martin L, Baracos VE, Fearon KC. Sarcopenia in an overweight or obese patient is an adverse prognostic factor in pancreatic cancer. *Clin Cancer Res.* (2009) 15:6973–9. doi: 10.1158/1078-0432.CCR-09-1525
20. Wan F, Zhu Y, Gu C, Yao X, Shen Y, Dai B, et al. Lower skeletal muscle index and early complications in patients undergoing radical. *World J Surg Oncol.* (2014) 12:14. doi: 10.1186/1477-7819-12-14
21. Rutten IJ, Ubachs J, Kruitwagen RF, Van Dijk D, Beets-Tan R, Massuger L, et al. The influence of sarcopenia on survival and surgical complications in ovarian cancer patients undergoing primary debulking surgery. *Eur J Surg Oncol.* (2017) 43:717–24. doi: 10.1016/j.ejso.2016.12.016
22. Mason RJ, Boorjian SA, Bhindi B, Rangel L, Frank I, Karnes RJ, et al. The association between sarcopenia and oncologic outcomes after radical prostatectomy. *Clin Genitourin Cancer.* (2018) 16:e629–36. doi: 10.1016/j.clgc.2017.11.003
23. McDonald A, Swain T, Mayhew D, Cardan R, Baker C, Harris D, et al. CT measures of bone mineral density and muscle mass can be used to predict noncancer death in men with prostate cancer. *Radiology.* (2017) 282:475–83. doi: 10.1148/radiol.2016160626
24. Chang AJ, Autio KA, Roach M III, Scher HI. High-risk prostate cancer-classification and therapy. *Nat Rev Clin Oncol.* (2014) 11:308–23. doi: 10.1038/nrclinonc.2014.68
25. Martin L, Birdsell L, MacDonald N, Reiman T, Clandinin MT, McCargar LJ, et al. Cancer cachexia in the age of obesity: skeletal muscle depletion is a powerful prognostic factor, independent of body mass index. *J Clin Oncol.* (2013) 31:1539–47. doi: 10.1200/JCO.2012.45.2722
26. Ethgen O, Beaudart C, Buckinx F, Bruyere O, Reginster JY. The future prevalence of sarcopenia in Europe: a claim for public health action. *Calcif Tissue Int.* (2017) 100:229–34. doi: 10.1007/s00223-016-0220-9
27. Herman MP, Raman JD, Dong S, Samadi D, Scherr DS. Increasing body mass index negatively impactsoutcomes following robotic radical prostatectomy. *J Soc Laparoendosc Surg.* (2007) 11:438–42.
28. Calle EE, Rodriguez C, Walker-Thurmond K, Thun M. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. *N Engl J Med.* (2003) 348:1625–38. doi: 10.1056/NEJMoa021423
29. Freedland SJ, Terris MK, Presti JCJ, Amling CL, Kane CJ, Trock B, et al. Obesity and biochemical outcome following radical prostatectomy for organ confined disease with negative surgical margins. *J Urol.* (2004) 172:520–4. doi: 10.1097/01.ju.0000135302.58378.ae
30. Ruszat R, Bachmann A, Wyler S, Forster T, Zimmermann M, Sulser T. Einfluss des body-mass-index (BMI) auf die perioperativen Ergebnisse der endoskopischen radikalen Prostatektomie. *Aktuelle Urol.* (2006) 37:122. doi: 10.1055/s-2006-947511
31. Ha YS, Kim SW, Kwon TG, Chung SK, Yoo ES. Decrease in skeletal muscle index 1 year after radical cystectomy as a prognostic indicator in patients with urothelial bladder cancer. *Int Braz J Urol.* (2019) 45:686–94. doi: 10.1590/s1677-5538.ibju.2018.0530

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Mesorectal Lymph Node Metastases as Index Lesion in ^{68}Ga-PSMA-PET/CT Imaging for Recurrent Prostate Cancer

Conrad Leitsmann[1], Marianne Schmid[1], Carsten-Oliver Sahlmann[2], Lutz Trojan[1] and Arne Strauss[1]*

[1] Department of Urology, University Medical Center Goettingen, Goettingen, Germany, [2] Department of Nuclear Medicine, University Medical Center Goettingen, Goettingen, Germany

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****Correspondence:***
Conrad Leitsmann
conrad.leitsmann@med.uni-goettingen.de
orcid.org/0000-0001-5158-9706

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Purpose: Several studies have demonstrated an advantage of ^{68}Ga-PSMA-PET/CT as staging modality for detection of prostate cancer (PCa) metastases. Data concerning metastatic manifestation and impact on PCa development of mesorectal lymph nodes (MLN) is limited. Our investigation describes MLN metastases as index lesion in ^{68}Ga-PSMA PET/CT imaging for recurrent PCa.

Methods: Twelve PCa patients with biochemical recurrence (BCR) after primary therapy who prospectively underwent a baseline ^{68}Ga-PSMA-PET/CT initially showed MLN metastases. Eight of these patients received a follow-up ^{68}Ga-PSMA-PET/CT to evaluate treatment response and further evolution. Prostate-specific antigen (PSA)-levels, changes in PSMA-uptake of MLN metastases and further ^{68}Ga-PSMA PET/CT findings were recorded.

Results: Median PSA at the first ^{68}Ga-PSMA-PET/CT was 5.39 ng/ml. In all patients therapeutic management changed after the first ^{68}Ga-PSMA-PET/CT. Androgen deprivation therapy (ADT) was initiated in seven of eight patients, one patient restarted initial ADT. Three patients additionally received salvage radiation therapy (sRT) including the prostatic lodge and docetaxel chemotherapy was started in one case. At follow-up, a decrease of PSA-level was detected in all patients (median 2.05 ng/ml) after median 10 months. In six of eight patients we observed a decrease or complete regress of PSMA-uptake in MLN in the follow-up ^{68}Ga-PSMA-PET/CT.

Conclusion: MLN metastases detected by ^{68}Ga-PSMA-PET/CT seem to be a relevant localization of tumor manifestation and may serve as index lesion in the treatment of recurrent PCa. Besides the known oncological benefits of ADT and sRT, in case of sole MLN metastases individualized therapy like salvage lymphadenectomy or RT with a defined radiation field could be options for these patients.

Keywords: prostate cancer, metastases, mesorectal lymph node, PSMA, ^{68}Ga-PSMA-PET/CT imaging

INTRODUCTION

In Europe the most common cancer in male is prostate cancer (PCa) with growing incidence in the past two decades (1). Radical prostatectomy (RP) and radiation therapy (RT) are curative therapeutic options (2). Nonetheless, within 10 years after primary therapy up to 40% of patients develop biochemical recurrence (BCR) (3). Here, due to limited sensitivity and specificity conventional imaging methods, such as computed tomography (CT) and magnetic resonance imaging (MRI), might struggle to accurately determine the presence or absence of metastatic or recurrent PCa (4, 5).

The Type-II transmembrane protein prostate specific membrane antigen (PSMA) is overexpressed in almost all PCa cells (6). Luiting et al. demonstrated promising results for detecting PCa relapse by Gallium (^{68}Ga)-labeled PSMA positron emission tomography/computed tomography (PET/CT) (^{68}Ga-PSMA PET/CT) (7). Further studies have confirmed the advantage of ^{68}Ga-PSMA PET/CT compared to conventional imaging as well as functional ^{18}F-choline-based PET/CT for patients with BCR (5, 8–11). Increasingly discussed salvage treatment of recurrent PCa also demands exact staging (4, 10, 12, 13). Roach et al. prospectively investigated the value of ^{68}Ga-PSMA PET/CT in the management of PCa (14). They found that ^{68}Ga-PSMA PET/CT scans detected previously unsuspected disease and assumed a greater impact in patients with BCR.

PCa typically spreads to the proximal external iliac, the lower sacral vessel, the obturator, the upper sacral, the common iliacal and, at last, the paraaortic lymph nodes (15). A previous retrospective analysis by Hijazi et al. however showed PCa metastases in mesorectal lymph nodes (MLN) in 12 of 76 patients with BCR, which were detected by ^{68}Ga-PSMA PET/CT (11). Current studies addressing this issue are limited. Previous reports either described MLN metastases of PCa occurring in sentinel lymph node scintigraphy or as a random result during anterior rectal resection in patients with rectal cancer (16–19). We are considering MLN as a relevant region for lymph node metastasis in patients with recurrent PCa and as an important therapeutic target. The rationale behind is to further improve PCa-outcomes. A recent analysis by Horn et al. mentioned the correlation of a single lesion on PSMA PET/CT and low PSA as favorable prognosticators following PSMA-targeted radioguided surgery (20).

The current study presents observations of MLN metastases as index lesion for recurrent PCa and describes the depiction of treatment changes in patients with BCR and confirmed MLN metastases. In this context we discuss therapeutic options such as the surgical challenge of MLN dissection and the definition of the radiation field.

METHODS

Patients' Characteristics

Patients with BCR after RT or RP or primary androgen deprivation therapy (ADT) were included. Twelve patients with BCR according to the EAU guidelines showed solitary MLN metastases in a baseline ^{68}Ga-PSMA PET/CT (21). These 12 patients derive from a cohort, which was previously reported by Hijazi et al. of 76 patients with BCR, which were detected by 68Ga-PSMA PET/CT (11). One patient died during follow-up and was excluded from further investigation. Three of 12 patients were not available for follow-up. A total of eight patients received a follow-up ^{68}Ga-PSMA PET/CT.

For each patient initial TNM (2), initial Gleason-Score, initial PSA-value (iPSA), year and type of primary treatment, date of the baseline ^{68}Ga-PSMA PET/CT, date of the follow-up ^{68}Ga-PSMA PET/CT, PSA-value at the follow-up ^{68}Ga-PSMA PET/CT, treatment since the baseline ^{68}Ga-PSMA PET/CT, treatment (change) after the second ^{68}Ga-PSMA PET/CT, oncological status and PSA-value at follow-up were available. The study was performed as an individual diagnostic pathway per patient in consensus with the patient and was approved by the local Ethics Committee of the University Medical Center Goettingen (approval June 7, 2015).

^{68}Ga-PSMA-PET/CT Imaging

Baseline ^{68}Ga-PSMA PET/CT was performed between November 2014 and June 2015. Eight patients underwent a follow-up ^{68}Ga-PSMA PET/CT between February and May 2016 to measure changes in the PSMA-uptake of MLN metastases or other PCa metastases. The ^{68}Ga-PSMA PET/CT was performed as previously described (11, 22). An experienced nuclear medicine physician analyzed the images. The maximal standard uptake volume (SUV_{max}) 1 and 3 h post injection was recorded.

Statistical Analysis

Descriptive statistics of variables focused on frequencies. Means and standard deviations, medians and interquartile ranges were reported. Covariates consisted of initial TNM, initial Gleason-Score, iPSA, year and type of primary treatment, date of the baseline ^{68}Ga-PSMA PET/CT, date of the follow-up ^{68}Ga-PSMA PET/CT, PSA-value at the follow-up ^{68}Ga-PSMA PET/CT, treatment since the first ^{68}Ga-PSMA PET/CT, treatment change since the follow-up ^{68}Ga-PSMA PET/CT, oncological status and PSA-value at follow-up.

All analyses were performed using Statistical Package for the IBM (SPSS, Inc., Chicago, IL, version 25). All parameters were analyzed with Fisher exact test.

RESULTS

Patients' Characteristics

Characteristics of the total cohort are displayed in **Table 1**. Median age was 74 years (range 66–81 years), median iPSA was 19.25 ng/ml (range 4.6–90 ng/ml). Eight of the 12 patients underwent RP with standardized lymph node dissection as primary therapy (21). Two patients received primary ADT, one received a prostate-hyperthermia therapy and one received percutaneous RT. Median PSA at the first ^{68}Ga-PSMA PET/CT was 5.39 ng/ml (range 0.31–67.21 ng/ml). Baseline ^{68}Ga-PSMA-PET/CT showed predominantly one MLN metastasis (only one patient had two lesions). Time interval between primary therapy

TABLE 1 | Patients' characteristics of the initial study group ($n = 12$).

ID	Age	TNM	iPSA (ng/ml)	Gleason score	PSA at first ^{68}Ga-PSMA-PET/CT (ng/ml)	Initial treatment (date)
1	76	pT2c (only Biopsy)	90	9	67.21	AA 11/2014
2	74	pT4, pN0, L1, V0, Pn1, R0	8	9	2.57	RP 03/09
3	75	pT2c, pN1, L1, V0, Pn1, R0	32	8	20	AA 12/2014
4	79	pT2b, pN1, L0, V0, Pn0, R0	93	9	23	Hyperthermia and immunotherapy 03/2014
5	66	pT2c, pN0, L0, V0, Pn0, R0	23	7b	0.31	RP 10/2012
6	79	pT3a, pN0, L0, V0, Pn0, R0	9.56	7a	1.84	RP 04/2013
7	59	pT3a, pN0, L1, V1, Pn0, R0	15.5	9	0.6	RP 03/2014
8	77	pT3b, pN0, L1, V1, Pn0, R0	12	6	6.18	RP 04/1996
9	81	pT3b, pN1, L1, V1, Pn0, R0	90	9	10	RP 19/2014
10	78	pT3b, pN0, L1, V1, Pn0, R0	5.6	8	0.6	RP 02/2012
11	54	pT2b (only Biopsy)	35	7	13	RT 03/2010
12	74	pT2c, pN0, L0, V1, Pn1, R0	4.6	9	4.6	RP 06/2015

AA, Antiandrogen therapy; iPSA, initial Prostate specific antigen-value; RP, Radical prostatectomy; RT, Radiation therapy.

TABLE 2 | Patient's follow up data ($n = 8$).

ID	PSA value at 1. scan	PSA value at 2. scan	PSA-difference (ng/ml)	Time between scans (months)	Treatment after first ^{68}Ga-PSMA-PET/CT	Treatment after second ^{68}Ga-PSMA-PET/CT	Follow-up-time (months)	PSA (ng/ml)
1	67.21	0.7	−66.51	14	ADT (Trenantone)	ADT (Trenantone)	24	0.38
2	2.57	0.08	−2.49	14	ADT (Trenantone)	ADT (Trenantone)	22	0.001
5	0.31	0.001	−0.309	13	ADT (Trenantone)	ADT (Trenantone)	21	0.001
6	1.84	0.001	−1.839	10	RT + ADT (Trenantone)	ADT (Trenantone)	20	0.001
7	0.6	0.001	−0.599	10	ADT (Bicalutamid)	ADT (Bicalutamid)	22	0.001
8	6.18	3.98	−2.2	9	ADT (Trenantone) + Docetaxel	Best supportive care	–	–
11	13	9.35	−3.65	8	RT + ADT (Trenantone)	Chance ADT (Abiraterone)	22	13.5 (CR)
12	2	0.1	−1.9	10	RT + ADT (Firmagone)	ADT (Firmagone)	19	0.001

AA, Antiandrogen therapy; CR, castration resistance within the FU; PSA, Prostate specific antigen; RP, Radical prostatectomy; RT, Radiation therapy (follow-up-time = months between second scan/treatment change until last follow up).

and first ^{68}Ga-PSMA PET/CT was median 36 month (range 9–231 months). Median FU of the total study period was 32 months (range 29–38 months).

Follow-Up

Follow-up data are shown in **Table 2**. Median time between the two ^{68}Ga-PSMA-PET/CT imaging was 10 months (range 8–14 months). A decrease of PSA serum value was demonstrated in all patients (median decrease −2.02 ng/ml, range −0.3 to −66.9 ng/ml). In all patients therapeutic management changed after the diagnosis of MLN metastases in the baseline ^{68}Ga-PSMA-PET/CT. ADT [Luteinizing hormone-releasing hormone (LHRH) receptor agonists and antagonists] was initiated in seven of eight patients. One patient restarted initial ADT. Three patients received additional salvage RT including the prostatic lodge and docetaxel chemotherapy was started in one case. Three of these eight patients demonstrated a PSA <0.001 at the second ^{68}Ga-PSMA-PET/CT.

Oncologic treatments after the follow-up ^{68}Ga-PSMA-PET/CT are shown in **Table 2**. Six of eight patients continued ADT and no change of treatment was needed. These patients showed hormone-sensitive PCa. In one patient antiandrogen therapy was changed (LHRH agonist replaced by Abiraterone acetate) as the follow-up ^{68}Ga-PSMA-PET/CT showed a regression of the MLN metastasis but revealed one new metastasis next to the left kidney vessel. This patient developed castration resistant disease. Because of a massive disease progression decision for best supportive care strategy was made

for one patient. For this patient we could not evaluate the castration level in the follow up.

PSA-values at the last follow-up between November 2017 and March 2018 [follow-up time median 22 months (range 19–24 months)] measured below 0.001 ng/ml in five of these six patients.

Comparison of ^{68}Ga-PSMA-PET/CT Imaging

We summarized results of the baseline and follow-up ^{68}Ga-PSMA-PET/CT in **Table 3**. Median SUV_{max} of the MLN 3 h post injection (p.i.) was 7.5 (range 3.2–13.8). Only one patient showed more than one MLN metastasis in the baseline scan.

In the follow-up scan five patients showed no more uptake of PSMA in ^{68}Ga-PSMA-PET/CT imaging at all. An example is shown in **Figure 1**. The uptake declined in one patient from SUV_{max} 10.5–3.5 3 h p.i. One patient presented an increase of the one MLN metastasis from SUV_{max} 7.7–8.8 3 h p.i. and revealed new metastases in the liver (SUV_{max} 7.1 3 h p.i.), retroperitoneal (SUV_{max} 12.7 3 h p.i.), and mediastinal (SUV_{max} 8.1 3 h p.i.) as well as local tumor recurrence (SUV_{max} of 5.8 3 h p.i.). Another

TABLE 3 | Comparison of ^{68}Ga-PSMA-PET/CT imaging ($n = 8$).

ID	Mesorectal lymph node count in first scan	SUV_{max} 3 h p.i.	^{68}Ga-PSMA-PET/CT findings
1	1	13.8	No PSMA-uptake
2	1	10.5	Reduction of SUV_{max} to 3.5
5	1	3.2	No PSMA-uptake
6	1	–	No PSMA-uptake
7	1	7.5	No PSMA-uptake
8	1	7.6	Increase of one MLN metastasis (SUV_{max} 8.8), new metastases of the liver (SUV_{max} 7.1), retroperitoneal (SUV_{max} 12.7), and mediastinal (SUV_{max} 8.1); local recurrence (SUV_{max} 5.8)
11	2	5.5	Reduction of two MLN metastases (SUV_{max} to 3.7); new metastasis next to the left kidney vessels (SUV_{max} of 7.8)
12	1	6.1	No PSMA-uptake

Ga, Gallium; PSMA, Prostate specific membrane antigen; SUV, Standard uptake volume; p.i., post injection.

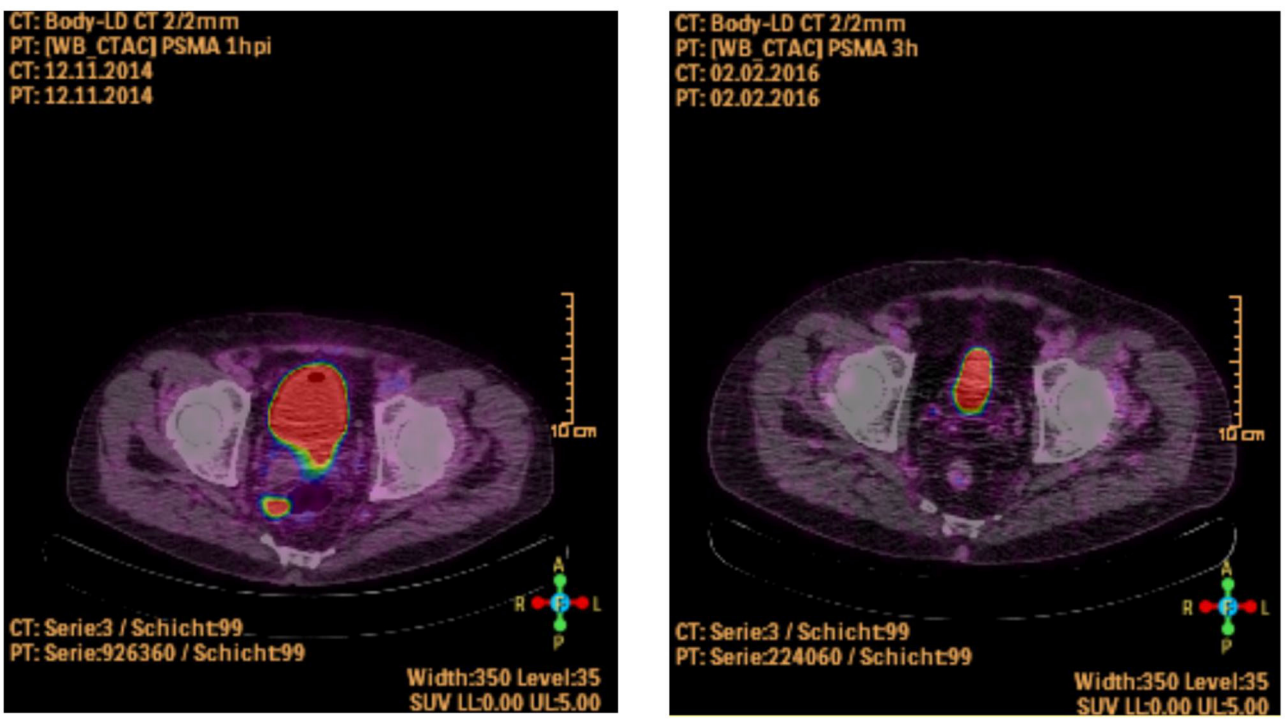

FIGURE 1 | Patient with a singular MLN metastasis in the first ^{68}Ga-PSMA-PET/CT (picture on the left side) and showing no more PSMA-uptake following ADT in the second scan after 13 months (picture on the right side, Patient ID 1).

patient showed regression of the two MLN metastases (SUV_{max} 5.5–3.7 3 h p.i.), but the follow-up ^{68}Ga-PSMA-PET/CT revealed one new metastasis next to the left kidney vessels (SUV_{max} of 7.8 3 h p.i.).

DISCUSSION

The aim of our study was to evaluate MLN metastases as "index lesion" in patients with recurrent PCa. Hijazi et al. showed solitary metastasis in MLN detected by ^{68}Ga-PSMA-PET/CT in 12 of 76 patients (11). We could include eight of these 12 patients into a follow-up and present our observations. All of these patients started ADT with LHRH agonists or antagonists after the first scan. Two of these six patients were additionally treated with RT including pelvic lymph nodes and the prostatic bed. Six patients showed definitive benefit of secondary treatments and PSA-values decreased significantly ($p < 0.01$). ADT and RT resulted in complete regress or at least reduced PSMA-uptake of MLN metastases in six of eight patients in the follow-up ^{68}Ga-PSMA-PET/CT. Additionally, PSA was <0.001 ng/ml in three of these patients at the second ^{68}Ga-PSMA-PET/CT and in five at last follow-up. Usually, in PCa patients with PSA-values below 0.001 ng/ml after treatment further imaging would not be recommend. However, previous investigations report of superior imaging and detection of metastases with ^{68}Ga-PSMA PET/CT (14). As our study intended to investigate its value in treatment monitoring, five patients with PSA-values below 0.001 ng/ml underwent a follow-up ^{68}Ga-PSMA-PET/CT in this context. In these patients no additional metastases were found.

In the current literature comparable studies are rare. For a long time MNL have been never considered as a route of PCa spread. Murray et al. and Mourra et al. identified metastases of PCa in MLN in 4.5 and 9.4% of histologically examined lymph nodes in patients who underwent anterior rectal resection (16, 17). These studies demonstrated a relevant number of patients with MLN metastases of PCa. Additionally, Swanson et al. showed in an investigation of lymphatic drainage of PCa that PCa rarely metastasizes in MLN and that an assessment of nodal staging based on obturator lymph node dissection had an accuracy of 50% (15). A standard dissection of pelvic lymph nodes does not include the mesorectum region or the posterior pelvic subsite (PPS) (23).

Current data showed a promising opportunity using ^{68}Ga-PSMA-PET/CT for assessment of lymph node metastases in PCa patients with BCR prior to salvage lymphadenectomy (24). These studies use this fact to investigate possible PSMA-guided surgery in these patients (25). A very recent review revealed PSMA-PET/CT as an indicator for metastasis targeted therapies in patients with recurrent PCa (26). So, it is most important to exactly detect and locate lymph node metastases before salvage treatment of PCa, as well as in recurrent PCa. This could affect the choice of treatment strategies like salvage lymphadenectomy or PSMA-guided surgery that has been proved to be successful concerning intraoperative detection and removal of metastatic lesions promises to improve prognosis of recurrent PCa-patients (27). However, patients with MLN metastases of PCa, like demonstrated in our study, are a small subgroup of patients which have unfavorable ratio of risk/benefit for a salvage lymph dissection because of the difficult surgical approach. Due to the difficulty of the surgical approach to MNL metastases three of eight patients of our study therefore underwent adjuvant RT. Two of these had no PSMA-uptake in the second scan and a significant decrease of PSA-values. Although our study could not prove an additional positive effect of adjuvant RT due to the small number of patients, this option may serve as possible treatment modality for patients with MLN metastases. Resent publications used ^{68}Ga-PSMA-PET/CT for the planning of RT (28, 29). Schiller et al. and Habl et al. showed a significant influence of the higher detection rate of PCa lesions with ^{68}Ga-PSMA-PET/CT imaging for radiation planning in recurrent PCa patients allowing individually personalized treatment compared to conventional CT or MRI staging. Of note, unless lymph node involvement is assured, the posterior pelvic subsite (PPS) below S3 or the mesorectal region is usually not comprised in the radiation filed of PCa (30).

Limitations of our study include the small number of patients, heterogenic baseline oncologic parameters like iPSA or Gleason and an incomplete follow-up of all 12 patients. Additionally, no comparison or control group was present. We focused on patients with mesorectal lymph node metastases to evaluate this index lesion and we did not investigate the total initial study group with a follow up PSMA-PET/CT. Reasons were the justification of exposure to radiation and the high rate of patients lost to follow up. Two patients seemed to have no benefit of the initiated treatment. One patient showed a new PSMA-positive lymph node next to a kidney vessel. A possible reason for this new metastasis might concern the irradiation area, which was focused on pelvic lymph nodes and the prostatic fossa and not on the aortocaval lymph node region. One patient presented a severe tumor progression in the follow-up ^{68}Ga-PSMA-PET/CT. This patient had the longest time interval between the initial PCa therapy and the change of oncological treatment (9 years) and was one of the oldest patients in our cohort (77 years).

Further studies with larger number of patients need to be performed to evaluate the relevance of our findings. Future investigations should focus on the potential benefit of individual RT vs. (challenging) guided surgery vs. systemic treatments.

CONCLUSIONS

Recent studies showed an optimized detection of metastasis in recurrent PCa by ^{68}Ga-PSMA-PET/CT imaging. This investigation used MLN metastases as index lesion. Considering such a rare localization like the mesorectum reveals individualized treatment options for such patients and may lead to improved oncological outcomes.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethic Committee, University Medical Center Goettingen. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

CL, LT, and AS: protocol/project development, data collection and management, data analysis, and manuscript writing. MS: manuscript editing and data collection and management. C-OS: protocol/project development, data collection and management, and data analysis. All authors contributed to the article and approved the submitted version.

REFERENCES

1. Bray F, Lortet-Tieulent J, Ferlay J, Forman D, Auvinen A. Prostate cancer incidence and mortality trends in 37 European countries: an overview. *Eur J Cancer.* (2010) 46:3040–52. doi: 10.1016/j.ejca.2010.09.013
2. Mottet N, Bellmunt J, Bolla M, Briers E, Cumberbatch MG, De Santis M, et al. EAU-ESTRO-SIOG guidelines on prostate cancer. Part 1: screening, diagnosis, and local treatment with curative intent. *Eur Urol.* (2017) 71:618–29. doi: 10.1016/j.eururo.2016.08.003
3. Roehl KA, Han M, Ramos CG, Antenor JA, Catalona WJ. Cancer progression and survival rates following anatomical radical retropubic prostatectomy in 3,478 consecutive patients: long-term results. *J Urol.* (2004) 172:910–4. doi: 10.1097/01.ju.0000134888.22332.bb
4. Kosuri S, Akhtar NH, Smith M, Osborne JR, Tagawa ST. Review of salvage therapy for biochemically recurrent prostate cancer: the role of imaging and rationale for systemic salvage targeted anti-prostate-specific membrane antigen radioimmunotherapy. *Adv Urol.* (2012) 2012:921674. doi: 10.1155/2012/921674
5. Afshar-Oromieh A, Avtzi E, Giesel FL, Holland-Letz T, Linhart HG, Eder M, et al. The diagnostic value of PET/CT imaging with the (68)Ga-labelled PSMA ligand HBED-CC in the diagnosis of recurrent prostate cancer. *Eur J Nucl Med Mol Imaging.* (2015) 42:197–209. doi: 10.1007/s00259-014-2949-6
6. Perera M, Papa N, Christidis D, Wetherell D, Hofman MS, Murphy DG, et al. Sensitivity, specificity, and predictors of positive (68)Ga-prostate-specific membrane antigen positron emission tomography in advanced prostate cancer: a systematic review and meta-analysis. *Eur Urol.* (2016) 70:926–37. doi: 10.1016/j.eururo.2016.06.021
7. Luiting HB, Van Leeuwen PJ, Busstra MB, Brabander T, Van Der Poel HG, Donswijk ML, et al. Use of gallium-68 prostate-specific membrane antigen positron-emission tomography for detecting lymph node metastases in primary and recurrent prostate cancer and location of recurrence after radical prostatectomy: an overview of the current literature. *BJU Int.* (2020) 125:206–14. doi: 10.1111/bju.14944
8. Afshar-Oromieh A, Zechmann CM, Malcher A, Eder M, Eisenhut M, Linhart HG, et al. Comparison of PET imaging with a (68)Ga-labelled PSMA ligand and (18)F-choline-based PET/CT for the diagnosis of recurrent prostate cancer. *Eur J Nucl Med Mol Imaging.* (2014) 41:11–20. doi: 10.1007/s00259-013-2525-5
9. Ceci F, Uprimny C, Nilica B, Geraldo L, Kendler D, Kroiss A, et al. (68)Ga-PSMA PET/CT for restaging recurrent prostate cancer: which factors are associated with PET/CT detection rate? *Eur J Nucl Med Mol Imaging.* (2015) 42:1284–94. doi: 10.1007/s00259-015-3078-6
10. Morigi JJ, Stricker PD, Van Leeuwen PJ, Tang R, Ho B, Nguyen Q, et al. Prospective comparison of 18F-fluoromethylcholine versus 68Ga-PSMA PET/CT in prostate cancer patients who have rising PSA after curative treatment and are being considered for targeted therapy. *J Nucl Med.* (2015) 56:1185–90. doi: 10.2967/jnumed.115.160382
11. Hijazi S, Meller B, Leitsmann C, Strauss A, Ritter C, Lotz J, et al. See the unseen: mesorectal lymph node metastases in prostate cancer. *Prostate.* (2016) 76:776–80. doi: 10.1002/pros.23168
12. Heidenreich A, Moul JW, Shariat S, Karnes RJ. Role of salvage lymph node dissection in prostate cancer. *Curr Opin Urol.* (2016) 26:581–9. doi: 10.1097/MOU.0000000000000343
13. Pfister D, Porres D, Heidenreich A, Heidegger I, Knuechel R, Steib F, et al. Detection of recurrent prostate cancer lesions before salvage lymphadenectomy is more accurate with (68)Ga-PSMA-HBED-CC than with (18)F-Fluoroethylcholine PET/CT. *Eur J Nucl Med Mol Imaging.* (2016) 43:1410–7. doi: 10.1007/s00259-016-3366-9
14. Roach PJ, Francis R, Emmett L, Hsiao E, Kneebone A, Hruby G, et al. The impact of (68)Ga-PSMA PET/CT on management intent in prostate cancer: results of an Australian prospective multicenter study. *J Nucl Med.* (2018) 59:82–8. doi: 10.2967/jnumed.117.197160
15. Swanson GP, Hubbard JK. A better understanding of lymphatic drainage of the prostate with modern imaging and surgical techniques. *Clin Genitourin Cancer.* (2013) 11:431–40. doi: 10.1016/j.clgc.2013.04.031
16. Murray SK, Breau RH, Guha AK, Gupta R. Spread of prostate carcinoma to the perirectal lymph node basin: analysis of 112 rectal resections over a 10-year span for primary rectal adenocarcinoma. *Am J Surg Pathol.* (2004) 28:1154–62. doi: 10.1097/01.pas.0000131543.80147.3d
17. Mourra N, Parc Y, Mcnamara D, Tiret E, Flejou JF, Parc R. Lymph node metastases of prostatic adenocarcinoma in the mesorectum in patients with adenocarcinoma or villous tumor of the rectum with collision phenomenon in a single lymph node: report of five cases. *Dis Colon Rectum.* (2005) 48:384–9. doi: 10.1007/s10350-004-0776-8
18. Ganswindt U, Schilling D, Muller AC, Bares R, Bartenstein P, Belka C. Distribution of prostate sentinel nodes: a SPECT-derived anatomic atlas. *Int J Radiat Oncol Biol Phys.* (2011) 79:1364–72. doi: 10.1016/j.ijrobp.2010.01.012
19. Rousseau C, Le Thiec M, Ferrer L, Rusu D, Rauscher A, Maucherat B, et al. Preliminary results of a (68) Ga-PSMA PET/CT prospective study in prostate cancer patients with occult recurrence: diagnostic performance and impact on therapeutic decision-making. *Prostate.* (2019) 79:1514–22. doi: 10.1002/pros.23869
20. Horn T, Kronke M, Rauscher I, Haller B, Robu S, Wester HJ, et al. Single lesion on prostate-specific membrane antigen-ligand positron emission tomography and low prostate-specific antigen are prognostic factors for a favorable biochemical response to prostate-specific membrane antigen-targeted radioguided surgery in recurrent prostate cancer. *Eur Urol.* (2019) 76:517–23. doi: 10.1016/j.eururo.2019.03.045
21. Cornford P, Bellmunt J, Bolla M, Briers E, De Santis M, Gross T, et al. EAU-ESTRO-SIOG guidelines on prostate cancer. Part II: treatment of relapsing, metastatic, and castration-resistant prostate cancer. *Eur Urol.* (2017) 71:630–42. doi: 10.1016/j.eururo.2016.08.002
22. Hijazi S, Meller B, Leitsmann C, Strauss A, Meller J, Ritter CO, et al. Pelvic lymph node dissection for nodal oligometastatic prostate cancer detected by 68Ga-PSMA-positron emission tomography/computerized tomography. *Prostate.* (2015) 75:1934–40. doi: 10.1002/pros.23091
23. Rigatti P, Suardi N, Briganti A, Da Pozzo LF, Tutolo M, Villa L, et al. Pelvic/retroperitoneal salvage lymph node dissection for patients treated with radical prostatectomy with biochemical recurrence and nodal recurrence detected by [11C]choline positron emission tomography/computed tomography. *Eur Urol.* (2011) 60:935–43. doi: 10.1016/j.eururo.2011.07.060

24. Rauscher I, Maurer T, Beer AJ, Graner FP, Haller B, Weirich G, et al. Value of 68Ga-PSMA HBED-CC PET for the assessment of lymph node metastases in prostate cancer patients with biochemical recurrence: comparison with histopathology after salvage lymphadenectomy. *J Nucl Med.* (2016) 57:1713–9. doi: 10.2967/jnumed.116.173492
25. Rauscher I, Duwel C, Wirtz M, Schottelius M, Wester HJ, Schwamborn K, et al. Value of (111) In-prostate-specific membrane antigen (PSMA)-radioguided surgery for salvage lymphadenectomy in recurrent prostate cancer: correlation with histopathology and clinical follow-up. *BJU Int.* (2017) 120:40–7. doi: 10.1111/bju.13713
26. Wondergem M, Van Der Zant FM, Broos WA, Knol RJ. Clinical impact of PSMA PET in biochemically recurrent prostate cancer; a review of the literature. *Tijdschrift voor Urol.* (2020) 10:109–21. doi: 10.1007/s13629-020-00296-6
27. Maurer T, Robu S, Schottelius M, Schwamborn K, Rauscher I, Van Den Berg NS, et al. (99m)Technetium-based prostate-specific membrane antigen-radioguided surgery in recurrent prostate cancer. *Eur Urol.* (2019) 75:659–66. doi: 10.1016/j.eururo.2018.03.013
28. Habl G, Sauter K, Schiller K, Dewes S, Maurer T, Eiber M, et al. (68) Ga-PSMA-PET for radiation treatment planning in prostate cancer recurrences after surgery: Individualized medicine or new standard in salvage treatment. *Prostate.* (2017) 77:920–7. doi: 10.1002/pros.23347
29. Schiller K, Sauter K, Dewes S, Eiber M, Maurer T, Gschwend J, et al. Patterns of failure after radical prostatectomy in prostate cancer - implications for radiation therapy planning after (68)Ga-PSMA-PET imaging. *Eur J Nucl Med Mol Imaging.* (2017) 44:1656–62. doi: 10.1007/s00259-017-3746-9
30. Lawton CA, Michalski J, El-Naqa I, Buyyounouski MK, Lee WR, Menard C, et al. RTOG GU Radiation oncology specialists reach consensus on pelvic lymph node volumes for high-risk prostate cancer. *Int J Radiat Oncol Biol Phys.* (2009) 74:383–7. doi: 10.1016/j.ijrobp.2008.08.002

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frontiers in Surgery

SYSTEMATIC REVIEW
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Penile Rehabilitation and Treatment Options for Erectile Dysfunction Following Radical Prostatectomy and Radiotherapy: A Systematic Review

Melianthe Nicolai[1,2], Ahmet Urkmez[3], Selcuk Sarikaya[4], Mikkel Fode[5], Marco Falcone[6], Maarten Albersen[7], Murat Gul[8], Georgios Hatzichristodoulou[9], Paolo Capogrosso[10] and Giorgio Ivan Russo[11]*

[1] Urology Department, The Netherlands Cancer Institute (NKI), Amsterdam, Netherlands, [2] Urology Department, Diakonessenhospital, Utrecht, Netherlands, [3] Haydarpasa Numune Training and Research Hospital, Istanbul, Turkey, [4] Gulhane Training and Research Hospital, Ankara, Turkey, [5] Urology Department, University of Copenhagen, Copenhagen, Denmark, [6] Urology Department, Molinette Hospital, Turin, Italy, [7] Urology Department, University Hospitals Leuven, Leuven, Belgium, [8] School of Medicine, Selcuk University, Konya, Turkey, [9] Martha-Maria Hospital Nuremberg, Nuremberg, Germany, [10] Vita-Salute San Raffaele University, Milan, Italy, [11] Urology Department, University of Catania, Catania, Italy

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Clemens Mathias Rosenbaum, Asklepios Klinik Barmbek, Germany

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Simone Albisinni, Université libre de Bruxelles, Belgium

***Correspondence:**
Melianthe Nicolai
m.nicolai@nki.nl

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After radical prostatectomy (RP) or radiotherapy (RT) for prostate cancer, erectile dysfunction (ED) is the main complication next to urinary incontinence, affecting quality of life. The pathophysiology of ED after these treatments is believed to include neuropraxia causing reduced oxygenation and structural changes of the tissue in the corpora cavernosa. Next to the option of sparing the nerves during RP, research has been focusing on methods for penile rehabilitation after RP and RT, since it occurs often, even after nerve-sparing techniques were used. In animal studies, the use of phosphodiesterase type 5 inhibitors (PDE5i) after cavernous nerve damage is supported, but results in human studies are contradictory. Non-medical treatment options such as vacuum device therapy, hyperbaric oxygen therapy, yoga, aerobic, or pelvic floor training may be helpful, but evidence is scarce. Clear guidelines for penile rehabilitation are not yet available. However, care and support for ED after RP and RT is highly demanded by a large group of patients, so measures have to be taken even though the evidence is not strong yet. In this systematic review, an overview of the literature for penile rehabilitation and treatment options for ED after RP and RT is provided, using only randomized controlled trials (RCT).

Keywords: penile rehabilitation, erectile dysfunction, phosphodiesterase 5 (PDE 5) inhibitors, vacuum devices, intracavernosal injection, pelvic floor therapy

INTRODUCTION

Prostate cancer (PCa) is the second most common cancer among men, its prevalence is increasing, at the moment it accounts for 15% of all and 10% of male cancers (1). Radical prostatectomy (RP) and radiotherapy (RT) are important treatment options for localized PCa, but these techniques lead to erectile dysfunction in many of those receiving them. Erectile function (EF) is, next to urinary symptoms, the main concerns for patients after treatment for PCa (2).

Approximately 45% of patients diagnosed with PCa undergo RP (3); using the nerve-sparing technique leads to lower rates of erectile dysfunction (ED) (4). The pathophysiology causing ED after RP mainly depends on neural injury (5), because even using nerve-sparing techniques, manipulation and physical traction of the nerves may still lead to varying degrees of ED (5).

Intraoperative neurostimulation has been appointed as a useful option, making it easier to save the neurovascular bundle without impairing chances of survival. However, it's use is still not widely spread (3). Several modalities for penile rehabilitation have been described in literature. Mainly involving long term treatment with the established modalities for ED, such as phosphodiesterase-5 inhibitors (PDE5Is) (6–8). Besides this medicinal treatment options, extracorporeal shockwave lithotripsy (ESWT) has been described as a potential option for penile rehabilitation while this treatment may stimulate the Schwann cells (9). In addition, as it is clearly known that the pelvic floor is involved in male sexual function, it may be important to consider pelvic floor rehabilitation in the treatment of ED (10). Other modalities for penile rehabilitation and treatment of ED after RP described in this review are penile vibratory nerve stimulation (PVS), intracavernosal injection therapy, hyperbaric oxygen therapy, and aerobic training.

Shortly after RT, ED is seen in ∼40% of the patients. This number rises in the first 2 years after RT to 61.5% (11). RT is often combined with neoadjuvant or adjuvant ADT for localized disease, and even a short term of ADT, negatively affects EF as well (12). PDE5i may protect against ED when started directly after RT. Vacuum erectile devices (VED) and even yoga practice have been studied for their effects on EF after RT. In this systematic review, the literature on this topic is evaluated.

MATERIALS AND METHODS

This systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement. Three authors (S.S., A.U., and M.N.) independently searched PubMed, MEDLINE, EMBASE, PsychINFO, OVID, and Web of Science using the following terms: (prostate cancer OR prostate neoplasm OR prostatic neoplasm OR cancer of the prostate OR prostatic cancer OR prostatic cancers OR prostate neoplasms OR prostate cancer OR prostate neoplasms) AND (radiotherapy OR radiotherapy OR radiotherapies OR radiation therapy OR radiation therapies OR radiation treatment OR radiation treatments OR targeted radiotherapies OR targeted radiotherapy OR targeted radiation therapy OR targeted radiation therapies OR radical prostatectomy) AND (erectile dysfunction OR erectile dysfunction OR male sexual impotence OR male impotence OR impotence OR impotence).

Search criteria were limited to full-text English articles. Only randomized controlled trials (RCT) were included. All relevant papers from 2000 to 2020 were retrieved. References of selected articles and international guidelines were hand searched to identify additional reports.

As this systematic review focused on the management of ED after RP and RT in curative setting, studies that did not focus on specific PCa treatments were excluded. Data extraction was independently performed by three authors (S.S., A.U., and M.N.) and was cross checked afterwards. Disagreements were resolved in consultation with the other authors. When two or more studies were reported by the same institution and/or authors in overlapping time periods, the one which was published more recently was included.

RESULTS

A search of the selected databases revealed 283 articles and two articles identified through other sources. Fifty-six articles were removed as duplicates, and 172 articles were excluded based on inclusion and exclusion criteria. Fifty-seven full-text articles were assessed for eligibility, and 34 articles excluded because they were either systematic reviews, not written in English, or represented non-randomized controlled trials (**Figure 1**).

PENILE REHABILITATION FOLLOWING RADICAL PROSTATECTOMY

We identified 14 RCTs on therapeutic options for ED after RP. **Table 1** summarizes the key findings from these studies.

PDE-5 Inhibitors

To date, five RCTs have evaluated the impact of early usage of PDE5i in men on the recovery of spontaneous erections following nerve-sparing RP (nsRP).

The first of these trials showed that administration of sildenafil every night for 36 weeks, starting 4 weeks after surgery, did significantly increased return of spontaneous erections. However, enrollment was prematurely ended and only 76 men completed the trial because of the fact that the placebo response rate of 25% at blinded interim review, suggested a lack of treatment effect. On the contrary, spontaneous EF [a total score of >8 for questions 3 and 4 of the International Index of Erectile Function (IIEF)] and a positive response to "Were erections good enough for satisfactory sexual activity?" were seen in only 4% of the placebo group vs. 27% ($P = 0.0156$) of the sildenafil group (6).

The second trial was performed by Montorsi et al. (2). They conducted a randomized, double-blind, double-dummy, multicenter study with parallel groups at 87 centers across the world. A total of 628 men after bilateral nsRP were included. One month preoperatively, all had a normal erectile function domain (IIEF-EF) score of more or equal to 26. The primary endpoint: spontaneous erections after wash-out, was not met because no significant differences were observed among treatment groups following washout. IIEF-EF scores of 22 or higher were achieved in 28.9% for placebo, in 24.1% for vardenafil nightly, and in 29.1% for vardenafil on demand. The effect of on-demand use of vardenafil during the double-blind treatment period was chosen as a secondary endpoint. On demand, vardenafil use was associated with significantly higher IIEF-EF scores at all double-blind visits when compared with placebo. It was associated with significantly better sexual encounters over the entire double-blind treatment period as well.

Comparing the usage of an oral PDE5i and intraurethral alprostadil, McCullough et al. (13) performed a prospective,

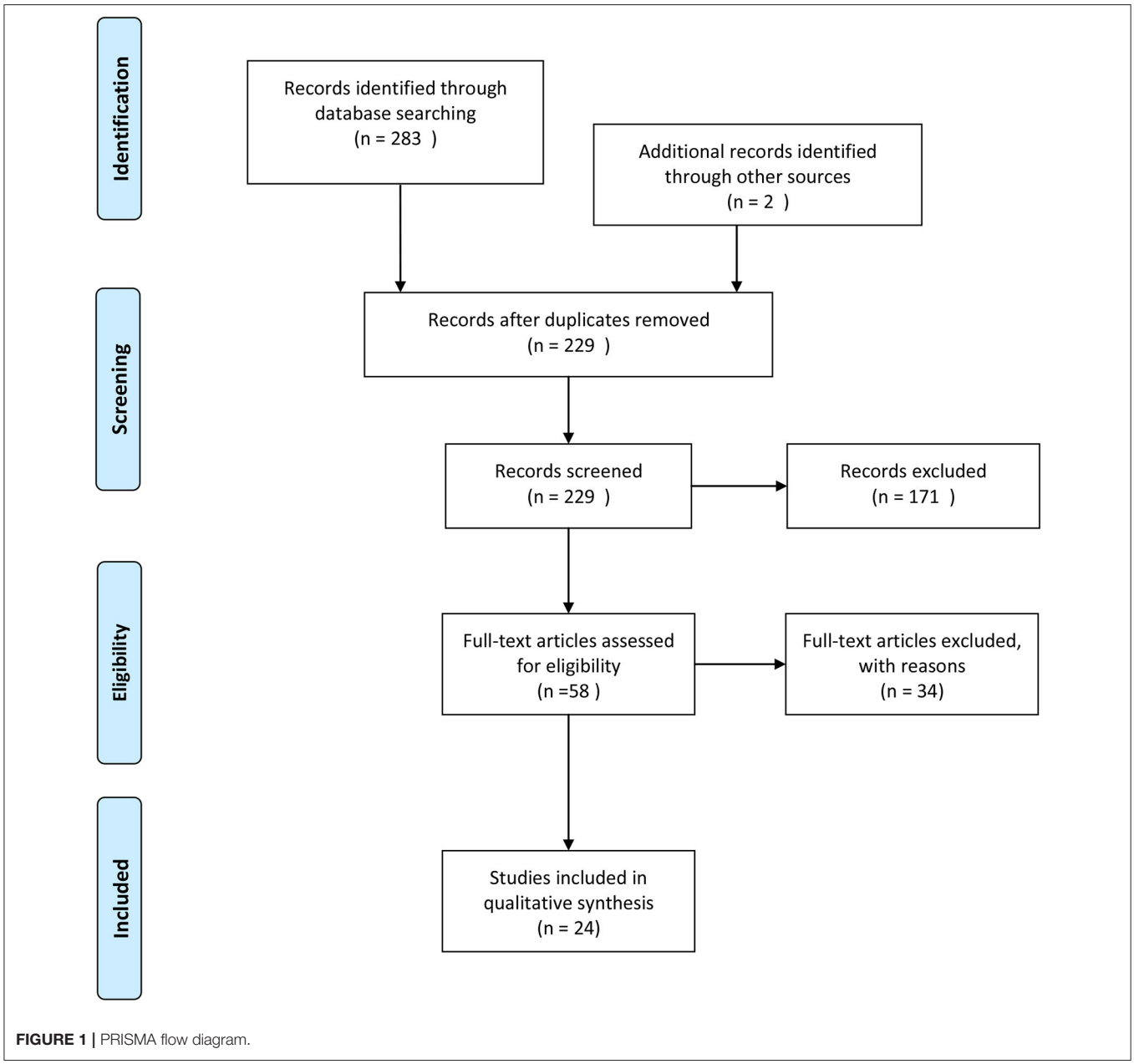

FIGURE 1 | PRISMA flow diagram.

randomized, open-label, multicenter study in American men with normal EF who underwent bilateral nsRP. Subjects started nightly treatment with intraurethral alprostadil or oral sildenafil citrate (50 mg) within 1 month of nsRP and continued for 9 months. No statistical differences were seen for any of the endpoints between these two groups.

Another trial performed by Bannowsky et al. (14), randomized 43 patients into two different follow-up groups. Groups were matched by preoperative IIEF score, age, numbers of nocturnal erections, and status of nsRP and EF before nsRP as evaluated with the IIEF-5. After catheter removal, post-nsRP nightly penile rigidity was measured during Rigiscan®. No medications influencing EF were used during this period. Patients that kept their nocturnal erections as detected during Rigiscan recordings received sildenafil 25 mg/days at night after catheter removal. Controls with a similar number of nocturnal erections were used. Between the groups, a significant difference in IIEF-5 scores and time to recovery of EF was seen at 36 and 52 weeks (both $P < 0.001$). In the sildenafil group, penile erection sufficient for vaginal intercourse were achieved and maintained by 47% at 1 year after nsRP without usage of "on-demand" sildenafil. In the control group, this was 28%. However, the trial did not include a wash-out period, so these findings represented erections with sildenafil treatment vs. erections without sildenafil treatment and not spontaneous erectile function.

The fifth trial evaluating penile rehabilitation with PDE5i was the REACTT trial (15), comparing efficacy of tadalafil 5 mg once daily and tadalafil 20 mg on demand vs. placebo in

TABLE 1 | Overview of RCT about penile rehabilitation after radical prostatectomy.

References	Treatment	Sample size	Study design	Intervention	Assessment	Outcome measurements
PDE5i						
Padma-Nathan et al. (6)	nsRP start after catheter removal	41 Sildenafil 50 mg 40 sildenafil 100 mg 42 patients placebo	RCT (1:1:1) double-blind Placebo-controlled Multi-center	Either sildenafil 50 or 100 mg nightly or placebo	Erectile function w IIEF (15-item)	Premature closure of study however "erections good enough for satisfactory sexual activity?" in 4% of the placebo group vs. 27% of the sildenafil users.
Montorsi et al. (2)	nsRP start after catheter removal	210 Vardenafil nightly, 210 Vardenafil on demand, 208 placebo	RCT (1:1:1) Phase II trial Double-blind Placebo-controlled Multi-center	9-mo double-blind treatment with a Vardenafil regimen, a 2-mo single-blind washout period + optional 2-mo open-label period, vs. placebo	Erectile function w IEF-EF score (15 item) and Sexual Encounter Profile (SEP) questions 2 and 3	No statistically significant differences among treatment groups in patients with an IIEF-EF score of ≥22 or in SEP3 success rates after washout period. On-demand vardenafil treatment resulted in significantly greater IIEF-EF scores and better SEP3 response rates than placebo over the entire treatment period.
McCullough et al. (13)	nsRP <1 month after surgery	139 intraurethral alprostadil 73 sildenafil citrate 50 mg	RCT (1:1) Prospective, randomized, open label, multicenter	Intraurethral alprostadil nightly or sildenafil 50 mg nightly. After 1-month sildenafil citrate (100 mg) on demand (6 attempts/ month)	Erectile function w IIEF (15-item) and SEP and Erectile Dysfunction Inventory of Treatment Satisfaction and measured stretched penile length	Nightly subtherapeutic intraurethral alprostadil and sildenafil 50 mg both improved penile base and tip rigidity in 24% compared to placebo. The benefit to return of erectile function of nightly sildenafil citrate and subtherapeutic intraurethral alprostadil appears to be comparable within the first year of surgery.
Bannowsky et al. (14)	11 unilateral nsRP 32 bilateral nsRP	23 sildenafil 25 mg nightly 18 no PDE-5 inhibitor	RCT (1:1) prospective, single center	Rigiscan measurement nocturnal erections after catheter removal, patients with preserved nocturnal erections randomized: sildenafil mg/day at night vs. no treatment	Erectile function w IIEF-5 questionnaire at 6, 12, 24, 36, and 52 weeks after NSRP	There was a significant difference in IIEF-5 score and time to recovery of erectile function between the groups ($P < 0.001$), with potency rates of 86 vs. 66%.
Montorsi et al. (15) (REACTT)	nsRP 4 months after surgery	139 tadalafil once daily *143 tadalafil* on demand *141* placebo	RCT (1:1:1) Double-blind, three-arm, parallel-group study, Multicenter, phase 4	9 mo of treatment with tadalafil 5 mg once daily, tadalafil 20 mg on demand, or placebo followed by a 6-wk wash out and 3-mo open-label tadalafil once daily (all patients)	Erectile function w IIEF (15-item), SEP- 3 and penile length	Early initiation of tadalafil (once daily or on demand) had no effect on unassisted erectile function at 10.5 mo after nsRP. Secondary endpoints: IIEF-EF scores ≥22 and SEP-3 significantly higher for tadalafil once daily compared with placebo, exceeding the minimum clinically relevant difference. IIEF-EF and SEP-3 decreased during drugs free washout in all groups and improved during open-label treatment. Penile length loss was reduced vs. placebo in the tadalafil once daily group.
Patel et al. (7)	nsRP 4 months after surgery (data REACTT trial)	139 tadalafil once daily *143 tadalafil* on demand *141* placebo	RCT (1:1:1) double-blind, three-arm, parallel-group study, multicenter, phase 4	9 mo of treatment with tadalafil 5 mg once daily, tadalafil 20 mg on demand, or placebo followed by a 6-wk wash out and 3-mo open-label tadalafil once daily (all patients)	QoL: Expanded Prostate Cancer Index Composite (EPIC-26), Erectile Dysfunction Inventory of Treatment Satisfaction (EDITS), and Self-Esteem and Relationship (SEAR) questionnaires	During dubble blind treatment, IIEF-EF, EPIC sexual domain score, and EDITS score improved significantly with tadalafil dialy vs. placebo but not with tadalafil on demand.

(Continued)

TABLE 1 | Continued

References	Treatment	Sample size	Study design	Intervention	Assessment	Outcome measurements
Jo et al. (16)	nsRP	60 patients directly after surgery 60 patients ≥ 3 month after surgery	RCT (1:1) prospective	sildenafil 100 mg (2×/week, for 3 month) immediately after urethral catheter removal recovery or ≥ 3 months after surgery	Erectile function w IIEF (5-item)	Significant improvement of erectile function in early treatment vs. late treatment: 41.4% EF recovery in the early group vs. 17.7% EF recovery in the delayed group at 12 months after surgery.
INTRACAVERNOSAL INJECTION THERAPY						
Montorsi et al. (17)	nsRP	30 patients	RCT (1:1) prospective	alprostadil injections 3×/weeks for 12 weeks or observation, 6 mo follow up	sexual history, physical examination, color Doppler sonograph and polysomnographic recording of nocturnal erections	67% recovery of spontaneous erection sufficient for satisfactory sexual intercourse in treatment group vs. 20% in observation group ($p < 0.01$)
VACUUM DEVICE THERAPY						
Köhler et al. (18)	Uni or bilateral nsRP	14 patients early intervention protocol with VED 1 month after RP, 14 control group, 6 months after RP using VED	RCT (1:1) Prospective	daily rehabilitation protocol consisting of 10 min/days using the VED without constriction ring, for 5 months. Up visit was 9.5 (6–12) months after RP.	IIEF-5 questionnaire and measurements of penile flaccid length, stretched length, prepubic fat pad, and midshaft circumference before and at 1, 3, 6, 9, and 12 months after RP	IIEF scores higher in early intervention at 3 months ($P = 0.008$) and 6 months ($P = 0.012$), after RP. No significant changes in penile flaccid length, prepubic fat pad, or mid-shaft circumference in either group. Stretched penile length was preserved in early group and decreased by ∼2 cm ($P = 0.013$) in late intervention group.
Raina et al. (19)	nsRP and non-nerve-sparing (NNS) RP	74 patients daily VED use for 9 months 35 observation	14 patients Early intervention protocol with VED 1 month after RP, 14 control group, 6 months after RP using VED	RCT (1:1) Prospective	Sexual Health Inventory of Men, IIEF-5, stratified by the NS status. compliance, change in penile length, return of natural erection, and ability for vaginal intercourse	32% in intervention group reported return of natural erections at 9 months vs. 37% in controls with 17% having erections sufficient for vaginal intercourse vs. 11% in controls (significance not mentioned). IIEF-5 score significantly increased after VCD use in both the NS and NNS groups. After a mean use of 3 months, 18% discontinued treatment.
PVS						
Fode et al. (20)	nsRP	42 penile vibratory stimulation 31 control	RCT (1:1) Multicenter	Daily penile vibratory stimulation (PVS) Start 1 week before nsRP and for 6 weeks after catheter removal.	Erectile function w IIEF (5-item)	IIEF-5 scores higher in the PVS group at all time points after surgery, but no statistical significance. 12 months after surgery 53% in the PVS group had a IIEF-5 score ≥ 18, vs. 32% in controls ($P = 0.07$).
TRACOLIMUS						
Mulhall et al. (21)	nsRP	62 tacrolimus 69 placebo	RCT (1:1) Double-blinded Multicenter	Either Tracolimus or placebo 27 weeks (1 week prior to and 6 months after RP), followed up for 2 years post-RP.	Erectile function w IIEF (15-item) questionnaire	Use of Tracolimus was not associated with improvement in recovery of erectile function after RP.
LiESWT						
Baccaglini et al. (22)	Open RP or laparoscopic RP, nerve sparing and non-nervesparing	36 low-intensity extracorporeal shockwave therapy (LiESWT) 41 control	RCT (1:1) open-label, 2 parallel arms	Both arms started 5 mg tadalafil/day after removal of catheter., LiESWT received 2,400 shocks/session-week on four different penile regions. The full treatment: 19,200 impulses in 8 weeks.	Erectile function w IIEF (5-item)	Comparing the proportion of patients with an IIEF-5 score ≥17: no significant difference between groups was noted (17.1 vs. 22.2%; $P = 0.57$) 16 weeks after RP.

(Continued)

TABLE 1 | Continued

References	Treatment	Sample size	Study design	Intervention	Assessment	Outcome measurements
HYPERBARIC OXYGEN THERAPY						
Chiles et al. (23)	nsRP	40 hyperbaric oxygenation (100% oxygen) therapy 43 oxygen enriched air (controls)	RCT (1:1) Double blind, prospective Multicenter	Either exposition 100% oxygen (hyperbaric conditions) or higher pressured air (controls). The primary outcome: erectile function at 18 months.	Erectile function w IIEF (5-item) And EPIC-26	No statistically significant differences between the two groups on any outcome measure.
AEROBIC TRAINING						
Jones et al. (24)	nsRP	25 aerobic training 25 usual care (controls)	RCT (1:1) Single center	Aerobic therapy consisted of 5 supervised walking sessions/ week, 30–45 min /session, at 55–100% of VO_{2peak} for 6 mo. Usual care participants maintained their usual exercise levels.	Erectile function w IIEF (15-item)	ED prevalence decreased in both groups from baseline to 6 mo and from baseline to 12 mo, with no significant differences between groups.
PELVIC FLOOR MUSCLE TRAINING						
MIlios et al. (25)	Open RP or laparoscopic RP, nerve sparing and non-nervesparing	50 high intensity pelvic floor muscle training 47 control group "usual" pelvic floor muscle training.	RCT (1:1) Single center	Either the usual pelvic floor muscle training of 3 sets/d (controls) Or high intensity pelvic muscle training of 6 sets/d pelvic floor muscle training in standing, both groups Commencing 5 weeks before RP for total of 3 month. Evaluation, 2, 6 and 12 weeks post RP.	Erectile function w IIEF (5-item) Expanded Prostate Cancer Index Composite for Clinical Practice (EPIC-CP)	No statistically significant differences between the two groups on any outcome measure.

Summary of randomized controlled trials on penile rehabilitation following radical prostatectomy.

improving unassisted EF following nsRP when taken over 9 months. EF was defined by the proportion of patients achieving an IIEF score equal or over 22 after 6 weeks of drug-free washout (DFW). The primary endpoint of the trial: quicker return to spontaneous erections was not met. At 10.5 months after nsRP, after DFW, no effect was seen of early initiated tadalafil (once daily or on-demand) on unassisted EF. The authors suggest that the treatment period of 9 months may have been too short to achieve optimal EF recovery. Indeed, recovery rates of EF were low at 10.5 months after nsRP with 25.2% in the tadalafil once daily group, 19.7% in the tadalafil on demand group, and 14.2% with placebo at this time point. Secondary measures included Sexual Encounter Profile question 3 (SEP-3), IIEF-EF scores, and penile length. At the end of the double-blind treatment mean IIEF-EF scores were significantly improved in both the tadalafil on demand and daily groups compared with placebo. For the SEP-3 group, this was seen for tadalafil once daily only. Penile length loss was significantly reduced at 9 months when compared with placebo in the tadalafil once daily group (mean difference 4.1 mm; $P = 0.032$).

In addition to the REACTT trial, Patel et al. (7) secondary outcome measures on QoL and treatment satisfaction were addressed in early post-nsRP patients who participated in the REACTT trial. They evaluated several aspects of QoL using, for example, the Expanded Prostate Cancer Index Composite Short Form (EPIC-26) which addresses sexual, urinary, bowel, and hormonal function, the Erectile Dysfunction Inventory of Treatment Satisfaction (EDITS) and the Self-Esteem and Relationship (SEAR) instrument (assessing patient and partner sexual relationship confidence and self-esteem). EF was measured using the IIEF-EF domain score at three timepoints: baseline (post-nsRP), after double-blind treatment, and after open-label treatment of tadalafil. During double-blind treatment, the IIEF-EF, the EPIC sexual domain score, and the EDITS score did significantly improve with tadalafil daily when compared with placebo. This was not the case for tadalafil on demand. On demand vs. placebo at end of double-blind treatment did not differ. And, after open label treatment tadalafil daily and on demand vs. placebo did not significantly differ either. However, satisfaction with treatment increased significantly in both tadalafil groups. During double-blind treatment, EDITS total scores increased significantly with daily tadalafil ($P = 0.05$) and on-demand tadalafil ($P = 0.041$) vs. placebo. Improvement was significant for tadalafil daily vs. placebo only at the end of open-label treatment ($P = 0.035$).

Timing was showed to be an important factor in penile rehabilitation in the trial of Jo et al. (16), which randomized start of PDE5i directly vs. 3-months post-nsRP. The proportion of patients receiving PDE5i (3× per week sildenafil 100 mg) directly after nsRP during a period of 12 months, achieved full recovery of EF significantly more often than those starting sildenafil in the delayed group, 3 months after the operation ($P = 0.034$).

In conclusion: comparing on-demand and daily tadalafil for the improvement of spontaneous erections after nsRP, no statistical differences were found. However, with the available evidence nothing can be said about the inferiority of tadalafil daily compared to on-demand use. Vardenafil showed good treatment effect for on-demand use, but daily use did not lead to a quicker return to spontaneous erections. Sildenafil used daily did show a positive effect on erectile function, and in one trial, a shorter time to return to spontaneous erections. All PDE5i showed to have beneficial effects on satisfaction with sexual life and especially tadalafil increased quality of intercourse and sexual activity when used daily. Intraurethral alprostadil appears to have similar beneficial effects on penile rehabilitation as sildenafil daily, but the evidence is not bulky enough to draw strong conclusions.

Intracavernosal Injection Therapy

One trial as perfomed after nsRP, including 30 patients with preoperative good erections that underwent nsRP. They were randomized to alprostadil injections three times per week, for a total of 12 weeks, or observed directly afterwards, starting directly after nsRP. After 6 months, patients were assessed using sexual history, physical examination, color Doppler sonography of the cavernous arteries, and recording of nocturnal erections with polysomnography. In the treatment group, 67% noted recovery of spontaneous erection that was sufficient for sexual intercourse after the 6-months follow-up (in comparison with 20% in the observation group, $P < 0.01$). In the treatment group, all but one patient showed normal erections at nocturnal erection measurement and normal penile hemodynamics with color Doppler sonography. In the observation group 53% showed cavernous veno-occlusive dysfunction and 20% showed cavernous nerve injury.

In conclusion, alprostadil injection therapy 3× per week after nsRP may be an effective treatment to promote recovery rate of spontaneous erections (17).

Vacuum Erection Device Therapy

In rats after cavernous nerve crushing, vacuum therapy showed to improve intracarvernosal pressure using nerve stimulation and to help preserve penile size in comparison with controls (26, 27). Furthermore, vacuum erectile devices (VED) reduced hypoxia-inducible factors and increased endothelial NO synthase expression and smooth muscle/collagen ratios in these rodent studies (26, 27).

Two randomized trials have tested VED after RP.

The first study from Kohler et al. (18) randomized 28 men in an early or a delayed treatment group after unilateral or bilateral nerve-sparing RP. Starting 4 weeks after surgery, the early treatment group had to use VED daily for two consecutive 5-min intervals (not using the constriction band). The delayed treatment group had to use VED before intercourse (with constriction band). Both groups were offered PDE5Is in addition. Significantly higher IIEF scores were seen in the early treatment group at 3 and 6 months. However, no difference was seen between the groups after 1 year ($P = 0.75$). PDE5I usage did not significantly differ between the groups. Spontaneous erections adequate enough for intercourse were not reported in either group after 1 year follow-up.

The second trial by Raina et al. (19) randomized for daily VED for 9 months after RP (nerve-sparing and non-nerve-sparing) or to no treatment ($n = 109$). Penile constriction bands for intercourse were allowed in the VED group. In the VED group, 20% was excluded because they discontinued the treatment: 55% due to discomfort, 20% due to penile bruising, 17% due to social inconvenience, and 8% due to inability to use the device. After 9 months of follow-up, the mean IIEF-5 score was significantly higher in the treatment group compared with the no-treatment group (16 ± 7.33 vs. 11.1 ± 1.76, $P < 0.05$). From the VED group, 17% reported return spontaneous erections sufficient for intercourse vs. 11% in the no-treatment group; this difference was not significant.

In conclusion, VED may be offered as a supportive measure in the period after RP, increasing chances of successful intercourse, especially when used next to a PDE5i. Conclusions about efficacy on penile rehabilitation cannot be drawn with the current literature.

Penile Vibratory Nerve Stimulation

Penile vibratory nerve stimulation (PVS) has been shown to stimulate the nerves of the pelvic floor. In up to 90% of men with spinal cord injuries, PVS could induce ejaculation (28). Fode et al. (20) conducted a trial to examine the effect of PVS in the preservation and restoration of EF in conjunction with nsRP. It was hypothesized that PVS in the early postoperative period after RP may stimulate the cavernous nerves through the reflex arch and would help in the restitution from neuropraxia and improvement of long-term EF (20). A total of 68 patients were randomized between daily stimulation at the frenulum from a minimum of 1 week before the surgery and after catheter removal, for 6 weeks after nsRP. At all-time points after surgery, IIEF-5 scores were highest in the PVS group (median 18 points vs. 7.5 points in control group at 12 months, $P = 0.09$) (28); 53% of patients in the PVS group reached IIEF-5 scores of at least 18, compared with 32% of patients in the control group ($P = 0.07$).

In conclusion, there may be a place for PNS in penile rehabilitation; however, more trials are needed to affirm the existing evidence.

Tacrolimus

Immunophilin ligands are found to have neuroprotective effects in various animal models, including the rat cavernous nerve injury model. This model is believed to be representative of the neural injury that occurs in human beings at the time of RP (29). The immunophilin ligands bind to a series of intracellular signaling proteins: the immunophilins. While found in immune tissue, immunophilins are even more abundant in neural tissue, peripherally as well as centrally (30). Tacrolimus (Prograf, Astellas Pharmaceuticals) is a macrolide immunophilin ligand approved by the Food and Drug Administration for prevention of allograft rejection in liver and kidney transplantation. However, in animal models, tacrolimus was also shown to have neuroprotective and neuroregenerative properties (31).

Mulhall et al. (21) randomized 132 patients with excellent erections prior to RP, receiving tacrolimus or placebo for 27 weeks and followed them up for 2 years post-RP. No differences in IIEF scores were found between these two groups. Other trials evaluating the effects of tacrolimus in EF have not been performed up until to date.

Low-Intensity Extracorporeal Shockwave Lithotripsy

Evidence has shown improvement of EF after low-intensity extracorporeal shockwave lithotripsy (LiESWT). For example, in patients with vasculogenic ED, it occurs to induce neovascularization and as a consequence to enhancing penile perfusion. This might convert PDE5i non-responders to responders (9). Furthermore, neuroinjury disease models indicated LiESWT to have neuroprotective and neurodegenerative effects (32).

Baccaglini et al. (22) performed the first randomized clinical trial using LiESWT. Ninety-two patients were randomized between application of the LiESWT (2-months period) in the 6th week after bilateral nsRP or in the control group, patients in both groups started tadalafil 5 mg directly after removal of the catheter postoperatively. In the experimental group, the full LiESWT treatment consisted of 19,200 impulses across 2 months. An improvement of EF was seen over the period of the study in the treatment group in which 22.2% of the patients reached an IIEF-5 score of 17 or higher, compared with 17.1% in the control group. However, the difference was not statistically significant. To shine light on the true effect of LiESWT after nsRP, a trial using a larger cohort has to be performed.

In conclusion, no statements can be made for the effect of LiESWT on penile rehabilitation after RP, more RCTs are necessary.

Hyperbaric Oxygen Therapy

Up until now, just one RCT (23) has been performed randomizing patient post-robot-assisted RP to hyperbaric oxygen therapy or placebo therapy. A total of 109 potent men who underwent robot-assisted bilateral nsRP were randomized to a hyperbaric oxygenation therapy group or a control group. A total of 43 men in the control group (normal air) and 40 in the hyperbaric oxygenation therapy group completed the 18-months follow-up. No statistical differences were seen between the groups looking at the IIEF-5 scores ($P = 0.611$) or any of the other outcome measures. This trial may be limited by the lack of a sham hyperbaric condition in which participants would receive air but at lower pressures than men in the treatment group. Whereas, in this study, controls received air at increased pressure, leading to a partial pressure of oxygen of twice the oxygen available at standard atmospheric conditions.

In conclusion, with only one RCT available, no conclusions can be drawn about the effects of hyperbaric oxygen therapy on return to spontaneous erections after RP.

Aerobic Training

Erectile dysfunction following nsRP is mainly caused by neuronal damage. However, vascular endothelial cell dysfunction is an important factor as well, leading to impaired penile tissue oxygenation, resulting in smooth muscle apoptosis, fibrosis, and veno-occlusion dysfunction (33). Aerobic training (AT) may be

used to improve EF (24). AT leads to a variety of vascular adaptations such as improvements in peripheral artery flow-mediated dilation. Artery flow-mediated dilation provides a good measure of vascular endothelial function. The efficacy of aerobic training (AT) was investigated by a trial conducted by Jones et al., examining AT compared with usual care on ED prevalence in 50 men after nsRP. AT consisted of five walking sessions per week at 55–100% of peak oxygen uptake (VO_{2peak}) for 0.5 to 1 h/session following a non-linear prescription (24). ED, measured as an IIEF score under 21, decreased by 20% in the AT group and by 24% in the usual-care group ($P = 0.406$). No significant differences where seen in any of the EF subscales ($P > 0.05$). Although significant differences between groups were observed for changes in flow-mediated dilation and VO_{2peak}, favoring AT (24). The authors appointed this lack of significant difference to the different mechanism inducing ED. In heart failure, endothelial-derived nitric oxide (NO) release is the principal contributor to ED, but in the post-RP setting, surgery-induced neuronal injury is the most important contributor. Furthermore, 6 months of AT may be too short to achieve effect on EF.

In conclusion, although aerobic training significantly improves vascular health, AT does not lead to significant differences in erectile function after RP in the first 6 months after surgery.

Pelvic Floor Therapy

Pelvic floor muscle (PFM) function is shown to be involved in enhancement of penile blood flow. It is well-known that the ischiocavernous muscle facilitates erection and that the bulbocavernous is involved in maintaining it. Blood is blocked from escaping from the corpora carvernosa by contraction of the bulbocavernous muscles by pressing on the deep dorsal vein of the penis. However, literature regarding the role of PFM training in recovery of sexual function after RP is limited. Although, a couple RCTs confirmed a direct link between PFM strength and increased rigidity in erection (34, 35).

Recently, the effects of PFM training on RP-related ED was evaluated in a RCT using a high-intensity vs. "usual-care" PFM training for the pre-rehabilitation of RP-related ED which started 5 weeks prior to surgery (25). Assessments were undertaken using the EPIC-CP and IIEF-5 questionnaires at 5 weeks preoperatively and at 2, 6, and 12 weeks after surgery. As was expected, after RP, a drastic and immediate reduction of EF was seen in both groups. There were no group differences seen in the ED domain scores across the time points. IIEF-5 scores also were similar. This trial was limited in several ways, however, at first by the fact that PFM was performed in both groups. The follow-up was performed only in the first 12 weeks postoperatively in which not much effect on EF is to be expected, and most importantly, no selection was made by the surgical technique used: non-nerve-sparing RP patients were included in both treatment groups together with unilateral and bilateral nsRP patients (25).

In conclusion, a larger randomized trial using clear methodology has to be conducted to assess the true effects of PFM on EF in patient after RP; with the current data, no statements can be made.

PENILE REHABILITATION FOLLOWING RADIATION THERAPY

We identified 9 RCTs on therapeutic options for erectile dysfunction after RT. **Table 2** summarizes the key findings from these studies.

PDE-5 Inhibitors

So far, three RCTs have evaluated the effect of early PDE5i usage on EF preservation and recovery of spontaneous erections in men who underwent RT for PCa. Ilic et al. (38), who investigated daily use of sildenafil 50/100 mg after RT (mainly seed brachytherapy), suggested that early use of regular sildenafil does not improve long-term EF, although short-term sexual function may be improved while on medication. However, this study was limited by the small number of patients (14 patients with sildenafil and 13 patients with placebo) and long period of recruiting time. Similarly, Pisansky et al. (41), who conducted a RCT to explore the protective effect of daily tadalafil 5 mg on EF during and after RT, have shown no improvement in EF and sexual satisfaction compared with placebo. Apart from these two RCTs, Zelefsky et al. (43) have reported significant improvement in EF and overall sexual satisfaction at 6th and 12th months with daily use of sildenafil 50 mg during and for half a year after the initiation of RT. However, this positive effect on EF and IIEF scores was no longer significantly prominent at 24 months, yet improvement in satisfaction and desire were persistent at the 24th month (82 vs. 56%). Aside from the rehabilitation studies, daily and on-demand uses of tadalafil has been shown to be effective in improving EF and increasing the ratio of successful sexual intercourse (up to 70% of patients) in two RCTs (39, 42). Higher treatment compliance was observed with daily tadalafil 5 mg usage compared with on-demand tadalafil 20 mg (100 vs. 86%) (42). However, no difference was observed between daily and on-demand use of tadalafil in terms of EF improvement and successful sexual intercourse (42). On-demand uses of Sildenafil 50/100 mg were also shown to be effective in improving EF and increasing the ratio of successful sexual intercourse in four RCTs (12, 37, 40, 43). In the RCTs which use the beginning dose of sildenafil 50 mg, most of the patients (up to 90%) needed a dose adjustment to 100 mg sildenafil (12, 40).

Differences in findings among the studies may also be related to duration of androgen deprivation treatment (ADT) and when ADT had been discontinued and testosterone recovery occurred. Greater benefit in erectile response to sildenafil was shown in patients who received shorter period of ADT ($\leq$4 months) (12). Also, it has been shown that longer time period to start medical therapy after RT is related to poor response to sildenafil (44).

In all of the eight RCTs, sildenafil and tadalafil both appeared well-tolerated with no serious adverse effects even with daily doses of sildenafil 100 mg.

All studies used IIEF questionnaire (15 items) to assess EF. Additionally, two RCTs used the sexual adjustment questionnaire (12, 41) and one RCT used Locke Marital adjustment test (12) to evaluate patient- and partner-reported outcomes. Sexual encounter profile (SEP) patient diary were also used in two RCTs

TABLE 2 | Overview of RCT about penile rehabilitation after radiotherapy.

References	Treatment	Sample size	Study design	Intervention	Assessment	Outcome measurements
YOGA						
Ben-Josef et al. (36)	EBRT (6- to 9- weeks course) for clinical stage I-II PCa	34 patients w yoga, 34 patients w/o yoga	RCT (1:1) Phase II trial	Biweekly yoga interventions (each session 75 min) throughout the 6–9 weeks courses of RT	General quality of life (FACT-G), fatigue (BFI), erectile function (IIEF-5) and IPSS	Less cancer related fatigue w yoga ($p < 0.001$) Higher IIEF-5 scores w yoga ($p = 0.0333$) No significant effect of yoga on IPSS No adverse event w yoga
PDE5i						
Harrington et al. (37)	EBRT T1c-3 PCa Completed RT btw 6 months and 3 years prior to study	33 patients w sildenafil-placebo 33 patients w placebo-sildenafil	RCT (1:1) Double-blind Placebo-controlled Cross-over	Either sildenafil 50/100 mg-placebo or placebo-sildenafil 50–00 mg (on demand) Two sexual activity attempts→ crossover→ 2 attempts	Erectile function w IIEF (15-item)	Significant increase in all domains of IIEF w sildenafil In nearly half of the patients, the improvement in erectile function domain score was more than 5 points.
Ilic et al. (38)	EBRT (11%) BCT (89%) T1c-3 PCa	14 patients w sildenafil 13 patients w placebo	RCT (1:1) Single-center Double-blind Placebo-controlled	Either sildenafil 50–100 mg/days or placebo 1 month after RT for 6 months	Erectile function w IIEF (15-item)	No significant difference in IIEF scores between groups during study and at 2-years follow-up Daily sildenafil 50–100 mg well-tolerated, no serious adverse events
Incrocci et al. (39)	EBRT T1c-3 PCa Completed RT at least 12 months prior to study	30 patients w tadalafil-placebo 30 patients w placebo-tadalafil	RCT (1:1) Double-blind Placebo-controlled Cross-over	Either tadalafil 20 mg-placebo or placebo-tadalafil 20mg (on demand) 6 weeks→ crossover→ 6 weeks	Erectile function w IIEF (15-item) and Sexual Encounter Profile (SEP) patient dairy	Significant increase in IIEF scores w tadalafil Improvement of erectile function in 67% (tadalafil) vs. 20% (placebo) of patients Successful intercourse w tadalafil (48%) vs. placebo (9%)
Incrocci et al. (40)	EBRT T1c-3 PCa Completed RT at least 6 months prior to study	30 patients w sildenafil-placebo 30 patients w placebo-sildenafil	RCT (1:1) double-blind placebo-controlled cross-over	Either sildenafil 50/100 mg-placebo or placebo-sildenafil 50/100 mg (on demand) 6 weeks→ crossover→ 6 weeks	Erectile function w IIEF (15-item)	Significant increase in IIEF scores w sildenafil Improvement of erectile function in 45% (sildenafil) vs. 8% (placebo) of patients Successful intercourse w sildenafil (55%) vs. placebo (18%) 90% of patients needed a dose adjustment to 100 mg sildenafil
Pisansky et al. (41)	EBRT (63%) BCT (37%) for Clinical stage I-II PCa	112 patients w tadalafil 5 mg 109 patients w placebo	RCT (1:1) multicenter double-blind placebo-controlled	Either daily tadalafil 5mg or placebo within 7 days after the initiation of EBRT or the date of BCT. Administration was continue for 24 weeks	Erectile function w IIEF (15-item) and Sexual Adjustment Questionnaire (20-item)	No significant difference in any domain of IIEF questionnaire Partners of men treated w tadalafil noted no significant effect on sexual satisfaction and marital adjustment
Ricardi et al. (42)	EBRT cT1-3 PCa	27 patients w on-demand tadalafil 20 mg 25 patients w daily tadalafil 5 mg	RCT (1:1) Phase II trial Not-blinded No control	Either daily tadalafil 5 mg or on-demand tadalafil 20 mg for 12 weeks	Erectile function w IIEF (15-item) and Sexual Encounter Profile (SEP) patient dairy	Significant improvement in all domains of the IIEF in both arms→ No difference btw two arms Successful sexual intercourse in nearly 70% of patients in both arms at 3 months Higher treatment compliance w daily tadalafil 5 mg (100 vs. 86%)
Watkins et al. (12)	EBRT cT1b-4 PCa	30 patients w sildenafil-placebo 31 patients w placebo-sildenafil	RCT (1:1) Double-blinded Placebo-controlled Cross-over	Either sildenafil-placebo or placebo-sildenafil 12 weeks→ 1 week washout→ crossover→ 12 week	Erectile function w IIEF (15-item), the Sexual Adjustment Questionnaire (20-item) and Locke's Marital Adjustment test	Only 21% of patients had a treatment-specific response (during sildenafil phase) Significant benefit in erectile response only for patients receiving ≤ 120 days of ADT ($p = 0.009$)
Zelefsky et al. (43)	EBRT BCT	186 patients w sildenafil 93 patients w placebo	RCT (2:1) Double-blinded Placebo-controlled	Either sildenafil (50 mg/days) or placebo Administration was continue for 6 months	Erectile function w IIEF (15-item) questionnaire	Better erectile function and overall satisfaction w sildenafil at 12 months No significant difference in erectile function and IIEF scores at 24 months

Summary of randomized controlled trials on penile rehabilitation following radiotherapy.

to assess whether sexual attempt was successful or not and the quality of sexual intercourse (39, 42).

In conclusion, overall, daily as well as on demand use of PDE5i are improving EF and satisfaction with sexual intercourse after RT. However, it is still not clear whether PDE5i started shortly after EBRT protects against EF in the first 2 years after RT.

Vacuum Erectile Devices

The effectiveness of vacuum erectile devices as first-line treatment option of erectile dysfunction is well-established (45). Although, currently, no high-quality evidence exists, ongoing research suggests in addition to early PDE5i, VEDs may be effective in preventing penile shrinkage and preserving the EF in the context of RT (45).

Yoga Practice During Radiation Therapy

In a RCT (36), biweekly yoga interventions were shown to be feasible and well-tolerated during the course of 6–9 weeks of radiation therapy and effective in improving fatigue and EF. Sixty-eight patients were randomized to yoga and no-yoga cohorts. Twenty-two patients completed all the yoga sessions, whereas 28 patients stayed in no-yoga cohort at the end of the study. Patients who agreed to participate in yoga practice remained unchanged during the RT course, but the control group showed a decrease in sexual function (IIEF score) during the same period. The authors attributed the observed favorable effect of yoga on EF to improved strength of PFM, induction of a relaxation response through nitrite oxide release, and yoga's effect on patients' mental health (36).

DISCUSSION

Prostate cancer is the most common malignancy among men. PDE5is have been shown to be effective in the treatment of ED after both RP and RT.

Chronic dosing of PDE5i was proposed as a measure to accelerate recovery of return to spontaneous erections after nsRP (7). Nightly and long-term administration of sildenafil did indeed show to increase the return of spontaneous erections (6). The other PDE5i did not show significant increase in faster return to spontaneous erections after surgery. But, follow-up periods used may have been short. In the available trials, follow-up was never longer than 12 months; although neuronal recovery after nsRP has been shown to take up to as long as 4 years (46, 47). Therefore, hard conclusion about the true effects on daily PDE5i on return to spontaneous erections after nsRP cannot be made yet. Looking at the other outcome measures, daily use of avanafil and tadalafil did show to improve rates of successful intercourse attempts after RP (8, 15). Moreover, on-demand use of vardenafil and tadalafil has shown to be effective in raising IIEF-EF domain scores after surgery (2, 15).

There may be a role for intraurethral alprostadil and intracavernosal injection therapy after nsRP; the available data point to positive effects of penile rehabilitation if regularly used. Unfortunately, not enough evidence is available to make clear recommendations on this point either.

Penile vibratory stimulation might be effective for the preservation and restoration of EF after nsRP in one trial, but more evidence is needed (20). Immunophilin ligands, especially tacrolimus, may be neuroprotective however, RCT did not affirm this (21). There is a controversy about the efficacy of shockwave therapy for ED in the literature. Some studies revealed improved outcomes for ED after RP when liESWT is used together with tadalafil, but these results were not statistically significant (22). Hyperbaric oxygen therapy showed no significant improvement on EF when used after RP (23).

Increased aerobic training after RP was shown to improve peripheral artery flow and restore the endothelial function (24), but it did not lead to better erections after surgery. Similarly, pelvic floor therapy is known to enhance blood flow to the penis, which is strongly correlated with EF (10). However, no statistically sound RCT have been conducted to demonstrate its positive effects on EF after RP (25).

After RT, sildenafil was shown to be an effective option for penile rehabilitation in several trials (12, 37, 40, 43); some could not demonstrate this positive effect (38).

On demand as well as daily PDE5i use after EBRT did improve patients' satisfaction with sexual intercourse in the first 2 years after RT (42). No studies have been conducted to evaluate the efficacy of PDE5i after RT in the long term. As it is well-known that ED often occurs several years after RT, more research is needed to point out whether PDE5i usage has protective effects 2–10 years after RT. Apart from the widely used treatment modalities for ED after RT, yoga interventions were shown to have positive effects on restoring EF after RT (36).

This study is limited due to a shortage of literature available when specifically looking for RCTs: only 24 of the 229 records could be included. There is a big inhomogeneity among studies, which makes it even more difficult to formulate clear recommendations.

However, this review presents an extensive overview of the different option for a big group of patients and points to the omissions in current literature.

When considering all aspects of EF recovery after RP and RT, other variables should be considered such as orgasmic dysfunction, climacturia, urinary incontinence, and the other adjuvant therapies that will decrease sexual function. To this regard, we believe that when evaluating sexual function, it is mandatory to take each aspect of sexuality into account and not just EF in its single form.

CONCLUSION

This systematic review points to the positive effects of several non-medicinal therapy modalities that may contribute to recovery of spontaneous erections after RT and RP. Clear guidelines for penile rehabilitation after treatment for localized PCa are not easily provided based on current RCT available in literature. However, the importance of expectation management and provision of correct information for patients and their partners in the trajectory of Pca treatment cannot be overestimated.

Thus, until better evidence is available, results point to the positive effects of regular or daily use of a PDE5i directly after nsRP, so this treatment should not be withheld. PDE5i should be offered after a nsRP to all motivated patients with good erections prior to therapy.

In order to maximize chances of return to spontaneous erections or maintenance of erections after nsRP as well as RT, a combination of pelvic floor physiotherapy, vacuum device therapy, PVS, regular exercise and/or yoga may be recommended to be used together with pro-erectile medication. An holistic and multimodal approach may be the key to recovery of sexual function following RP or RT in patients with localized PCa.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

REFERENCES

1. Cornford P, van den Bergh RCN, Briers E, Van den Broeck T, Cumberbatch MG, De Santis M, et al. EAU-EANM-ESTRO-ESUR-SIOG guidelines on prostate cancer. Part II-2020 update: treatment of relapsing and metastatic prostate cancer. *Eur Urol*. (2021) 79:263–82. doi: 10.1016/j.eururo.2020.09.046
2. Montorsi F, Brock G, Lee J, Shapiro J, Van Poppel H, Graefen M, et al. Effect of nightly vs. on-demand vardenafil on recovery of erectile function in men following bilateral nerve-sparing radical prostatectomy. *Eur Urol.* (2008) 54:924–31. doi: 10.1016/j.eururo.2008.06.083
3. Schiff JD, Mulhall JP. Neuroprotective strategies in radical prostatectomy. *BJU Int.* (2005) 95:11–14. doi: 10.1111/j.1464-410X.2005.05239.x
4. Rabbani F, Patel M, Cozzi P, Mulhall JP, Scardino PT. Recovery of erectile function after radical prostatectomy is quantitatively related to the response to intraoperative cavernous nerve stimulation. *BJU Int.* (2009) 104:1252–7. doi: 10.1111/j.1464-410X.2009.08519.x
5. Mulhall J. Neuroimmunophilin ligands protect cavernous nerves after crush injury in the rat: new experimental paradigms. *Eur Urol.* (2007) 51:1488–9. doi: 10.1016/j.eururo.2007.01.043
6. Padma-Nathan H, McCullough AR, Levine LA, Lipshultz LI, Siegel R, Montorsi F, et al. Randomized, double-blind, placebo-controlled study of postoperative nightly sildenafil citrate for the prevention of erectile dysfunction after bilateral nerve-sparing radical prostatectomy. *Int J Impot Res.* (2008) 20:479–86. doi: 10.1038/ijir.2008.33
7. Patel HR, Ilo D, Shah N, Cuzin B, Chadwick D, Andrianne R, et al. Effects of tadalafil treatment after bilateral nerve-sparing radical prostatectomy: quality of life, psychosocial outcomes, and treatment satisfaction results from a randomized, placebo-controlled phase IV study. *BMC Urology*. (2015) 15:31. doi: 10.1186/s12894-015-0022-9
8. Mulhall JP, Burnett AL, Wang R, McVary KT, Moul JW, Bowden CH, et al. A phase 3, placebo controlled study of the safety and efficacy of avanafil for the treatment of erectile dysfunction after nerve sparing radical prostatectomy. *J Urol.* (2013) 189:2229–36. doi: 10.1016/j.juro.2012.11.177
9. Schuh CM, Hausner T, Redl HR. A therapeutic shock propels Schwann cells to proliferate in peripheral nerve injury. *Brain Circ.* (2016) 2:138–40. doi: 10.4103/2394-8108.192520
10. Rosenbaum TY. Pelvic floor involvement in male and female sexual dysfunction and the role of pelvic floor rehabilitation in treatment: a literature review. *J Sex Med.* (2007) 4:4–13. doi: 10.1111/j.1743-6109.2006.00393.x
11. Faiena I, Patel N, Seftel AD. Prevention of erectile dysfunction after radiotherapy for prostate cancer. *Asian J Androl.* (2014) 16:805–6. doi: 10.4103/1008-682X.133327
12. Watkins Bruner D, James JL, Bryan CJ, Pisansky TM, Rotman M, Corbett T, et al. Randomized, double-blinded, placebo-controlled crossover trial of treating erectile dysfunction with sildenafil after radiotherapy and short-term androgen deprivation therapy: results of RTOG 0215. *J Sex Med.* (2011) 8:1228–38. doi: 10.1111/j.1743-6109.2010.02164.x
13. McCullough AR, Hellstrom WG, Wang R, Lepor H, Wagner KR, Engel JD. Recovery of erectile function after nerve sparing radical prostatectomy and penile rehabilitation with nightly intraurethral alprostadil vs. sildenafil citrate. *J Urol.* (2010) 183:2451–6. doi: 10.1016/j.juro.2010.01.062
14. Bannowsky A, Schulze H, van der Horst C, Hautmann S, Jünemann KP. Recovery of erectile function after nerve-sparing radical prostatectomy: improvement with nightly low-dose sildenafil. *BJU Int.* (2008) 101:1279–83. doi: 10.1111/j.1464-410X.2008.07515.x
15. Montorsi F, Brock G, Stolzenburg JU, Mulhall J, Moncada I, Patel HR, et al. Effects of tadalafil treatment on erectile function recovery following bilateral nerve-sparing radical prostatectomy: a randomised placebo-controlled study (REACTT). *Eur Urol.* (2014) 65:587–96. doi: 10.1016/j.eururo.2013.09.051
16. Jo JK, Jeong SJ, Oh JJ, Lee SW, Lee S, Hong SK, et al. Effect of starting penile rehabilitation with sildenafil immediately after robot-assisted laparoscopic radical prostatectomy on erectile function recovery: a prospective randomized trial. *J Urol.* (2018) 199:1600–6. doi: 10.1016/j.juro.2017.12.060
17. Montorsi F, Guazzoni G, Strambi LF, Da Pozzo LF, Nava L, Barbieri L, et al. Recovery of spontaneous erectile function after nerve-sparing radical retropubic prostatectomy with and without early intracavernous injections of alprostadil: results of a prospective, randomized trial. *J Urol.* (1997) 158:1408–10.
18. Kohler TS, Pedro R, Hendlin K, Utz W, Ugarte R, Reddy P, et al. A pilot study on the early use of the vacuum erection device after radical retropubic prostatectomy. *BJU Int.* (2007) 100: 858–62. doi: 10.1111/j.1464-410X.2007.07161.x
19. Raina R, Agarwal A, Ausmundson S, Lakin M, Nandipati KC, Montague DK, et al. Early use of vacuum constriction device following radical prostatectomy facilitates early sexual activity and potentially earlier return of erectile function. *Int J Impot Res.* (2006) 18:77–81. doi: 10.1038/sj.ijir.3901380
20. Fode M, Borre M, Ohl DA, Lichtbach J, Sønksen J. Penile vibratory stimulation in the recovery of urinary continence and erectile function after nerve-sparing radical prostatectomy: a randomized, controlled trial. *BJU Int.* (2014) 114:111–7. doi: 10.1111/bju.12501
21. Mulhall JP, Klein EA, Slawin K, Henning AK, Scardino PT. A randomized, double-blind, placebo-controlled trial to assess the utility of tacrolimus (FK506) for the prevention of erectile dysfunction following bilateral nerve-sparing radical prostatectomy. *J Sex Med.* (2018) 15:1293–9. doi: 10.1016/j.jsxm.2018.07.009
22. Baccaglini W, Pazeto CL, Corrêa Barros EA, Timóteo F, Monteiro L, Saad Rached RY, et al. The role of the low-intensity extracorporeal shockwave therapy on penile rehabilitation after radical prostatectomy: a randomized clinical trial. *J Sex Med.* (2020) 17:688–94. doi: 10.1016/j.jsxm.2019.12.024
23. Chiles KA, Staff I, Johnson-Arbor K, Champagne A, McLaughlin T, Graydon RJ. A double-blind, randomized trial on the efficacy and safety of hyperbaric oxygenation therapy in the preservation of erectile function after radical prostatectomy. *J Urol.* (2018) 199:805–11. doi: 10.1016/j.juro.2017.10.016
24. Jones LW, Hornsby WE, Freedland SJ, Lane A, West MJ, Moul JW, et al. Effects of nonlinear aerobic training on erectile dysfunction and cardiovascular function following radical prostatectomy for clinically localized prostate cancer. *Eur Urol.* (2014) 65:852–5. doi: 10.1016/j.eururo.2013.11.009

25. Milios JE, Ackland TR, Green DJ. Pelvic floor muscle training and erectile dysfunction in radical prostatectomy: a randomized controlled trial investigating a non-invasive addition to penile rehabilitation. *Sex Med.* (2020) 8:414–21. doi: 10.1016/j.esxm.2020.03.005
26. Yuan J, Westney OL, Wang R. Design and application of a new rat-specific vacuum erectile device for penile rehabilitation research. *J Sex Med.* (2009) 6:3247–53. doi: 10.1111/j.1743-6109.2009.01500.x
27. Yuan J, Lin H, Li P, Zhang R, Luo A, Berardinelli F, et al. Molecular mechanisms of vacuum therapy in penile rehabilitation: a novel animal study. *Eur Urol.* (2010) 58:773–80. doi: 10.1016/j.eururo.2010.07.005
28. Sønksen J, Biering-Sørensen F, Kristensen JK. Ejaculation induced by penile vibratory stimulation in men with spinal cord injuries. The importance of the vibratory amplitude. *Paraplegia.* (1994) 32:651–60. doi: 10.1038/sc.1994.105
29. Valentine H, Chen Y, Guo H, McCormick J, Wu Y, Sezen SF, et al. Neuroimmunophilin ligands protect cavernous nerves after crush injury in the rat: new experimental paradigms. *Eur Urol.* (2007) 51:1724–31. doi: 10.1016/j.eururo.2006.11.026
30. Snyder SH, Sabatini DM, Lai MM, Steiner JP, Hamilton GS, Suzdak PD. Neural actions of immunophilin ligands. *Trends Pharmacol Sci.* (1998) 19:21–6. doi: 10.1016/s0165-6147(97)01146-2
31. Sezen SF, Hoke A, Burnett AL, Snyder SH. Immunophilin ligand FK506 is neuroprotective for penile innervation. *Nat Med.* (2001) 7:1073–4. doi: 10.1038/nm1001-1073
32. Burnett AL, Lue TF. Neuromodulatory therapy to improve erectile function recovery outcomes after pelvic surgery. *J Urol.* (2006) 176:882–7. doi: 10.1016/j.juro.2006.04.020
33. Watts GF, Chew KK, Stuckey BG. The erectile-endothelial dysfunction nexus: new opportunities for cardiovascular risk prevention. *Nat Clin Pract Cardiovasc Med.* (2007) 4:263–73. doi: 10.1038/ncpcardio0861
34. Colpi GM, Negri L, Nappi RE, Chinea B. Perineal floor efficiency in sexually potent and impotent men. *Int J Impot Res.* (1999) 11:153–7. doi: 10.1038/sj.ijir.3900413
35. Dorey G, Speakman M, Feneley R, Swinkels A, Dunn C, Ewings P. Pelvic floor exercises for treating post-micturition dribble in men with erectile dysfunction: a randomized controlled trial. *Urol Nurs.* (2004) 24:490–7.
36. Ben-Josef AM, Chen J, Wileyto P, Doucette A, Bekelman J, Christodouleas J, et al. Effect of eischens yoga during radiation therapy on prostate cancer patient symptoms and quality of life: a randomized phase ii trial. *Int J Radiat Oncol Biol Phys.* (2017) 98:1036–44 doi: 10.1016/j.ijrobp.2017.03.043
37. Harrington C, Campbell G, Wynne C, Atkinson C. Randomised, placebo-controlled, crossover trial of sildenafil citrate in the treatment of erectile dysfunction following external beam radiation treatment of prostate cancer. *J Med Imaging Radiat Oncol.* (2010) 54:224–8 doi: 10.1111/j.1754-9485.2010.02168.x
38. Ilic D, Hindson B, Duchesne G, Millar JL. A randomised, double-blind, placebo-controlled trial of nightly sildenafil citrate to preserve erectile function after radiation treatment for prostate cancer. *J Med Imaging Radiat Oncol.* (2013) 57:81–8. doi: 10.1111/j.1754-9485.2012.02461.x
39. Incrocci L, Slagter C, Slob AK, Hop WC. A randomized, double-blind, placebo-controlled, cross-over study to assess the efficacy of tadalafil (Cialis) in the treatment of erectile dysfunction following three-dimensional conformal external-beam radiotherapy for prostatic carcinoma. *Int J Radiat Oncol Biol Phys.* (2006) 66:439–44. doi: 10.1016/j.ijrobp.2006.04.047
40. Incrocci L, Koper PC, Hop WC, Slob AK. Sildenafil citrate (Viagra) and erectile dysfunction following external beam radiotherapy for prostate cancer: a randomized, double-blind, placebo-controlled, cross-over study. *Int J Radiat Oncol Biol Phys.* (2001) 51:1190–5 doi: 10.1016/s0360-3016(01)01767-9
41. Pisansky TM, Pugh SL, Greenberg RE, Pervez N, Reed DR, Rosenthal SA, et al. Tadalafil for prevention of erectile dysfunction after radiotherapy for prostate cancer: the Radiation Therapy Oncology Group [0831] randomized clinical trial. *JAMA.* (2014) 311:1300–7 doi: 10.1001/jama.2014.2626
42. Ricardi U, Gontero P, Ciammella P, Badellino S, Valentino F, Munoz F, et al. Efficacy and safety of tadalafil 20 mg on demand vs. Tadalafil 5 mg once-a-day in the treatment of post-radiotherapy erectile dysfunction in prostate cancer men: a randomized phase II trial. *J Sex Med.* (2010) 7:2851–9. doi: 10.1111/j.1743-6109.2010.01890.x
43. Zelefsky MJ, Shasha D, Branco RD, Kollmeier M, Baser RE, Pei X, et al. Prophylactic sildenafil citrate improves select aspects of sexual function in men treated with radiotherapy for prostate cancer. *J Urol.* (2014) 192:868–74 doi: 10.1016/j.juro.2014.02.097
44. Teloken PE, Parker M, Mohideen N, Mulhall JP. Predictors of response to sildenafil citrate following radiation therapy for prostate cancer. *J Sex Med.* (2009) 6:1135–40. doi: 10.1111/j.1743-6109.2008.01170.x
45. Pahlajani G, Raina R, Jones S, Ali M, Zippe C. Vacuum erection devices revisited: its emerging role in the treatment of erectile dysfunction and early penile rehabilitation following prostate cancer therapy. *J Sex Med.* (2012) 9:1182–9. doi: 10.1111/j.1743-6109.2010.01881.x
46. Le JD, Cooperberg MR, Sadetsky N, Hittelman AB, Meng MV, Cowan JE, et al. CaPSURE Investigators. Changes in specific domains of sexual function and sexual bother after radical prostatectomy. *BJU Int.* (2010) 106:1022–9. doi: 10.1111/j.1464-410X.2010.09231.x
47. Glickman L, Godoy G, Lepor H. Changes in continence and erectile function between 2 and 4 years after radical prostatectomy. *J Urol.* (2009) 181:731–5. doi: 10.1016/j.juro.2008.10.019

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REVIEW
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Current Management of Membranous Urethral Strictures Due to Radiation

Marjan Waterloos[1,2†], Francisco Martins[3], Wesley Verla[2†], Luis Alex Kluth[4†] and Nicolaas Lumen[2] for the Trauma Reconstructive Urology Working Party of the European Association of Young Academic Urologists*

[1] Department of Urology, AZ Maria Middelares Ghent, Ghent, Belgium, [2] Department of Urology, University Hospital Ghent, Ghent, Belgium, [3] Department of Urology, University of Lisbon School of Medicine, Lisbon, Portugal, [4] Department of Urology, University Hospital Frankfurt, Frankfurt am Main, Germany

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***Correspondence:**
Luis Alex Kluth
luis.kluth@kgu.de

[†]Senior members of the Trauma and Reconstructive Urology Working Party of the European Association of Young Academic Urologists

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Radiotherapy is a frequently used treatment for prostate cancer. It does not only causes the intended damage to cancer cells, but also affects healthy surrounding tissue. As a result radiation-induced urethral strictures occur in 2.2% of prostate cancer patients. Management of urethral strictures is challenging due to the presence of poor vascularized tissue for reconstruction and the proximity of the sphincter, which can impair the functional outcome. This review provides a literature overview of risk factors, diagnostics and management of radiation-induced urethral strictures.

Keywords: urethal stricture, radiotherapy, membranous urethral stricture, radiation-induced, urethroplasty

INTRODUCTION

Prostate cancer is the second most frequent cancer in men. Treatment options in localized prostate cancer are active surveillance, surgical treatment or radiation therapy (External Beam Radiotherapy EBRT, Brachytherapy BT or combination of both).

Radiation therapy for prostate cancer is the chosen treatment in approximately 25–34% (1, 2).

Radiation causes ionization events and production of free radicals resulting in different types of DNA damage, eventually leading to vascular injury (endarteritis) and stem cell damage. This leads to atrophy and poorly oxygenated tissue with eventual tissue scarring (3). While intended in cancer cells, it also affects healthy tissue, resulting in a range of side-effects and pathology.

Radiation induced urethral strictures usually occur at the bulbomembranous urethra, even though theoretically receiving lower radiation dose (4).

Hughes et al. examined the specimens of patients who underwent a urethroplasty for a membranous stricture and found that post-radiation specimens had a significantly decreased vascularity compared to specimens of non-radiated etiology (5).

The management of radiation induced strictures remains challenging. It differs from non-radiotherapy related strictures by the scarred tissue with reduced healing capacity. Due to the proximity of the sphincter functional outcome may be impaired (6).

Since the high rates of curation or disease control of prostate cancer nowadays, quality of life is very important to consider in the treatment of these strictures (1).

For the purpose of this review we searched the pubmed library from the year 2000 to 2020.

EPIDEMIOLOGY, ETIOLOGY, AND RISK FACTORS

The prevalence of radiation induced urethral strictures in prostate cancer patients is 2.2% at a median follow-up of 4 years: 1.5% in patients undergoing External Beam Radiotherapy (EBRT), 1.9% in patients undergoing Brachytherapy (BT) and 4.9% in patients receiving a combination of both EBRT-BT. When EBRT is used as a salvage treatment stricture incidence increases to 3–10% (1, 6, 7).

Stricture incidence will increase with time, in contradiction with strictures after radical prostatectomy (8, 9). Median time to stricture formation is estimated between 2.2 and 3.4 years after radiation therapy (1). The CaPSURE database revealed a stricture rate of 1% directly after treatment to 16% after 4 years (7).

A systematic review of Awad showed no difference in urethral stricture development concerning age, proportion of patients on Androgen Deprivation Therapy (ADT) and biochemically equivalent dose (BED) (1). This last observation is also found in the ASCENDE-RT trial, where only little correlation between urethral stricture and dose to the prostate was found (10). Other studies (case series, case control series) demonstrated a clear dose-related effect on urinary morbidity (11–13). Hindson et al. reports an increased stricture rate when radiotherapy was separated in 2 sessions, in comparison of 3 and 4 treatments (14).

In brachytherapy the region inferior to the apex is commonly referred to as "the hotspot" (15). Decreasing the radiation dose to the hot spot, special care during BT-needle placement, avoiding midline insertions, and using plastic needles instead of steel needles, have shown to be effective measures to reduce the rate of urethral strictures (1).

Multiple studies demonstrated clearly an increased risk of urethral stricture in patients who had a TURP prior to radiation therapy. Underlying mechanism is thought to be devascularization of the urethra after TURP in combination with mucosal impairment due to radiation damage (4, 16, 17).

It remains controversial whether combination with hormonal therapy increases the risk of urinary morbidity (11, 18). According to the CaPSURE database there was no change in stricture rate therapy when ADT was associated to another treatment (7). This was also the conclusion in the systematic review of Awad (1).

DIAGNOSTICS

Diagnostic workup is important for planning of the surgical intervention, and can be tailored on a case per case base.

Patients with radiation-induced strictures will present more often with storage lower urinary tract symptoms (LUTS) as a side-effect of their prior radiotherapy treatment. It can be important to determine the pre-operative bladder function by performing a urodynamic study. In other cases uroflowmetry will be sufficient. Radiographic evaluation of the length and location of the stricture is necessary. When a retrograde urethrogram (RUG) is insufficient to evaluate the bladder neck a voiding urethrocystogram (VCUG) can be performed (6).

According to the SIU/ICUD consultation on urethral strictures diagnostic workup for posterior urethral stricture should consist of history, physical examination, laboratory investigations (urine, renal function, prostate-specific antigen), uroflowmetry an postvoid residual volume, cystoscopy and antegrade cystoscopy when evaluation of the anatomy proximal of the stenosis is needed. On indication a retrograde urethrography, voiding cystourethrography, prostate and upper urinary tract imaging or urodynamic evaluation can be performed (2).

TREATMENT

Conservative

In case surgical management is not useful or feasible, chronic urinary catheter will allow urinary drainage. A chronic suprapubic catheter can be a viable option in frail or therapy refractory patients with complete urethral obliteration (19).

Incontinence can be a predominant feature even in patients with urethral strictures. Conservative options for incontinence include penile clamp, condom catheter, and use of sanitary pads (20).

In a study of Fuchs urinary diversion is also used as a measure to obtain urethral rest prior to reconstructive surgery. At a follow-up period of 6 months 49% of the patients preferred to keep their chronic suprapubic tube, instead of undergoing a urethroplasty (21).

All complications related to chronic urinary drainage, such as irritative symptoms, bladder pain, infection and stone formation should be taken in consideration.

Endoluminal

Even in non-radiation related strictures endoluminal treatment has poor results, especially in longer and high grade strictures. Due to impaired tissue quality the outcome in radiation-induced strictures is even poorer. When there is a complete obliteration of the urethral lumen, endoluminal treatment is contra-indicated.

Brandes et al. reports different results after Direct Vision Internal Urethrotomy (DVIU) or dilatation according to the treatment modality: stricture recurrence time of 3.7, 26, and 10.9 months after BT, EBRT and combination BT-EBRT, respectively. Total success rate at 4 years follow-up is 20% with EBRT and 0% with BT, concluding to endoluminal treatment as a palliative option (22). Chen et al. demonstrated a stricture recurrence rate of 50% within 16–60 months after DVIU or dilatation (23).

Sullivan et al. studied a relatively large cohort of patients treated with brachytherapy, followed by endoluminal treatment and a recurrence rate of 49% was reported at a median follow-up of 16 months (4).

Merrick reports a higher patency rate of 69% in a retrospective case series (13).

To stabilize fibrosis after endoluminal treatment intermittent self-dilatation (ISD) can be attempted (6). This should be considered as a palliative treatment, in patients who are unwilling or unable to undergo more invasive surgical strategies (4, 13, 24). On the other hand some authors state that repetitive endoluminal treatment might induce further fibrosis (25).

The conclusion of a study of Lubahn about quality of life in patients performing ISD, states that it is inappropriate to implement ISD in patients that are still amenable for reconstruction, since it's associated with a decrease in quality of life (26).

Open Reconstruction

Excision and Primary Anastomosis

This technique will provide a durable long-term outcome, when surrounding scarred tissue is resected and a tension-free anastomosis can be achieved (**Table 1**).

Rourke published a case series of 35 patients, in which EPA was performed in 65.7% of the cases, and in the other cases buccal mucosa or penile skin flap was used for substitution urethroplasty. All patients had failed prior endoscopic treatment. Strictures treated with EPA and substitution urethroplasty had a mean length of 2.1 and 6.1 cm, respectively. They were all located at the bulbomembranous urethra. Patency rate after follow-up of 4 years was 91% for EPA and 75% for substitution urethroplasty.

One out of four patients complained of worsening or new onset of urinary incontinence, of which 50% had a prior TURP.

In total 68.6% of patients reported a change in continence, erectile function or voiding function after treatment, even when an unobstructed urethra was achieved. This last finding is most likely related to radiotherapy-induced bladder dysfunction (27).

Hofer et al. demonstrates a success rate of 70% with EPA in a group of 66 patients, with mean stricture length of 2.4 cm. *De novo* postoperative urinary incontinence was reported in 36% of the cases. Strictures longer than 2 cm were associated with a greater risk of incontinence.

New onset erectile dysfunction was reported in only 7% of the patients. Stricture location or length was not associated with erectile function (28).

A subsequent cohort from the same group a few years later showed an improved success rate of 85%, attributed to increased surgeon experience. There was a decreased incontinence rate, however presentation of more severe urinary incontinence. Risk of recurrence was not associated with the length of follow-up, concluding that recurrence occurred in the early postoperative period (31).

In a study of Glass et al. 29 patients were treated with EPA (76%), buccal graft urethroplasty (17%) and perineal flap urethroplasty (7%) for radiation-induced strictures with a median length of 2.6 cm. An overall success rate of 90% was reported. Outcome on continence and erectile function was not reported (29).

In another case series of Meeks et al. 30 patients underwent urethroplasty for radiation-induced strictures, all had previous failed endoscopic treatments. Overall patency rate after EPA (84%) and substitution urethroplasty (16%) was 73%. Follow-up was only 21 months. Urinary incontinence after surgery occurred in 50% of the patients. There was no significant change in erectile function (30).

Elliott et al. reports a success rate of 72% after urethroplasty for strictures after prostate cancer treatment, however this was a very heterogenous cohort and there was a wide range of stricture etiology and surgical techniques. Again, radiation therapy was suggested as an important predictive factor for stricture recurrence. An algorithm was developed, in which long radiation (EBRT) induced strictures are advised to be treated with perineal urethrostomy instead of other reconstructive techniques (flaps or two staged procedures) (34).

Higher urinary stress incontinence rates are reported when EPA is performed for radiation-induced strictures (33%), in comparison to pelvic fracture related injuries (12%) in a small retrospective case series of Chung (35).

TABLE 1 | Urethroplasty for radiation-induced strictures.

	Urethroplasty technique	*N*	FU (years)	EBRT	BT	EBRT/ BT	Other	Time to stricture development (years)	Mean stricture length (cm)	Patency rate (%)	Time to recurrence (months)	New onset incontinence (%)	Deterioration erectile function (%)
Rourke et al. (27)	EPA	23	4.25	20	15	NR	0	4.9	2.1	91	29.8	26	35
	Graft/Flap	12							6.1	75		25	0
Hofer et al. (28)	EPA	66	3.5	28	28	9	1	6.4	2.4	70	10.15	36	7
	Graft/Flap	6	5.5	5	1	0	0	13.05	4.3	83	7	50	NR
Glass et al. (29)	EPA	22	3.3	11	4	7	7	7	2.6	95	12	NR	NR
	BMG	5								80			
	Flap	2								50			
Meeks et al. (30)	EPA	24	1.75	15	7	6	NR	9.3	2.9	73	5.1	50	3
	BMG	2											
	Flap	4											
Fuchs et al. (31)	EPA	72	2.8	33	26	9	4	6	2.3	76	4.2	35	NR
Policastro et al. (32)	BMG	79	1.75	36	13	10	20	4	3	82.3	5	8.1	NR
Vetterlein et al. (33)	BMG	47	3.6	33	5	8	1	NR	NR	67	3	NR	NR

EPA, Excision and Primary Anastomosis; BMG, Buccal Mucosa Graft; FU, Follow-Up; EBRT, External Beam Radiotherapy; BT, Brachytherapy; NR, Not Reported.

Substitution Urethroplasty

Even more than in the EPA technique, urethroplasty using grafts or flaps is impaired by the poor quality of the irradiated surrounding tissue. Substitution urethroplasty is used for longer strictures and when EPA is no longer feasible (**Table 1**).

In a retrospective cohort of Vetterlein et al. 47 patients underwent buccal mucosa ventral urethroplasty. Mean graft length was 5 cm. A recurrence rate of 33% was observed. In this study validated questionaires (USS-PROM) were used to evaluate patient reported outcomes. Postoperatively 53% patients reported daily urinary incontinence, and 26% required an artificial urinary sphincter implantation. Erectile dysfunction or absence of sexual activity was present in almost all of the patients (33).

In the case series of Hofer et al. 6 patients with a median strictyure length of 4.25 cm were treated with substitution urethroplasty. Only one patient had a recurrence at 5.5 years follow-up. New onset urinary incontinence was present in 50% of the patients. There was no change in erectile function after surgery (28).

Palmer describes ventral onlay buccal mucosa urethroplasty and use of a gracilis muscle flap for long segment complex strictures. The gracilis muscle flap provides a well-vascularized graft bed for the buccal graft. Mean stricture length was 8.2 cm and in 9 of the 20 patients stricture etiology was radiotherapy. A patency rate of 80% was achieved at a mean follow-up of 40 months. Mean time to stricture recurrence was 10 months (36).

A multi-institutional retrospective series of dorsal onlay buccal mucosa urethroplasty in 79 patients, showed a patency rate of 82.3%, and a *de novo* incontinence rate of 8%. There was a short median follow-up of 21 months (32).

Urinary Diversion

When there are no more reconstructive options left and patients have a refractory bladder outlet obstruction or other severe symptoms such as uncontrollable pelvic pain, urinary diversion can be discussed.

In a case series of Sack et al. 15 patients with previous radiotherapy and/or cryotherapy were treated with surgical extirpation and urinary diversion for different radio- or cryotherapy induced problems including urethral strictures. There were on average 3.7 failed previous interventions. Surgical extirpation (cystectomy or cystoprostatectomy) was performed and urinary diversion was accomplished by ileal conduit, catheterizable pouch or colon conduit. Perioperative morbidity was higher than in a non-irradiated population. Postoperative quality of life (QoL) was measured, and patients reported a satisfying outcome and would have undergone the surgery sooner (37).

Al Hussein Al Awamlh et al. also reports a significant improve in QoL, despite perioperative complication risks, in patients with severe radiotherapy related complications (fistulas, radiation cystitis, pelvic pain or incontinence) (38).

In case of preserved bladder capacity bladder preservation can be attempted, with closure of the bladder neck and continent urinary diversion (20).

DISCUSSION

Radiotherapy induces oxidative stress, resulting in an effective cancer treatment as a short term result. However, on the long term it causes chronic inflammation and micro-angiopathy, resulting in tissue damage. This late side-effect explains the potential late onset of radiation-induced complications.

No studies so far were able to demonstrate a firm correlation between urethral strictures and urethral dose of radiation. However, more profound dosimetric studies should be performed to support this conclusion.

The management of radiation-induced urethral strictures is complicated due to several reasons: the proximity of the external urethral sphincter since most of these strictures are located in the bulbomembranous urethra, the poor quality of local tissue needed for reconstruction and impaired vascularity that will lead to a difficult wound healing process (25, 39).

Literature is still limited and most studies are small retrospective case series. As a result of this consideration as a late onset complication, a significant amount of studies has a high rate of loss to follow-up, possibly underestimating the prevalence.

Conservative management can be an option in frail patients, or when reconstructive surgery is no longer a viable option, and usually consists of chronic urinary drainage. Chronic catheter related problems should be taken into account.

Endoluminal treatment has a success rate between 0 and 51%, based on retrospective case series (4, 13, 22, 23). A single endoluminal treatment can be attempted since it has an acceptable patency rate and a much lower incontinence rate than open reconstruction. On the contrary repetitive DVIU or dilatation might provoke further fibrosis of the radiated tissue and can lead to a delay of more reliable reconstructive options. Intermittent selfcatheterization can be used as a palliative treatment, when no other reconstructive options are left (4, 6, 13, 24). However, it is often associated with a lower quality of life (26).

Excision and primary anastomosis of radiation-induced strictures provides durable long term results, with patency rates up to 90%. Most authors also emphasize the feasibility of this technique in most of the cases, provided the stricture is short enough to allow tension-free anastomosis.

For longer strictures, substitution urethroplasty must be performed. Although even more prone to the radiation induced reduction of tissue quality then EPA, long term success rates up to 84% are reported, in small case series. Since this technique is used less frequently then EPA, all studies consist of small case series, so results must be interpretated with caution.

When primary reconstructive techniques fail or concomitant severe symptoms are present, urinary diversion with or without extirpation should be discussed with the patient. Depending on the residual bladder function continent or incontinent diversions can be considered (20). These procedures have a higher complication rate in patients who underwent radiotherapy (37).

After endoluminal treatment a new onset urinary incontinence rate of 10% was reported (4, 13, 22, 23).

Deterioration or new onset of urinary incontinence after urethroplasty for radiation-induced strictures (EPA and

substitution urethroplasty) is present in 11–50% of the patients. Incontinence can be mild but a minority of patients will need an artificial urinary sphincter. Incontinence rates are higher after urethroplasty for radiation-induced strictures in comparison to other etiology (35).

Most of the studies report mainly unaltered erectile function after the treatment of radiation-induced strictures (28, 30). This is probably due to the high rates of erectile dysfunction present prior to surgery as a result of the radiotherapy itself. The cavernous nerves located dorsally to the posterior urethra are preserved during some techniques of substitution urethroplasty in contrast to EPA, however this doesn't seem to influence the already low deterioration in erectile function postoperatively.

Concerning the complications a limitation in almost all of these studies was a lack of validated questionnaires to evaluate patient reported outcome measures.

Even when a radiation-induced stricture is successfully treated patients can experience persistent symptoms due to radiation toxicity, for example impaired bladder capacity due to radiocystitis.

CONCLUSION

Management of radiation induced urethral strictures remains challenging, with an uncertain outcome and a significant amount of side-effects. Experienced operative skills with good knowledge of all the techniques are required to increase the chance of a good long-term outcome. Quality of life is important to take into account, especially since the prognosis of prostate cancer has been improved over the last decades.

Patients should be informed that returning to a urological situation prior to their prostate cancer treatment is not a realistic expectation, since radiation-induced bladder dysfunction can impair outcome of reconstructive surgery.

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All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

REFERENCES

1. Awad MA, Gaither TW, Osterberg EC, Murphy GP, Baradaran N, Breyer BN. Prostate cancer radiation and urethral strictures: a systematic review and meta-analysis. *Prostate Cancer Prostatic Dis.* (2018) 21:168–74. doi: 10.1038/s41391-017-0028-3
2. Herschorn S, Elliott S, Coburn M, Wessells H, Zinman L. SIU/ICUD consultation on urethral strictures: posterior urethral stenosis after treatment of prostate cancer. *Urology.* (2014) 83 (3 Suppl.):S59–70. doi: 10.1016/j.urology.2013.08.036
3. Stone HB, Coleman CN, Anscher MS, McBride WH. Effects of radiation on normal tissue: consequences and mechanisms. *Lancet Oncol.* (2003) 4:529–36. doi: 10.1016/S1470-2045(03)01191-4
4. Sullivan L, Williams SG, Tai KH, Foroudi F, Cleeve L, Duchesne GM. Urethral stricture following high dose rate brachytherapy for prostate cancer. *Radiother Oncol.* (2009) 91:232–6. doi: 10.1016/j.radonc.2008.11.013
5. Hughes M, Caza T, Li G, Daugherty M, Blakley S, Nikolavsky D. Histologic characterization of the post-radiation urethral stenosis in men treated for prostate cancer. *World J Urol.* (2020) 38:2269–77. doi: 10.1007/s00345-019-03031-y
6. Browne BM, Vanni AJ. Management of urethral stricture and bladder neck contracture following primary and salvage treatment of prostate cancer. *Curr Urol Rep.* (2017) 18:76. doi: 10.1007/s11934-017-0729-0
7. Elliott SP, Meng MV, Elkin EP, McAninch JW, Duchane J, Carroll PR, et al. Incidence of urethral stricture after primary treatment for prostate cancer: data from CaPSURE. *J Urol.* (2007) 178:529–34. Discussion 34. doi: 10.1016/j.juro.2007.03.126
8. Heyns C, Van der Merwe J, Basson A, Van der Merwe, A. Etiology of male urethral strictures-evaluation of temporal changes at a single center, and review of the literature. *Afr J Urol.* (2012) 18:4–9. doi: 10.1016/j.afju.2012.04.009
9. Lumen N, Hoebeke P, Willemsen P, De Troyer B, Pieters R, Oosterlinck W. Etiology of urethral stricture disease in the 21st century. *J Urol.* (2009) 182:983–7. doi: 10.1016/j.juro.2009.05.023
10. Rodda S, Tyldesley S, Morris WJ, Keyes M, Halperin R, Pai H, et al. ASCENDE-RT: an analysis of treatment-related morbidity for a randomized trial comparing a low-dose-rate brachytherapy boost with a dose-escalated external beam boost for high- and intermediate-risk prostate cancer. *Int J Radiat Oncol Biol Phys.* (2017) 98:286–95. doi: 10.1016/j.ijrobp.2017.01.008
11. Earley JJ, Abdelbaky AM, Cunningham MJ, Chadwick E, Langley SE, Laing RW. Correlation between prostate brachytherapy-related urethral stricture and peri-apical urethral dosimetry: a matched case-control study. *Radiother Oncol.* (2012) 104:187–91. doi: 10.1016/j.radonc.2012.06.001
12. Martinez AA, Gonzalez J, Ye H, Ghilezan M, Shetty S, Kernen K, et al. Dose escalation improves cancer-related events at 10 years for intermediate- and high-risk prostate cancer patients treated with hypofractionated high-dose-rate boost and external beam radiotherapy. *Int J Radiat Oncol Biol Phys.* (2011) 79:363–70. doi: 10.1016/j.ijrobp.2009.10.035
13. Merrick GS, Butler WM, Wallner KE, Galbreath RW, Anderson RL, Allen ZA, et al. Risk factors for the development of prostate brachytherapy related urethral strictures. *J Urol.* (2006) 175:1376–80. Discussion 81. doi: 10.1016/S0022-5347(05)00681-6
14. Hindson BR, Millar JL, Matheson B. Urethral strictures following high-dose-rate brachytherapy for prostate cancer: analysis of risk factors. *Brachytherapy.* (2013) 12:50–5. doi: 10.1016/j.brachy.2012.03.004
15. Mohammed N, Kestin L, Ghilezan M, Krauss D, Vicini F, Brabbins D, et al. Comparison of acute and late toxicities for three modern high-dose radiation treatment techniques for localized prostate cancer. *Int J Radiat Oncol Biol Phys.* (2012) 82:204–12. doi: 10.1016/j.ijrobp.2010.10.009
16. Deger S, Boehmer D, Roigas J, Schink T, Wernecke KD, Wiegel T, et al. High dose rate (HDR) brachytherapy with conformal radiation therapy for localized prostate cancer. *Eur Urol.* (2005) 47:441–8. doi: 10.1016/j.eururo.2004.11.014
17. Seymore CH, el-Mahdi AM, Schellhammer PF. The effect of prior transurethral resection of the prostate on post radiation urethral strictures and bladder neck contractures. *Int J Radiat Oncol Biol Phys.* (1986) 12:1597–600. doi: 10.1016/0360-3016(86)90283-X
18. Merrick GS, Butler WM, Tollenaar BG, Galbreath RW, Lief JH. The dosimetry of prostate brachytherapy-induced urethral strictures. *Int J Radiat Oncol Biol Phys.* (2002) 52:461–8. doi: 10.1016/S0360-3016(01)01811-9
19. Harrison SC, Lawrence WT, Morley R, Pearce I, Taylor J. British Association of Urological Surgeons' suprapubic catheter practice guidelines. *BJU Int.* (2011) 107:77–85. doi: 10.1111/j.1464-410X.2010.09762.x
20. Anderson KM, Higuchi TT, Flynn BJ. Management of the devastated posterior urethra and bladder neck: refractory incontinence and stenosis. *Transl Androl Urol.* (2015) 4:60–5. doi: 10.3978/j.issn.2223-4683.2015.02.02
21. Fuchs JS, Sheth K, Viers BR, Hofer MD, Pagliara TJ, Scott JM, et al. Role of chronic suprapubic tube in the management of radiation induced urethral strictures. *Urol Pract.* (2017) 4:479–85. doi: 10.1016/j.urpr.2016.10.004
22. Brandes SB. *Radiotherapy-Induced Urethral Strictures*. New York, NY: Humana Press (2014). p. 337–50
23. Chen ML, Correa AF, Santucci RA. Urethral strictures and stenoses caused by prostate therapy. *Rev Urol.* (2016) 18:90–102. doi: 10.3909/riu0685

24. Farrell MR, Sherer BA, Levine LA. visual internal urethrotomy with intralesional mitomycin C and short-term clean intermittent catheterization for the management of recurrent urethral strictures and bladder neck contractures. *Urology.* (2015) 85:1494–9. doi: 10.1016/j.urology.2015.02.050
25. Hofer MD, Liu JS, Morey AF. Treatment of radiation-induced urethral strictures. *Urol Clin North Am.* (2017) 44:87–92. doi: 10.1016/j.ucl.2016.08.005
26. Lubahn JD, Zhao LC, Scott JF, Hudak SJ, Chee J, Terlecki R, et al. Poor quality of life in patients with urethral stricture treated with intermittent self-dilation. *J Urol.* (2014) 191:143–7. doi: 10.1016/j.juro.2013.06.054
27. Rourke K, Kinnaird A, Zorn J. Observations and outcomes of urethroplasty for bulbomembranous stenosis after radiation therapy for prostate cancer. *World J Urol.* (2016) 34:377–82. doi: 10.1007/s00345-015-1608-2
28. Hofer MD, Zhao LC, Morey AF, Scott JF, Chang AJ, Brandes SB, et al. Outcomes after urethroplasty for radiotherapy induced bulbomembranous urethral stricture disease. *J Urol.* (2014) 191:1307–12. doi: 10.1016/j.juro.2013.10.147
29. Glass AS, McAninch JW, Zaid UB, Cinman NM, Breyer BN. Urethroplasty after radiation therapy for prostate cancer. *Urology.* (2012) 79:1402–5. doi: 10.1016/j.urology.2011.11.077
30. Meeks JJ, Brandes SB, Morey AF, Thom M, Mehdiratta N, Valadez C, et al. Urethroplasty for radiotherapy induced bulbomembranous strictures: a multi-institutional experience. *J Urol.* (2011) 185:1761–5. doi: 10.1016/j.juro.2010.12.038
31. Fuchs JS, Hofer MD, Sheth KR, Cordon BH, Scott JM, Morey AF. Improving outcomes of bulbomembranous urethroplasty for radiation-induced urethral strictures in post-urolume era. *Urology.* (2017) 99:240–5. doi: 10.1016/j.urology.2016.07.031
32. Policastro CG, Simhan J, Martins FE, Lumen N, Venkatesan K, Angulo JC, et al. A multi-institutional critical assessment of dorsal onlay urethroplasty for post-radiation urethral stenosis. *World J Urol.* (2020). doi: 10.1007/s00345-020-03446-y. [Epub ahead of print].
33. Vetterlein MW, Kluth LA, Zumstein V, Meyer CP, Ludwig TA, Soave A, et al. Buccal mucosal graft urethroplasty for radiation-induced urethral strictures: an evaluation using the extended urethral stricture surgery patient-reported outcome measure (USS PROM). *World J Urol.* (2020) 38:2863–72. doi: 10.1007/s00345-020-03102-5
34. Elliott SP, McAninch JW, Chi T, Doyle SM, Master VA. Management of severe urethral complications of prostate cancer therapy. *J Urol.* (2006) 176 (6 Pt 1):2508–13. doi: 10.1016/j.juro.2006.07.152
35. Chung PH, Esposito P, Wessells H, Voelzke BB. Incidence of stress urinary incontinence after posterior urethroplasty for radiation-induced urethral strictures. *Urology.* (2018) 114:188–92. doi: 10.1016/j.urology.2017.11.024
36. Palmer DA, Buckley JC, Zinman LN, Vanni AJ. Urethroplasty for high risk, long segment urethral strictures with ventral buccal mucosa graft and gracilis muscle flap. *J Urol.* (2015) 193:902–5. doi: 10.1016/j.juro.2014.09.093
37. Sack BS, Langenstroer P, Guralnick ML, Jacobsohn KM, O'Connor RC. Cystectomy and urinary diversion for the management of a devastated lower urinary tract following prostatic cryotherapy and/or radiotherapy. *WMJ.* (2016) 115:70–3.
38. Al Hussein Al Awamlh B, Lee DJ, Nguyen DP, Green DA, Shariat SF, Scherr DS. Assessment of the quality-of-life and functional outcomes in patients undergoing cystectomy and urinary diversion for the management of radiation-induced refractory benign disease. *Urology.* (2015) 85:394–400. doi: 10.1016/j.urology.2014.08.047
39. Lumen N, Oosterlinck W. Challenging non-traumatic posterior urethral strictures treated with urethroplasty: a preliminary report. *Int Braz J Urol.* (2009) 35:442–9. doi: 10.1590/S1677-55382009000400008

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REVIEW
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Current Management of Post-radical Prostatectomy Urinary Incontinence

Mohammad S. Rahnama'i[1]*, *Tom Marcelissen*[2], *Bogdan Geavlete*[3], *Manuela Tutolo*[4] and *Tanja Hüsch*[5]

[1] Urology Department, Uniklinik RWTH Aachen, Aachen, Germany, [2] Maastricht University Medical Center (MUMC+), Maastricht, Netherlands, [3] Bucharest University Emergency Hospital, Bucharest, Romania, [4] Division of Oncology, Unit of Urology, Urological Research Institute, IRCCS Ospedale San Raffaele, Milan, Italy, [5] Mainz University Hospital, Mainz, Germany

Prostate cancer is the second most common cancer in men worldwide. Radical prostatectomy and radiation beam therapy are the most common treatment options for localized prostate cancer and have different associated complications. The etiology of post prostatectomy incontinence is multifactorial. There is evidence in the literature that anatomic support and pelvic innervation are important factors in the etiology of post-prostatectomy incontinence. Among the many surgical and technical factors proposed in the literature, extensive dissection during surgery, damage to the neurovascular bundle and the development of postoperative fibrosis have a substantial negative impact on the continence status of men undergoing RP. Sparing of the bladder neck and anterior, and possibly posterior, fixation of the bladder-urethra anastomosis are associated with better continence rates. Overactive bladder syndrome (OAB) is multifactorial and the exact role of prostate surgery in the development of OAB is still under debate. There are several variables that could contribute to detrusor overactivity. Detrusor overactivity in patients after radical prostatectomy has been mainly attributed to a partial denervation of the bladder during surgery. However, together with bladder denervation, other hypotheses, such as the urethrovesical mechanism, have been described. Although there is conflicting evidence regarding the importance of conservative treatment after post-prostatectomy urinary incontinence, pelvic floor muscle training (PFMT) is still considered as the first treatment choice. Duloxetin, either alone or in combination with PFMT, may hasten recovery of urinary incontinence but is often associated with severe gastrointestinal and central nervous side effects. However, neither PFMT nor duloxetine may cure male stress urinary incontinence. The therapeutic decision and the chosen treatment option must be individualized for each patient according to clinical and social factors. During the recent years, the development of new therapeutic choices such as male sling techniques provided a more acceptable management pathway for less severe forms of urinary incontinence related to radical prostatectomy. Following this perspective, technological improvements and the emergence of new dedicated devices currently create the premises for a continuously positive evolution of clinical outcomes in this particular category of patients.

Keywords: prostate cancer, incontinence (male), detrusor activity, stress incontinence, prostatectomy

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Luis Alex Kluth,
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Juan Gomez Rivas,
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Jens Hansen,
Vivantes Auguste Viktoria Clinic, Germany
Tim Alexander Ludwig,
University Medical Center Hamburg-Eppendorf, Germany

***Correspondence:**
Mohammad S. Rahnama'i
sajjad_r@yahoo.com

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INTRODUCTION

Prostate cancer is the second most common cancer in men worldwide, affecting ∼1.1 million men per year (1). Radical prostatectomy (rPR) and radiation beam therapy are comparable treatment options for localized prostate cancer (2) whereas treatment associated complications and incidences differ significantly.

Male stress urinary incontinence (SUI) has a predominantly iatrogenic cause after radical prostatectomy (3). It is defined by the complaint of involuntary leakage on effort or exertion or on sneezing, or coughing (4, 5). The mechanism for post-radical prostatectomy incontinence remains unclear (6), however, several hypothesis have been discussed. Despite direct injury to the internal sphincter itself, injury to the external rhabdosphincter or its shortened lengthwise (7), injuries to the supporting structures of the urethra (7), lesions to the nerve supply (6) or even detrusor underactivity (8) may impair continence.

The incidence of post-radical prostatectomy incontinence has become an increasingly common urological problem with a prevalence of 2.5–90% (9) depending on the definition for urinary continence. In a recent prospective non-randomized trial comparing open retropubic rPR and robotic assisted rPR including a total of 2,625 men, urinary incontinence defined by no change pad in 24 h after 12 month follow-up was 21.3 and 20.2% for robotic-assisted and open rPR, respectively (10). A meta-analysis did not identify a significant difference of urinary continence in comparison between open retropubic and robot assisted rPR (11, 12). A prospective randomized trial comparing laparoscopic and robotic-assisted rPR demonstrated significant better continence rates for robotic-assisted than laparoscopic rPR (95.0 vs. 83.3%) (13). A meta-analysis identified evidence for improved continence rates with robotic-assisted in comparison to laparoscopic rPR accordingly (14). **Table 1** present the continence rates after radical prostatectomy reported by selected prospective trials.

Importantly, the impact of urinary incontinence to affected patients is substantial and include stigmatization and significant reduction of quality of life (20). In addition, the cost burden of urinary incontinence is currently estimated between $19 and $32 billion in the USA (9).

Overactive bladder (OAB), with or without urinary incontinence, can also occur after radical prostatectomy and is an underestimated cause for urinary incontinence after radical prostatectomy. However, so far there is a lack of robust data for its incidence.

In this non-systematic review, we provide an overview on pathophysiology and current treatment options of male stress urinary incontinence after radical prostatectomy.

PATHOPHYSIOLOGY

There are different factors responsible for the post-rPR urinary incontinence. The most well-known factors include the changes that occur in the anatomy, the preoperative bladder function as well as the operation technique and the experience of the surgeon (21, 22). In addition, the anatomic support and the pelvic innervation have been identified as important contributors to post rPR continence (21). Among the many surgical and technical factors proposed in the literature as contributing to the development of urinary incontinence following rPR, extensive dissection during surgery, damage to the neurovascular bundle, and the development of postoperative fibrosis have a substantial

TABLE 1 | Continence rates after radical prostatectomy of selected clinical trials.

References	Year	Study design	Number of patients	Follow-up time	Continence definition	Urinary continence, n/N (%)
Haglind et al. (10)	2015	Prospective, non-randomized	2,625	12 months	< 1 pad/24 h	RALP 366/1847 (21.3) RRP 144/778 (20, 2)
Choo et al. (15)	2012	Prospective, non-randomized	253	24 months	0–1 pad/24 h	RALP 73/77 (95) RRP 172/176 (98)
Rocco et al. (16)	2009	Prospective non-randomized Matched to historical control group	240	12 months	0–1 pad/24 h	RALP 77/79 (97) RRP 191/217 (88)
Son et al. (17)	2013	Prospective non-randomized	258	12 months	0–1 pad/24 h	RALP 146/146 (100) RRP /112 (98.2)
Kim et al. (18)	2018	Prospective non-randomized	529	12 months	0 pads/3 days and an absence of any unwanted urine leakage	RALP none or unilateral nerv-sparing 191/460 (41.5) RALP bilateral nerv-sparing 269/460 (58.5)
Olsson et al. (19)	2001	Prospective non-randomized	228	12 months	0 pads/24 h	LRP 29/37 (78.4)
Porpiglia et al. (13)	2012	Prospective randomized	120	12 months	0–1 pad/24 h	RALP 57/60 (95.0) LRP 50/60 (83.3)

RALP, Robotic assisted laparoscopic radical prostatectomy; RRP, open retropubic radical prostatectomy; LRP, laparoscopic radical Prostatectomy.

negative impact on the continence status of men undergoing rPR. Sparing of the bladder neck and anterior, and possibly posterior, fixation of the bladder-urethra anastomosis are associated with better continence rates (22).

Continence is generally facilitated by the combination of the action of the detrusor muscle, the proximal intrinsic sphincter, the rhabdosphincter (23), and the urethral suspensory mechanism composed of pubourethral ligaments (24). After rPR, the proximal urethral sphincter, the suspensory ligaments as well as parts of the proximal intrinsic sphincter are removed. As a consequence, post rPR urinary continence is largely dependent on the rhabdosphincter (25). In addition, the pudendal nerve fibers that innervate the rhabdosphincter are damaged during the operation which has functional implications. This has been studied by transurethral ultrasound, that has shown thinning or atrophy as well as impaired contractility of the rhabdosphincter (25). Moreover, the innervation of the detrusor muscle and trigonum are impair which leads to a decreased detrusor contractility and poor bladder compliance (26, 27). The most predominant finding in urodynamic measurements is the sphincteric incontinence (28). On the other hand, intrinsic detrusor dysfunction and overactivity or impaired detrusor contractility, and altered detrusor compliance play a role in the post rPR continence (29). Preoperative urodynamic abnormalities have been observed to be present in 41% of patients, with half of them having detrusor overactivity (28).

About 50% of patients have preoperative impaired bladder compliance and impaired detrusor contractility and 47% *de novo* postoperative changes (30). Urodynamic studies carried out 1 year after rPR have shown sphincteric incontinence as the most common finding, which was responsible for about 88–100% urinary incontinence after rPR (26, 31, 32). About a third of the patients had an intrinsic sphincter deficiency as the single cause of their urinary incontinence (26, 32). Furthermore, detrusor overactivity and impaired bladder contractility were each found in up to a 30% of the cases (26, 32). However, in <9% of the cases, these findings were the only urodynamic finding (26, 32). In one out of five patients, bladder outlet obstruction was found, but this was the sole urodynamic finding in only 1% of the cases (31). Delayed first sensation (42%), mixed urgency-urge incontinence (48%), and decreased bladder capacity (< 300 mL) (41%) were the other findings on urodynamic measurements after rPR (26). It must also be stressed that, a highly well-established predictor of functional outcomes is the surgeon. It is well-known that patients treated in high volume centers and in experienced hands, are more likely to be dry. When reviewing different series, the absence of this variable could represent a limitation since, in some cases, an individual surgeon's outcomes may be much better, or worse, than any nomogram prediction. Better urinary continence recovery results can be expected by patients who undergo rPR performed by a surgeon with greater experience (33). An annual surgical case load of >50 cases/year results in improved continence recovery outcomes following rPR (33).

OAB AND URGENCY INCONTINENCE

In the context of management of post-rPR OAB syndrome, it is important to understand its underlying pathophysiological mechanism (34). Since OAB is multifactorial (35), the exact role of prostate surgery in the development of OAB is still under debate as, after rPR, there are several variables that could contribute to detrusor overactivity.

Detrusor overactivity in patients after radical prostatectomy has been mainly attributed to a partial denervation of the bladder during surgery (30). However, together with bladder denervation, other hypotheses, such as the urethrovesical mechanism, have been described.

It has been demonstrated that urethral afferents are activated by urethral perfusion (36) and they could modulate the micturition reflex via pudendal and pelvic afferent and efferent signals, causing bladder contraction. This has been described as urethrovesical mechanism (37–39).

In a recent study, Mastukawa et al. identified that low maximum urethral closure pressure at baseline and its decrease postoperatively were strong predictors of *de novo* post-rPR OAB underlying the role of the intrinsic sphincter deficiency on the pathophysiology of OAB (40).

In contrast, detrusor underactivity may cause OAB syndrome as well, which seems contradictory at the first glance. Bladder underactivity may affect up to 40% of patients after radical prostatectomy mostly due to denervation (41).

Bladder outlet obstruction is a known cause of OAB. The obstruction after RP is mainly caused by bladder neck contracture and urethral stricture due to the anastomosis of the bladder neck with the urethra, which has an incidence up to 20% (42). BOO causes damage to the smooth muscle demonstrating histological changes in the bladder wall causing spontaneous myogenic contractions (43). Therefore, the presence of infravesical obstruction due to urethral stricture or bladder neck contracture must be excluded.

PREDICTING URINARY INCONTINENCE AFTER RADICAL PROSTATECTOMY

Damage to the urethral sphincter complex, the surrounding structures, or their innervation leads to higher rates of urinary incontinence after rPR. In addition, certain biological factors and parameters known preoperatively, including older age, higher BMI, pre-existing LUTS, lower motor unit lesion, and functional bladder changes, have been identified to have a negative impact on continence rates after rPR (22).

Recently, a preoperative model was presented to predict incontinence before rPR (**Figure 1**) (44). According this nomogram, high risk for biochemical recurrence, adjuvant radiotherapy, lower results in the validated quality of life questionnaire EORCT QLQ-C30/QoL, higher sum score of the validated questionnaire International Consultation of Incontinence Questionnaire—Urinary Incontinence—Short form (ICIQ-UI-SF) and higher patient age, were associated with statistically significant higher sum scores of the 12-month ICIQ-UI-SF, thus, representing higher impact of urinary incontinence (**Figure 1**) (44). Together with the preoperative model a new, postoperative nomogram was introduced to inform patients about the probability of an additional surgery

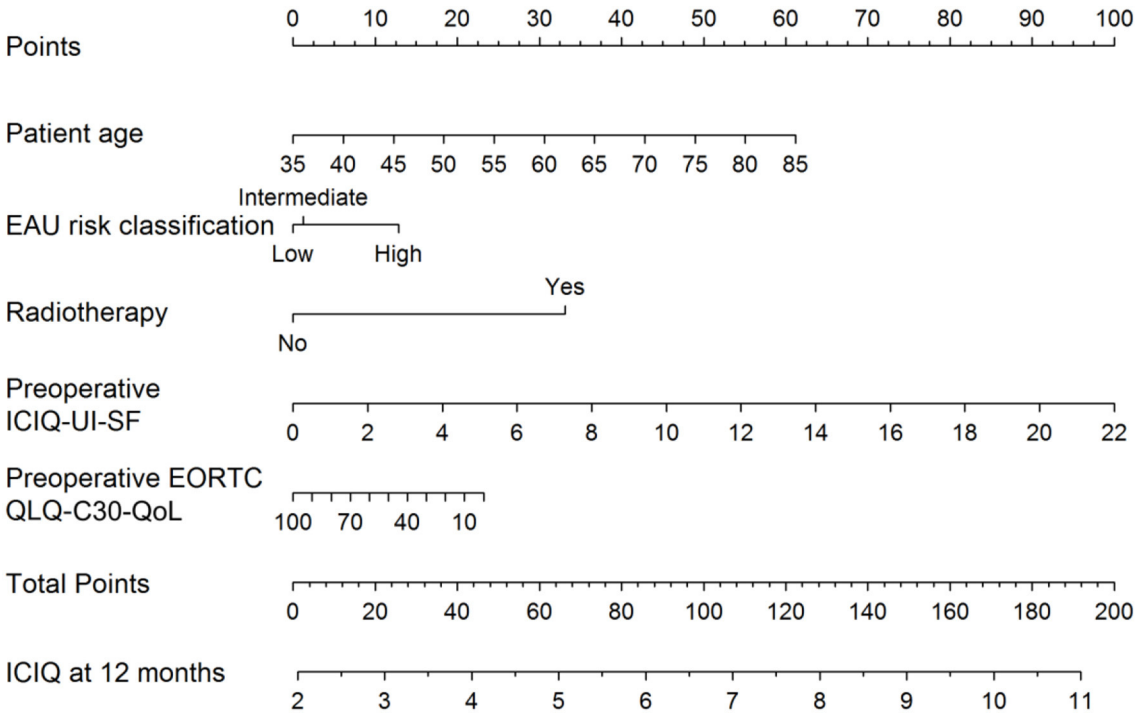

FIGURE 1 | Nomogram for the preoperative prediction of the 12-month ICIQ-UI-SF score among patients diagnosed with prostate cancer and treated with robotic-assisted prostatectomy. Instructions: locate the patient's values for age, EAU risk classification, baseline EORCT QLQ-C30/QoL and baseline ICIQ-UI-SF on the corresponding axes. Draw a straight line up to the Points axis for each value to determine the number of points for that value. Calculate the sum of the values on the Points axis and locate this sum score on the Total Points axis. Draw a straight line down to find the patient's predicted ICIQ-UI-SF score at 12 months. From Tutolo et al. (44). EORCT QLQ-C30/QoL, European Organization for Research and Treatment for Cancer Quality of Life Questionnaire of Prostate Cancer; ICIQ-UI-SF, International Consultation on Incontinence Questionnaire-Urinary Incontinence Short Form; EAU, European Association of Urology.

for incontinence or, on the other hand, about the importance of enduring with a strict pelvic floor muscle training protocol (**Figure 2**) (44).

Interestingly, these results did not show any association with ICIQ-UI-SF, when including surgery volume (namely <50, 50–100, or >100 cases per year) (44).

R-squared (R^2), the statistical measure that represents the proportion of the variance for a dependent variable, equalled 4% and 43% in the preoperative and postoperative models, respectively. This is mainly due to the retrospective nature of the study and to the intrinsic characteristics of the database (strict rules of the Belgian Cancer registry). The major drawback of this study, together with its retrospective nature, is that a single dataset has been used for development and validation of the model. Although a non-random splitting of the data is an acceptable design for evaluating model performance, external validation still has to be performed (42).

TREATMENT OF MALE STRESS URINARY INCONTINENCE

Conservative and Pharmacologic Therapy

Although there is conflicting evidence regarding the importance of conservative treatment after post-prostatectomy urinary incontinence (45), pelvic floor muscle training (PFMT) is still considered as the first treatment choice (46). Duloxetin, a serotonin/norepinephrine reuptake inhibitor, either alone or in combination with PFMT, may hasten recovery of urinary incontinence but is often associated with severe gastrointestinal and central nervous side effects (47, 48). However, neither PFMT nor duloxetine may cure male stress urinary incontinence.

Surgical Therapy

If conservative therapy fails, surgical treatment options should be offered to the patients. The artificial urinary sphincter (AUS) has been considered the gold standard for several decades. In a recent study urinary incontinence rates remained high, with no evidence of difference between male sling and AUS (49). The mode of function of AUS is a circumferential compression of the urethra based on a hydraulic mechanism. Nowadays, several alternative procedures with different operating principles compete against the AUS. These procedures are classified to bulking agents, male slings, and compressive devices. **Table 2** presents success and complications rates of different treatment options of selected clinical trials and **Figure 2** demonstrates the different surgical devices *in situ*. **Table 2** presents success and complications rates of different treatment options of selected

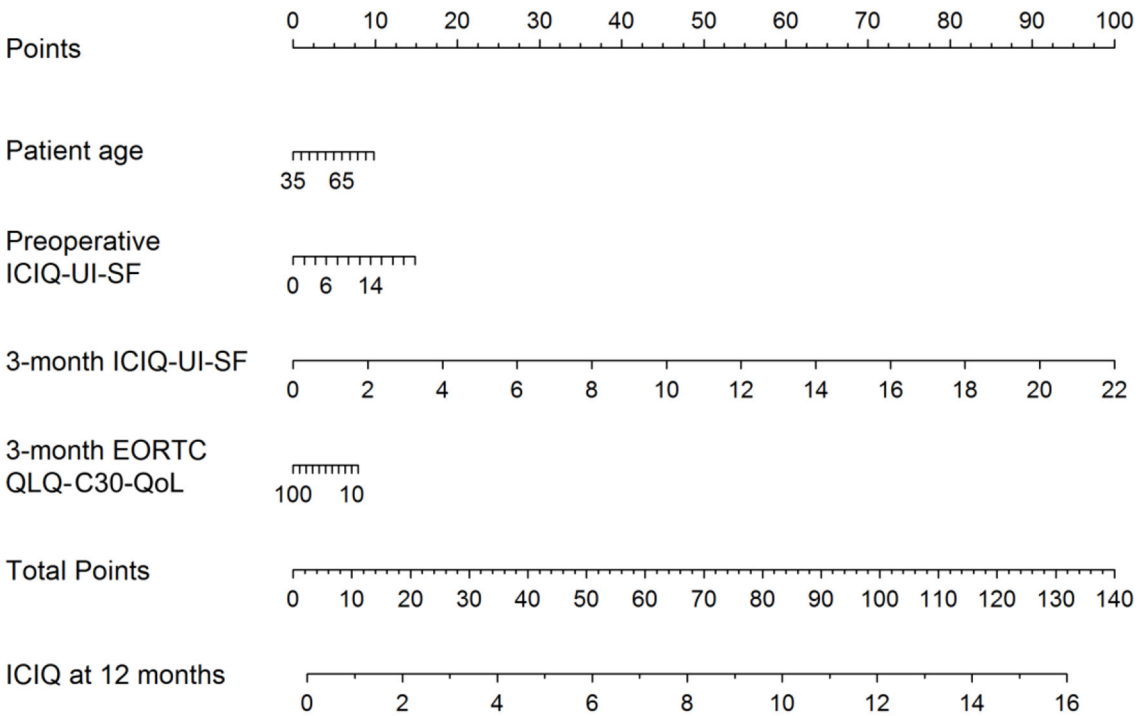

FIGURE 2 | Nomogram for the postoperative prediction of the 12-month ICIQ-UI-SF score among patients diagnosed with prostate cancer and treated with robotic-assisted laparoscopic prostatectomy. Instructions: locate the patient's values for age, 3-month EORCT QLQ-C30/QoL, intraoperative complications, preoperative ICIQ-UI-SF and 3-month ICIQ-UI-SF on the corresponding axes. Draw a straight line up to the Points axis for each value to determine the number of points for that value. Calculate the sum of the values on the Points axis and locate this sum score on the Total Points axis. Draw a straight line down to find the patient's predicted ICIQ-UI-SF score at 12 months. Taken From Tutolo et al. (44). EORCT QLQ-C30/QoL, European Organization for Research and Treatment for Cancer Quality of Life Questionnaire of Prostate Cancer; ICIQ-UI-SF, International Consultation on Incontinence Questionnaire-Urinary Incontinence Short Form.

clinical trials and **Figure 2** demonstrates the different surgical devices *in situ*.

Bulking Agents

Theoretically, bulking agents may be an attractive treatment option for patients with limited amount of urine loss, unfit for surgery, or unwilling for surgery with implantable devices (61). However, bulking agents have been discredited due to various complications, such as embolization, migration, absorptions, allergic, and fibrotic reactions. Novel bulking agents are characterized by their non-migrating and non-absorbable properties (62). Although bulking agents are commonly used in female SUI, evidence regarding the treatment of male SUI is scarce. Moreover, there is no standardized surgical technique regarding amount and position of injection. In a recent systematic review of bulking agents utilized for male SUI including polydimethylsiloxane elastomer (Macroplastique), polyacrylate polyalcohol copolymer (Opsys), carbon coated zirconium (Durasphere), and vinyl dimethyl terminated polydimethylsiloxane polymer (Urolastic), no final conclusion could be drawn due to the high risk of bias, incoherent reporting of urinary incontinence and surgical technique and contradictory results (61). It can be concluded that, there is currently, no recommendation for the utilization of bulking agents for the treatment of male stress urinary incontinence outside of clinical trials (46).

Male Slings

Male slings are minimally invasive procedures where a sling is positioned under the bulbar urethra through a retropubic or transobturator approach (46). They are distinguished into fixed and adjustable slings.

Fixed Slings

The mode of function of fixed slings is the reposition of the urethra to a proximal position without affecting the sphincter mechanism directly. This mechanism bases on the hypothesis, that urinary incontinence with residual sphincter function is caused by a urethral or perineal descent which is associated with lacity, iatrogenic causes, or aging in the levator ani complex (63). The distal urethral sphincter may be supported indirectly by a hammock underneath the urethral bulb though increasing the coaptative zone within the sphincteric membranous urethra. During increased physical exercise the blood flow is accumulated within the supported corpus spongiosum and hereby increases the zone of coaptation which is enabled by the male sling (7).

However, the current considerations base on the existence of an at least partial or complete presence of the urethral sphincter.

TABLE 2 | Continence and complications rates after different treatment modalities of male stress urinary incontinence in selected clinical trials.

References	Device	Device type	Year	Study design	Number of patients	Follow-up time	Continence definition	Urinary continence, n/N (%)	Complications
Bauer et al. (50)	AdVanceXP	Fixed sling	2015	Prospective non-randomized	94	24 months	0 pads and 0–5 g in 24 h pad test	35/46 (73.1)	Urinary tract infection $n = 1$, wound infection $n = 2$, urgency $n = 3$, explantation due to pain $n = 2$ or ineffectiveness $n = 3$
Collado Serra et al. (51)	AdVance AdVanceXP	Fixed sling	2013	Prospective non-randomized	61	26 months	0 pads/24h	49/61 (80.0)	Acute urinary retention $n = 9$(15%), perineal scrotal pain $n = 5$(8%), perineal hematoma $n = 2$(3%), *deNovo* urgency $n = 5$(8%)
Friedl et al. (52)	ATOMS	Adjustable sling	2017	Retrospective non-randomized	287	31 months	0–1 pad/24 h, <10 ml/day	184/287 (64.0)	Urinary retention $n = 8$(3%), early infection $n = 6$ (2%), hematoma $n = 6$(2%), removals $n = 56$ (20%) due to titanium intolerance $n = 23$ (41%), leak $n = 12$(21%), early infection $n = 6$ (11%) late infection $n = 6$(11%), dysfunction $n = 5$(9%), dislocation $n = 3$(5%), persistent pain $n = 1$(2%) reimplantation $n = 29$ (52%), solitary port change $n = 14$(5%), AUS solution $n = 11$ (4%)
Mühlstädt et al. (53)	ATOMS	Adjustable sling	2016	Retrospective nonrandomised	54	27.5 months	0–1 pad/24 h	26/54 (48.1)	Scrotal hematoma $n = 2$ (3.7%), pain $n = 3$ (5.6%), urinary retention $n = 1$ (1.9%), woundinfection perineal $n = 2$ (3.7%), wound infection port- $n = 4$ (7.4%), port erosion $n = 1$ (1.9%), incipient erosion of the port $n = 2$ (3.7%)
Cornel et al. (54)	Argus	Adjustable sling	2016	Prospective non-randomized	36	12 months	0–1 pad/24 h 0–2 g/24 h	29/36 (82.9)	Urinary retention $n = 7$, Hematoma $n = 1$, insensibility scrotum $n = 4$, perineal pain < 6 months $n = 9$, urinary tract infection $n = 1$, wound infection $n = 6$, inguinal wound reclosure removal sling column $n = 3$, sling infection and removal $n = 3$
Lima et al. (55)	Argus AdVance	Adjustable sling Fixed sling	2016	Prospective non-randomized	44	36.2 months 33.1 months	0–1 pad/24 h	23/25 (92) 16/19 (84)	Argus: $n = 1$ (4%) urinary retention, Revision surgery for incontinence $n = 6$ (24%) AdVance: $n = 2$ (11%)urinary retention
Leizour et al. (56)	Remeex	Adjustable sling	2017	Prospective non-randomized	25	31 months	0 pad/24 h	9/25 (41)	Explantation $n = 1$, infection $n = 3$.
Rocha et al. (57)	AMS800	Artificial urinary sphincter	2008	Prospective non-randomized	40	53 months	0 pad/24 h	20/40 (50.0)	Perineal hematoma $n = 1$, device infection $n = 3$ (7.5%), mechanical failure $n = 2$(5%), urethral atrophy $n = 2$(5%), overactive bladder syndrome $n = 4$ (10%)
Kaiho et al. (58)	AMS800	Artificial urinary sphincter	2018	Prospective non-randomized	135	12 months	0 pads	27/93 (37.3)	Wound infection $n = 5$, urinary retention $n = 4$ hematoma $n = 2$, others $n = 2$, mechanical failure $n = 7$, late infection $n = 4$, urethral erosion $n = 3$, urethral erosion and infection $n = 1$, pump malposition $n = 1$,
Yiou et al. (59)	ProAct	Non-circumferential compressive	2015	Prospective non-randomized	20	12 months	0 pads	12/18 (66.7)	Late infection of perineal wound $n = 2$ due to additional InVance implantation
Crivellaro et al. (60)	ProAct	Non-circumferential compressive	2008	Prospective non-randomized	46	19 months	0–1 pad/24 h	30/44 (68.0)	Erosion $n = 2$, spontaneous deflation $n = 1$, infection $n = 1$, migration $n = 2$, explantation $n = 6$

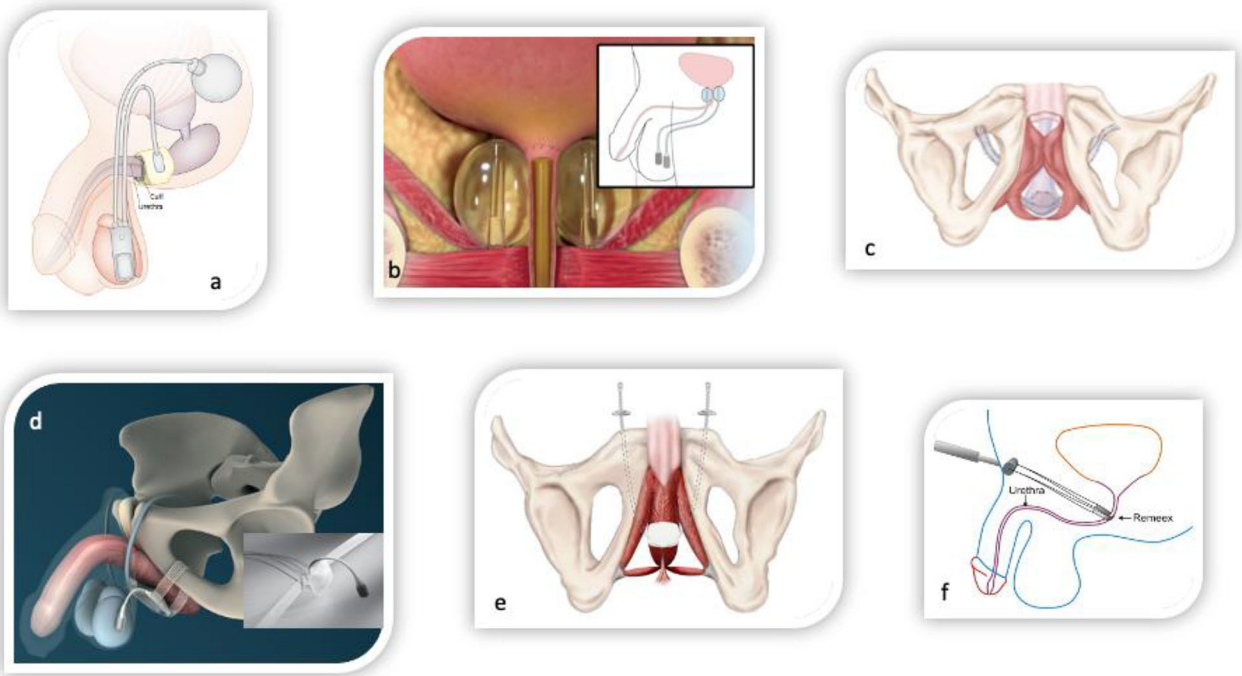

FIGURE 3 | Surgical devices for the treatment of male stress urinary incontinence. **(a)** Circumferential compressive three-piece artificial urinary sphincter AMS800 (Boston scientific, USA). **(b)** Non-circumferential compressive device ProACT (UroMedica, USA). **(c)** Fixed male sling AdVanceXP (Boston Scientific, USA). **(d)** Adjustable male sling ATOMS (A.M.I., Austria). **(e)** Adjustable male sling Argus (Promedon, Argentina). **(f)** Adjustable male sling Remeex (Neomedic, Spain).

Therefore, fixed slings are indicated in patients with mild to moderate male SUI (46) whereas, higher degrees of urinary incontinence should be reserved to compressive devices.

The most investigated fixed male sling is the AdVance, and second generation AdVanceXP (Boston Scientific, Marlborough, Massachusetts, USA). In mid-term follow up of the AdVanceXP in a selected patient population, 68.8% and 22.8% of the patients were either cured or improved, respectively, with a mean urine loss decreased to 19.1 g. Importantly, no intraoperative or long-term complications occurred in either of these patients (64). In a recent meta-analysis, the objective cure rates for fixed slings were reported between 8.3 and 87%. Pain was the most common complication although chronic pain was only reported in 1.3%. The second most common complication is urinary retention but being mostly a temporary condition (65).

Adjustable Slings

Adjustable slings offer the possibility of adjuvant adaptation of the sling tension or compression of the urethra by either tighten the sling arms or filling a cushion, which is localized beneath the urethra. The mode of function of adjustable slings are therefore complemented by the possibility of mechanical compression of the urethra (**Figure 3**).

Currently, there are three commercialized adjustable sling available: Remeex (Neomedic, Madrid, Spain), Argus (Promedon, Cordoba, Argentina), and ATOMS (A.M.I., Feldkirch, Austria). The currently most investigated adjustable sling is the ATOMS. In a recent meta-analysis including a total of 1.393 patients with an ATOMS, the mean cure rate was 67% and improvement of urinary SUI was 90%. The complication rate was 16.5% although major complications occurred in only 3% (66). Including all adjustable slings, the cure rate is reported between 17 and 92% in a meta-analysis. Chronic painful condition was 1.5% and the most common complication is infection with subsequent explantation of the device (65). These results are accordance with a large cohort trial, reporting a significant higher infection rate of 2.3% and pain rate of 11.9%. The total explantation rate was 4.0% (67). Furthermore, it could be demonstrated that adjustable slings are more commonly utilized in patients with higher degree of SUI and risk factors, although functional outcomes remained comparable to fixed slings.

In conclusion, there might be beneficial cure rates in adjustable slings in comparison to fixed slings. However, complications rates might be higher in adjustable slings.

Compressive Devices

Compressive devices can be distinguished between circumferential and non-circumferential devices.

Circumferential Compressive Devices

The AUS is a three-piece device including an urethral cuff, pump, and reservoir. The mode of function is a mechanical circumferential compression of the urethra and is based on

a hydraulic mechanism. The most investigated device is the AMS800 (Boston Scientific, Marlborough, Massachusetts, USA). Its predecessor has been introduced in 1972 (68) and is available in the current shape since 1982 (69). The continence rate of the AUS are reported between 61 and 100% (70) and in a long-term analysis with a mean of 15 years, the continence rate was still 77.2%. Including any degree of urinary incontinence independently of the existence of the urethral sphincter. Therefore, the AUS is recommended for the treatment of moderate to severe male SUI and in particular in patients with a history of pelvic irradiation or urethral stricture disease.

Despite the favorable functional outcome, the AUS is associated with higher complications rates than male slings (71). The mean rate of infection and erosion in a pooled analysis was 8.5%, mechanical failure 6.2%, urethral atrophy 7.9%, and the mean rate of reintervention was 26%. Nevertheless, in particular patients with higher degree of urinary incontinence facing limited treatment options. If the AUS fails, the ultima ratio is urinary diversion.

Apart from the AMS800, which offer the largest amount of literature and follow-up time, there are several other commercialized AUS available. Victo (Promedon, Cordoba, Argentina) is three-piece device similar to the AMS800 but offers additional the possibility to adjust the device by increasing the intraluminal pressure through percutaneous fluid injection into a port which is located in the bottom of the pump. Zephyr (Zephyr Surgical Implants, Geneva, Switzerland) offers a two-piece device including only a pump and an urethral cuff. Furthermore, the device also offers the possibility of postoperative adjustability in a similar approach as described.

Non-circumferential Compressive Devices

ProAct (Uromedica, Plymouth, USA) is a non-circumferential compressive device. The mechanism is based on two balloons which are positioned lateral to the proximal urethra. The balloons are filled in an ambulatory matter and results in a mechanical compression of the urethra. The success rates are reported between 62 and 68% accompanied by explantation rate of 12.3%. The most common complications are erosion (3.2–10.9 %) and dislocation (4–6.2 %) (72). Other prospective series even reported complication rates between 11 and 58% (46). There is currently no direct recommendation for the utilization of ProAct in mal SUI in the European guidelines. However, in the summary of very limited evidence, it is evaluated as effective in short term, although associated with a high risk of complications and should not be offered to patients with a history of pelvic irradiation (46).

FUTURE PERSPECTIVES AND CONCLUSIONS

Prostate cancer is one of the most problematic and frequently encountered malignancies in male patients. It often occurs when men are still in the active period of their lives. Consequently, there is a high demand for minimally invasive therapeutic approaches, susceptible of preserving urinary continence and sexual function. Unfortunately, stress urinary incontinence is a common adverse event in men with localized or locally advanced prostate cancer undergoing radical prostatectomy, but also secondary to radiotherapy (external beam radiotherapy as well as brachytherapy) and to cryosurgery (73).

Despite rehabilitative procedures such as pelvic floor muscle training, biofeedback, electrical stimulation, lifestyle changes, or a combination of these strategies, no fully efficient treatment alternative has yet been established for this pathology (74). On the other hand, it should be acknowledged that nursing care, including the understanding of the patient's needs, education, and psychosocial support remain essential features while aiming to improve the quality of life of prostate cancer patients.

Concerning the newest experimental treatments made available for urinary incontinence subsequent to prostate cancer surgery, there are studies that have shown a significant improvement of continence after ultrasound guided injection of fibroblasts and myoblasts into the sphincter (75). Other clinical trials also emphasized encouraging outcomes provided by stem-cells injection into the rhabdosphincter (76). Last but not least, promising outcomes have been outlined as a result of intravesical Onabotulinum toxin A injection (77).

Most importantly, the therapeutic decision and the chosen treatment option must be individualized for each patient according to clinical and social factors. During the recent years, the development of new therapeutic choices such as male sling techniques provided a more acceptable management pathway for less severe forms of urinary incontinence related to radical prostatectomy. Following this perspective, technological improvements and the emergence of new dedicated devices currently create the premises for a continuously positive evolution of clinical outcomes in this particular category of patients.

AUTHOR CONTRIBUTIONS

MR: data collection, coordination and drafting the manuscript, and supervising. TM and TH: data collection, drafting the manuscript, and supervising. BG and MT: data collection and drafting the manuscript.

REFERENCES

1. Ferlay J, Colombet M, Soerjomataram I, Dyba T, Randi G, Bettio M, et al. Cancer incidence and mortality patterns in Europe: estimates for 40 countries and 25 major cancers in 2018. *Eur J Cancer.* (2018) 103:356–87. doi: 10.1016/j.ejca.2018.07.005
2. EAU-EANM-ESTRO-ESUR-SIOG. Guidelines on prostate cancer 2020v4 2020. Available online at: https://uroweb.org/wp-content/uploads/EAU-EANM-ESTRO-ESUR-SIOG-Guidelines-on-Prostate-Cancer-2020v4.pdf.
3. Kretschmer A, Nitti V. Surgical treatment of male postprostatectomy incontinence: current concepts. *Eur Urol Focus.* (2017) 3:364–76. doi: 10.1016/j.euf.2017.11.007

4. Abrams P, Cardozo L, Fall M, Griffiths D, Rosier P, Ulmsten U, et al. The standardisation of terminology of lower urinary tract function: report from the Standardisation Sub-committee of the International Continence Society. *Neurourol Urodyn.* (2002) 21:167–78. doi: 10.1002/nau.10052
5. D'Ancona C, Haylen B, Oelke M, Abranches-Monteiro L, Arnold E, Goldman H, et al. The international continence society (ICS) report on the terminology for adult male lower urinary tract and pelvic floor symptoms and dysfunction. *Neurourol Urodyn*. (2019) 38:433–77. doi: 10.1002/nau.23897
6. John H, Sullivan MP, Bangerter U, Hauri D, Yalla SV. Effect of radical prostatectomy on sensory threshold and pressure transmission. *J Urol.* (2000) 163:1761–6. doi: 10.1016/S0022-5347(05)67537-4
7. Rehder P, Staudacher NM, Schachtner J, Berger ME, Schillfahrt F, Hauser V, et al. Hypothesis that urethral bulb (Corpus Spongiosum) plays an active role in male urinary continence. *Adv Urol.* (2016) 2016:6054730. doi: 10.1155/2016/6054730
8. Sallami S. Predictive factors of urinary incontinence after radical prostatectomy: systematic review. *Tunis Med.* (2017) 95:229–35.
9. Lee R, Te AE, Kaplan SA, Sandhu JS. Temporal trends in adoption of and indications for the artificial urinary sphincter. *J Urol.* (2009) 181:2622–7. doi: 10.1016/j.juro.2009.01.113
10. Haglind E, Carlsson S, Stranne J, Wallerstedt A, Wilderang U, Thorsteinsdottir T, et al. Urinary incontinence and erectile dysfunction after robotic versus open radical prostatectomy: a prospective, controlled, nonrandomised trial. *Eur Urol.* (2015) 68:216–25. doi: 10.1016/j.eururo.2015.02.029
11. Tang K, Jiang K, Chen H, Chen Z, Xu H, Ye Z. Robotic vs. Retropubic radical prostatectomy in prostate cancer: a systematic review and an meta-analysis update. *Oncotarget*. (2017) 8:32237–57. doi: 10.18632/oncotarget.13332
12. Coughlin GD, Yaxley JW, Chambers SK, Occhipinti S, Samaratunga H, Zajdlewicz L, et al. Robot-assisted laparoscopic prostatectomy versus open radical retropubic prostatectomy: 24-month outcomes from a randomised controlled study. *Lancet Oncol.* (2018) 19:1051–60. doi: 10.1016/S1470-2045(18)30357-7
13. Porpiglia F, Morra I, Lucci Chiarissi M, Manfredi M, Mele F, Grande S, et al. Randomised controlled trial comparing laparoscopic and robot-assisted radical prostatectomy. *Eur Urol.* (2013) 63:606–14. doi: 10.1016/j.eururo.2012.07.007
14. Basiri A, de la Rosette JJ, Tabatabaei S, Woo HH, Laguna MP, Shemshaki H. Comparison of retropubic, laparoscopic and robotic radical prostatectomy: who is the winner? *World J Urol*. (2018) 36:609–21. doi: 10.1007/s00345-018-2174-1
15. Choo MS, Choi WS, Cho SY, Ku JH, Kim HH, Kwak C. Impact of prostate volume on oncological and functional outcomes after radical prostatectomy: robot-assisted laparoscopic versus open retropubic. *Korean J Urol.* (2013) 54:15–21. doi: 10.4111/kju.2013.54.1.15
16. Rocco B, Matei DV, Melegari S, Ospina JC, Mazzoleni F, Errico G, et al. Robotic vs open prostatectomy in a laparoscopically naive centre: a matched-pair analysis. *BJU Int*. (2009) 104:991–5. doi: 10.1111/j.1464-410X.2009.08532.x
17. Son SJ, Lee SC, Jeong CW, Jeong SJ, Byun SS, Lee SE. Comparison of continence recovery between robot-assisted laparoscopic prostatectomy and open radical retropubic prostatectomy: a single surgeon experience. *Korean J Urol*. (2013) 54:598–602. doi: 10.4111/kju.2013.54.9.598
18. Kim M, Park M, Pak S, Choi SK, Shim M, Song C, et al. Integrity of the urethral sphincter complex, nerve-sparing, and long-term continence status after robotic-assisted radical prostatectomy. *Eur Urol Focus.* (2019) 5:823–30. doi: 10.1016/j.euf.2018.04.021
19. Olsson LE, Salomon L, Nadu A, Hoznek A, Cicco A, Saint F, et al. Prospective patient-reported continence after laparoscopic radical prostatectomy. *Urology*. (2001) 58:570–2. doi: 10.1016/S0090-4295(01)01261-4
20. Sumarsono B, Jong JJ, Wang JY, Liao L, Lee KS, Yoo TK, et al. The prevalence of urinary incontinence in men and women aged 40 years or over in China, Taiwan and South Korea: a cross-sectional, prevalence-based study. *Low Urin Tract Symptoms.* (2020) 12:223–34. doi: 10.1111/luts.12308
21. Averbeck MA, Marcelissen T, Anding R, Rahnama'i MS, Sahai A, Tubaro A. How can we prevent postprostatectomy urinary incontinence by patient selection, and by preoperative, peroperative, and postoperative measures? International Consultation on Incontinence-Research Society 2018. *Neurourol Urodyn.* (2019) 38(Suppl 5):S119–26. doi: 10.1002/nau.23972
22. Heesakkers J, Farag F, Bauer RM, Sandhu J, De Ridder D, Stenzl A. Pathophysiology and contributing factors in postprostatectomy incontinence: a review. *Eur Urol.* (2017) 71:936–44. doi: 10.1016/j.eururo.2016.09.031
23. Oelrich TM. The urethral sphincter muscle in the male. *Am J Anat.* (1980) 158:229–46. doi: 10.1002/aja.1001580211
24. Steiner MS. The puboprostatic ligament and the male urethral suspensory mechanism: an anatomic study. *Urology*. (1994) 44:530–4. doi: 10.1016/S0090-4295(94)80052-9
25. Strasser H, Frauscher F, Helweg G, Colleselli K, Reissigl A, Bartsch G. Transurethral ultrasound: evaluation of anatomy and function of the rhabdosphincter of the male urethra. *J Urol.* (1998) 159:100–4; discussion 4–5. doi: 10.1016/S0022-5347(01)64025-4
26. Gomha MA, Boone TB. Voiding patterns in patients with post-prostatectomy incontinence: urodynamic and demographic analysis. *J Urol.* (2003) 169:1766–9. doi: 10.1097/01.ju.0000059700.21764.83
27. John H. Bulbourethral composite suspension: a new operative technique for post-prostatectomy incontinence. *J Urol.* (2004) 171:1866–70; discussion 9–70. doi: 10.1097/01.ju.0000121413.62521.cc
28. Majoros A, Bach D, Keszthelyi A, Hamvas A, Romics I. Urinary incontinence and voiding dysfunction after radical retropubic prostatectomy (prospective urodynamic study). *Neurourol Urodyn*. (2006) 25:2–7. doi: 10.1002/nau.20190
29. Matsukawa Y, Hattori R, Komatsu T, Funahashi Y, Sassa N, Gotoh M. *De novo* detrusor underactivity after laparoscopic radical prostatectomy. *Int J Urol.* (2010) 17:643–8. doi: 10.1111/j.1442-2042.2010.02529.x
30. Porena M, Mearini E, Mearini L, Vianello A, Giannantoni A. Voiding dysfunction after radical retropubic prostatectomy: more than external urethral sphincter deficiency. *Eur Urol.* (2007) 52:38–45. doi: 10.1016/j.eururo.2007.03.051
31. Groutz A, Blaivas JG, Chaikin DC, Weiss JP, Verhaaren M. The pathophysiology of post-radical prostatectomy incontinence: a clinical and video urodynamic study. *J Urol.* (2000) 163:1767–70. doi: 10.1016/S0022-5347(05)67538-6
32. Kielb SJ, Clemens JQ. Comprehensive urodynamics evaluation of 146 men with incontinence after radical prostatectomy. *Urology*. (2005) 66:392–6. doi: 10.1016/j.urology.2005.03.026
33. Trieu D, Ju IE, Chang SB, Mungovan SF, Patel MI. Surgeon case volume and continence recovery following radical prostatectomy: a systematic review. *ANZ J Surg.* (2020). doi: 10.1111/ans.16491. [Epub ahead of print].
34. Peyronnet B, Brucker BM. Management of overactive bladder symptoms after radical prostatectomy. *Curr Urol Rep.* (2018) 19:95. doi: 10.1007/s11934-018-0847-3
35. Chapple C. Chapter 2: Pathophysiology of neurogenic detrusor overactivity and the symptom complex of "overactive bladder". *Neurourol Urodyn.* (2014) 33(Suppl 3):S6–13. doi: 10.1002/nau.22635
36. Jung SY, Fraser MO, Ozawa H, Yokoyama O, Yoshiyama M, De Groat WC, et al. Urethral afferent nerve activity affects the micturition reflex; implication for the relationship between stress incontinence and detrusor instability. *J Urol.* (1999) 162:204–12. doi: 10.1097/00005392-199907000-00069
37. Shafik A, Shafik AA, El-Sibai O, Ahmed I. Role of positive urethrovesical feedback in vesical evacuation. The concept of a second micturition reflex: the urethrovesical reflex. *World J Urol*. (2003) 21:167–70. doi: 10.1007/s00345-003-0340-5
38. Shafik A, el-Sibai O, Ahmed I. Effect of urethral dilation on vesical motor activity: identification of the urethrovesical reflex and its role in voiding. *J Urol.* (2003) 169:1017–9. doi: 10.1097/01.ju.0000046384.71563.51
39. Hubeaux K, Deffieux X, Desseaux K, Verollet D, Damphousse M, Amarenco G. Stand up urgency: is this symptom related to a urethral mechanism? *Prog Urol.* (2012) 22:475–81. doi: 10.1016/j.purol.2012.04.011
40. Matsukawa Y, Yoshino Y, Ishida S, Fujita T, Majima T, Funahashi Y, et al. De novo overactive bladder after robot-assisted laparoscopic radical prostatectomy. *Neurourol Urodyn.* (2018) 37:2008–14. doi: 10.1002/nau.23556
41. Chung DE, Dillon B, Kurta J, Maschino A, Cronin A, Sandhu JS. Detrusor underactivity is prevalent after radical prostatectomy: a urodynamic study including risk factors. *Can Urol Assoc J.* (2013) 7:E33–7. doi: 10.5489/cuaj.192
42. Jarosek SL, Virnig BA, Chu H, Elliott SP. Propensity-weighted long-term risk of urinary adverse events after prostate cancer surgery, radiation, or both. *Eur Urol.* (2015) 67:273–80. doi: 10.1016/j.eururo.2014.08.061
43. Drake MJ, Kanai A, Bijos DA, Ikeda Y, Zabbarova I, Vahabi B, et al. The potential role of unregulated autonomous bladder micromotions in

urinary storage and voiding dysfunction; overactive bladder and detrusor underactivity. *BJU Int*. (2017) 119:22–9. doi: 10.1111/bju.13598
44. Tutolo M, Bruyneel L, Van der Aa F, Van Damme N, Van Cleynenbreugel B, Joniau S, et al. A novel tool to predict functional outcomes after robot-assisted radical prostatectomy and the value of additional surgery for incontinence. *BJU Int*. (2020). doi: 10.1111/bju.15242. [Epub ahead of print].
45. Anderson CA, Omar MI, Campbell SE, Hunter KF, Cody JD, Glazener CM. Conservative management for postprostatectomy urinary incontinence. *Cochrane Database Syst Rev*. (2015) 1:CD001843. doi: 10.1002/14651858.CD001843.pub5
46. Burkhard FC, Bosch RJL, Cruz F, Lemack GE, Nambiar AK, Thiruchelvam N, et al. *EAU Guidelines on Urinary Incontinence* (2020).
47. Alan C, Eren AE, Ersay AR, Kocoglu H, Basturk G, Demirci E. Efficacy of duloxetine in the early management of urinary continence after radical prostatectomy. *Curr Urol.* (2015) 8:43–8. doi: 10.1159/000365688
48. Filocamo MT, Li Marzi V, Del Popolo G, Cecconi F, Villari D, Marzocco M, et al. Pharmacologic treatment in postprostatectomy stress urinary incontinence. *Eur Urol*. (2007) 51:1559–64. doi: 10.1016/j.eururo.2006.08.005
49. Abrams P, Constable LD, Cooper D, MacLennan G, Drake MJ, Harding C, et al. Outcomes of a noninferiority randomised controlled trial of surgery for men with urodynamic stress incontinence after prostate surgery (MASTER). *Eur Urol.* (2021). doi: 10.1016/j.eururo.2021.01.024. [Epub ahead of print].
50. Bauer RM, Gozzi C, Klehr B, Kretschmer A, Grabbert M, Rehder P, et al. AdVanceXP male sling: 2-year results of a multicentre study. *World J Urol*. (2015) 34:1025–30. doi: 10.1007/s00345-015-1731-0
51. Collado Serra A, Resel Folkersma L, Dominguez-Escrig JL, Gomez-Ferrer A, Rubio-Briones J, Solsona Narbon E. AdVance/AdVance XP transobturator male slings: preoperative degree of incontinence as predictor of surgical outcome. *Urology*. (2013) 81:1034–9. doi: 10.1016/j.urology.2013.01.007
52. Friedl A, Muhlstadt S, Zachoval R, Giammo A, Kivaranovic D, Rom M, et al. Long-term outcome of the adjustable transobturator male system (ATOMS): results of a European multicentre study. *BJU Int.* (2017) 119:785–92. doi: 10.1111/bju.13684
53. Muhlstadt S, Friedl A, Mohammed N, Schumann A, Weigand K, Kawan F, et al. Five-year experience with the adjustable transobturator male system for the treatment of male stress urinary incontinence: a single-center evaluation. *World J Urol.* (2017) 35:145–51. doi: 10.1007/s00345-016-1839-x
54. Cornel EB. Argus-T adjustable male sling: the influence of surgical technique on complications and short-term efficacy. *Urol Int*. (2016) 96:164–70. doi: 10.1159/000443673
55. Lima JP, Pompeo AC, Bezerra CA. Argus T(R) versus Advance(R) Sling for postprostatectomy urinary incontinence: a randomized clinical trial. *Int Braz J Urol.* (2016) 42:531–9. doi: 10.1590/S1677-5538.IBJU.2015.0075
56. Leizour B, Chevrot A, Wagner L, Droupy S, Costa P. Adjustable retropubic suburethral sling Remeex(®) in the treatment of male stress urinary incontinence: one-year results. *Prog Urol.* (2017) 27:238–43. doi: 10.1016/j.purol.2016.11.006
57. Trigo Rocha F, Gomes CM, Mitre AI, Arap S, Srougi M. A prospective study evaluating the efficacy of the artificial sphincter AMS 800 for the treatment of postradical prostatectomy urinary incontinence and the correlation between preoperative urodynamic and surgical outcomes. *Urology*. (2008) 71:85–9. doi: 10.1016/j.urology.2007.09.009
58. Kaiho Y, Masuda H, Takei M, Hirayama T, Mitsui T, Yokoyama M, et al. Surgical and patient reported outcomes of artificial urinary sphincter implantation: a multicenter, prospective, observational study. *J Urol.* (2018) 199:245–50. doi: 10.1016/j.juro.2017.08.077
59. Yiou R, Butow Z, Baron T, Salomon L, Audureau E. Adjustable continence therapy (ProACT) after male sling failure for patients with post-radical prostatectomy urinary incontinence: a prospective study with one-year follow-up. *World J Urol.* (2015) 33:1331–6. doi: 10.1007/s00345-014-1447-6
60. Crivellaro S, Singla A, Aggarwal N, Frea B, Kocjancic E. Adjustable continence therapy (ProACT) and bone anchored male sling: comparison of two new treatments of post prostatectomy incontinence. *Int J Urol.* (2008) 15:910–4. doi: 10.1111/j.1442-2042.2008.02161.x
61. Toia B, Gresty H, Pakzad M, Hamid R, Ockrim J, Greenwell T. Bulking for stress urinary incontinence in men: a systematic review. *Neurourol Urodyn*. (2019) 38:1804–11. doi: 10.1002/nau.24102
62. Chughtai B, Sedrakyan A, Isaacs AJ, Mao J, Lee R, Te A, et al. National study of utilization of male incontinence procedures. *Neurourol Urodyn*. (2016) 35:74–80. doi: 10.1002/nau.22683
63. Rehder P, Gozzi C. Transobturator sling suspension for male urinary incontinence including post-radical prostatectomy. *Eur Urol*. (2007) 52:860–6. doi: 10.1016/j.eururo.2007.01.110
64. Bauer RM, Grabbert MT, Klehr B, Gebhartl P, Gozzi C, Homberg R, et al. 36-month data for the AdVance XP(R) male sling: results of a prospective multicentre study. *BJU Int*. (2017) 119:626–30. doi: 10.1111/bju.13704
65. Meisterhofer K, Herzog S, Strini KA, Sebastianelli L, Bauer R, Dalpiaz O. Male slings for postprostatectomy incontinence: a systematic review and meta-analysis. *Eur Urol Focus*. (2020) 6:575–92. doi: 10.1016/j.euf.2019.01.008
66. Esquinas C, Angulo JC. Effectiveness of Adjustable Transobturator Male System (ATOMS) to Treat Male Stress Incontinence: a systematic review and meta-analysis. *Adv Ther*. (2019) 36:426–41. doi: 10.1007/s12325-018-0852-4
67. Hüsch T, Kretschmer A, Obaje A, Kirschner-Hermanns R, Anding R, Pottek T, et al. Fixed or adjustable sling in the treatment of male stress urinary incontinence: results from a large cohort study. *Transl Androl Urol.* (2020) 9:1099–107. doi: 10.21037/tau-19-852
68. Scott FB, Bradley WE, Timm GW. Treatment of urinary incontinence by an implantable prosthetic urinary sphincter. *J Urol*. (1974) 112:75–80. doi: 10.1016/S0022-5347(17)59647-0
69. Leicht W, Thuroff J. Therapy of male urinary incontinence: artificial sphincter versus male slings. *Der Urologe Ausg A*. (2012) 51:341–7. doi: 10.1007/s00120-012-2820-y
70. Van der Aa F, Drake MJ, Kasyan GR, Petrolekas A, Cornu JN. The artificial urinary sphincter after a quarter of a century: a critical systematic review of its use in male non-neurogenic incontinence. *Eur Urol*. (2013) 63:681–9. doi: 10.1016/j.eururo.2012.11.034
71. Hüsch T, Kretschmer A, Thomsen F, Kronlachner D, Kurosch M, Obaje A, et al. Risk factors for failure of male slings and artificial urinary sphincters: results from a large middle european cohort study. *Urol Int*. (2017) 99:14–21. doi: 10.1159/000449232
72. Crivellaro S, Morlacco A, Bodo G, Agro EF, Gozzi C, Pistolesi D, et al. Systematic review of surgical treatment of post radical prostatectomy stress urinary incontinence. *Neurourol Urodyn*. (2016) 35:875–81. doi: 10.1002/nau.22873
73. Parsons BA, Evans S, Wright MP. Prostate cancer and urinary incontinence. *Maturitas*. (2009) 63:323–8. doi: 10.1016/j.maturitas.2009.06.005
74. Tantawy SA, Elgohary HMI, Abdelbasset WK, Kamel DM. Effect of 4 weeks of whole-body vibration training in treating stress urinary incontinence after prostate cancer surgery: a randomised controlled trial. *Physiotherapy*. (2019) 105:338–45. doi: 10.1016/j.physio.2018.07.013
75. Mitterberger M, Marksteiner R, Margreiter E, Pinggera GM, Frauscher F, Ulmer H, et al. Myoblast and fibroblast therapy for post-prostatectomy urinary incontinence: 1-year followup of 63 patients. *J Urol.* (2008) 179:226–31. doi: 10.1016/j.juro.2007.08.154
76. Gotoh M, Yamamoto T, Kato M, Majima T, Toriyama K, Kamei Y, et al. Regenerative treatment of male stress urinary incontinence by periurethral injection of autologous adipose-derived regenerative cells: 1-year outcomes in 11 patients. *Int J Urol.* (2014) 21:294–300. doi: 10.1111/iju.12266
77. Apostolidis A, Dasgupta P, Denys P, Elneil S, Fowler CJ, Giannantoni A, et al. Recommendations on the use of botulinum toxin in the treatment of lower urinary tract disorders and pelvic floor dysfunctions: a European consensus report. *Eur Urol.* (2009) 55:100–19. doi: 10.1016/j.eururo.2008.09.009

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SYSTEMATIC REVIEW
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Is it Worth Starting Sexual Rehabilitation Before Radical Prostatectomy? Results From a Systematic Review of the Literature

Nadja Schoentgen[1], Gianluigi Califano[1,2], Celeste Manfredi[2,3], Javier Romero-Otero[3], Felix K. H. Chun[4], Idir Ouzaid[1,5], Jean-François Hermieu[1,5], Evanguelos Xylinas[1,5] and Paolo Verze[6]*

[1] Department of Urology, Bichat Claude Bernard Hospital, Paris, France, [2] Department of Neurosciences, Reproductive Sciences, Odontostomatology, University of Naples Federico II, Naples, Italy, [3] Department of Urology, Instituto de Investigation Sanitaria Hospital 12 de October (imas12), Hospital Universitario 12 October, Madrid, Spain, [4] Department of Urology, University Hospital Frankfurt, Goethe University Frankfurt, Frankfurt, Germany, [5] University of Paris, Paris, France, [6] Department of Medicine, Surgery, Dentistry "Scuola Medica Salernitana", University of Salerno, Salerno, Italy

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***Correspondence:**
Nadja Schoentgen
nadja.schoentgen@gmail.com

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Background and Purpose: Sexual dysfunction (SD) is a frequent side effect associated with radical prostatectomy (RP) for prostate cancer (PCa). Some studies have showed the benefit associated with preoperative sexual rehabilitation (prehabilitation) and Enhanced Recovery After Surgery (ERAS) for RP, but no clear clinical recommendations are available yet. Our aim was to conduct a systematic review on sexual prehabilitation prior to RP for patients with a localized PCa and analyze the impact on postoperative sexual health compared with the standard post-operative care.

Methods: We performed a systematic review of the literature following the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) recommendations.

Results: Four randomized control trials and one retrospective comparative study were included in the analyses. Three of the five studies showed an improved EF recovery post-RP in the prehabilitation group compared to the standard of care represented by: higher International Index of Erectile Function 5 score (IIEF5) or IIEF score ($p < 0.0001$) and a higher percentage of patients reporting return of EF based on the Sexual Encounter Profile (SEP) (56 vs. 24%, $p = 0.007$). Self-confidence, therapeutic alliance, and adherence to treatment were stronger for patients with preoperative consultations ($p < 0.05$) and EF recovery was better in cases of a higher number of follow-up visits (OR 4–5 visits vs. 1:12.19, $p = 0.002$).

Discussion: Despite heterogenous methods and high risks of bias in this systematic review, starting sexual rehabilitation prior to surgery seems to ensure better EF recovery. This prehabilitation should include information of both the patient and his or her partner, with a closer follow up and the use of a multimodal treatment approach that still remains to be defined and validated (oral medication, vacuum devices, pelvic floor muscle training, etc.).

Keywords: prehabilitation, sexual rehabilitation, sexual dysfunction, radical prostatecomy, prostate cancer

INTRODUCTION

Sexual dysfunction (SD) is a frequent side effect associated with radical prostatectomy (RP) for prostate cancer (PCa). In the Prostate Testing for Cancer and Treatment (ProtecT) trial, which randomized 1,643 patients in three treatments groups (active surveillance, radiotherapy, surgery) and followed-up for 6 years, surgery was associated with the worst rate of SD. At baseline, 67% of men reported erections firm enough for intercourse and this rate declined to 17% at 6 years (1). The lack of preoperative information on postoperative SD can lead to patient and couple distress (2). An approach in which the patient receives adequate treatment and information even prior to surgery seems to improve the rehabilitation phase following the surgical (3, 4) phase, which draws a lot of focus in order to improve the functional outcomes of the surgery. Enhanced recovery after surgery (ERAS) protocols have demonstrated their efficacy for bladder cancer surgery in randomized controlled trials and prehabilitation programs have also been proven to be effective in terms of a faster functional recovery (5, 6). Some studies showed the benefit of prehabilitation and ERAS for RP; however, they mostly focused on blood loss, length of stay, costs, and urinary continence (5, 7). Many studies are published on SD and its treatment after RP (8, 9), but there are really spare data on sexual prehabilitation and its potential impact on postoperative sexual function.

Our aim was to conduct a systematic review on sexual prehabilitation prior to RP for patients with localized PCa and analyze the impact on postoperative sexual recovery compared with the standard post-operative care.

METHODS

Review Question

According to the Participants, Intervention, Comparison, Outcome, and Study design (PICOS) framework (10), the research question was: In patients undergoing RP for PCa (P), what impact does sexual prehabilitation have (I), compared to the standard postoperative care (C), on the sexual function recovery in the first post-operative year (O), as evidenced by the comparative studies (randomized and non-randomized) (S)?

Inclusion and Exclusion Criteria

The inclusion criteria were as follows: (1) patients with PCa undergoing RP, regardless of a specific surgical approach; (2) studies that analyzed any type of sexual prehabilitation; (3) outcome measure (sexual function assessed by questionnaires, survey, and scale for psychological impact of sexual dysfunction); and (4) comparative studies [Randomized Controlled Trials (RCTs) and Non-Randomized Studies of Interventions (NRSI)].

The exclusion criteria were as follows: (1) patients undergoing RP for indications other than PCa; (2) patients with PCa managed with treatments other than RP; (3) studies not aimed at analyzing the impact of sexual prehabilitation on the postoperative sexual function recovery; and (4) non-comparative studies, literature reviews, editorials, abstracts, or unpublished research.

Search Strategy

The Preferred Reporting Items for the Systematic Review and Meta-Analysis (PRISMA) recommendations were followed. A systematic review of the literature was performed in November 2020 using the Cochrane Central Register of Controlled Trials (CENTRAL) and MEDLINE (*via* PubMed) databases. The following terms were combined for the search strategy: sexual prehabilitation, prehabilitation, sexual rehabilitation, prostate cancer, and radical prostatectomy. Search results were filtered by language (English), species (human), and publication date (from January 2000 to November 2020). Reference lists of relevant studies were also reviewed. For studies published by the same authors or institutions, only the most relevant study was reported. Two independent authors (N.S. and G.C.) performed title and abstract screening and full-text review, with a third part to arbitrate (P. V.).

Data Extraction

The following data were extracted from the included studies: study period, study design, number of subjects included, characteristics of intervention and control groups, study protocol, follow-up, sexual outcomes, results, limitations, and risk of bias.

Outcomes

The primary study outcome was to assess the impact of sexual prehabilitation vs. standard postoperative care on the sexual function recovery using validated questionnaires.

The secondary outcome was the psychological impact analysis of sexual prehabilitation using questionnaires.

Risk of Bias Assessment

The Risk of Bias in the included studies were assessed using the Jadad and the Methodological Index for Non-Randomized Studies (MINORS) scores for randomized and non-randomized studies, respectively (11, 12).

Data Synthesis

Due to the low number of studies included and the high data heterogeneity, we chose not to perform a meta-analysis.

RESULTS

We screened 92 studies and included five of them that met the inclusion criteria: four RCTs (13–16) and one retrospective comparative study (17), published between 2015 and 2020. The diagram of the studies' selection is displayed in **Figure 1**.

The study designs are summarized in **Table 1**. The number of subjects varied between 31 and 189, and one study included the patient's partner (13). One study protocol was based on counseling (with an additional DVD information tool) (13). In the intervention group, counseling content was education about prostate cancer, menopause, and sexuality; behavioral homework including increasing expression of affection and non-demanding sexual touch; challenging negative beliefs about prostate cancer, aging, and sexuality; and helping the couple choose a medical treatment for erectile dysfunction (ED)

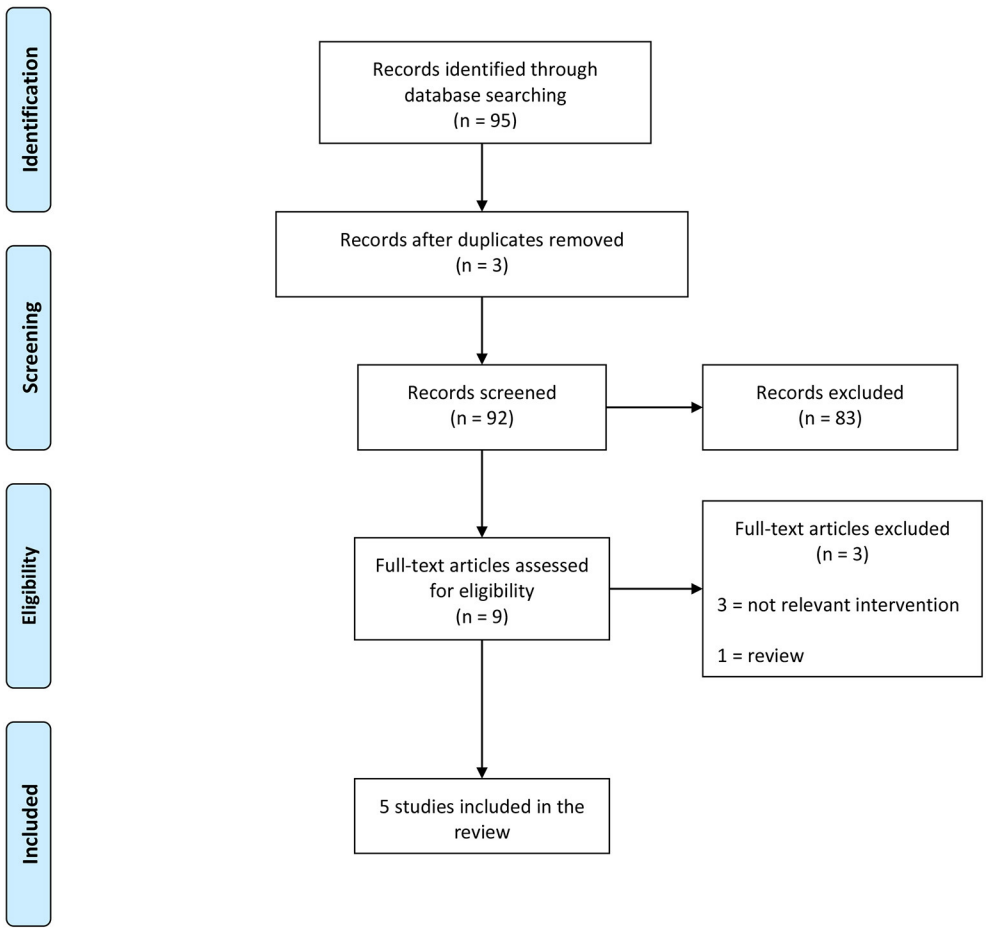

FIGURE 1 | PRISMA flowchart.

and integrating this into their sexual relationship. Three study protocols were based on pelvic floor muscle training (PFMT): in one case, the study only involved the use of total body exercise before RP (15); in the other two studies, the study plan included a pre- and post-intervention treatment (14, 16).

One study protocol was based on a combination of oral therapy, lifestyle counseling, and the continuous use of a vacuum device. Intervention group received 5 mg of tadalafil daily and 1,500 mg of L-citrulline twice daily, + lifestyle counseling 2 weeks before RP, and vacuum daily initiated 1 month post-RP (17).

Surgical technique of RP was not mentioned in the studies by Chambers and Lira (13, 14). Osadchiy et al. included only Nerve Sparing Robotic Assisted Laparoscopic Prostatectomy (NS-RALP) without details on uni or bilateral NS surgery (17). Santa Mina et al. included RALP (81%) and open RP (19%) without details on nerve preservation (15). Milios et al. included RALP [87%] and open RP [13%] with unilateral NS surgery (18%), bilateral NS surgery (77%), and non-NS surgery (5%) (16).

Follow-up ranged between 3 and 12 months.

Sexual outcomes were assessed by the International Index of Erectile F unction (IIEF) in one study (13), the short form 5-item IIEF (IIEF-5) in three studies (14–16), question 2 and 3 of the sexual encounter profile (SEP) questionnaire in one study (17), and EF domain of the Expanded Prostate Cancer Index Composite for Clinical Practice (EPIC-CP) in one study (16). In the study by Chambers et al. based on the counseling protocol, psychological scale and couple's assessment were also used.

Functional results derived from all the included studies are summarized in **Table 2**.

The RCT study by Chambers et al. showed that participants in the peer and nurse groups were 3.14 times and 3.67 times more likely to use medical treatment for ED, respectively, than those in the usual care group ($p = 0.016$ and $p = 0.008$). In this study, a significantly higher IIEF ($p < 0.0001$) and greater sexual self-confidence ($p < 0.05$) were associated with patients recruited before RP (13). The RCT study by Santa Mina et al. concluded that EF scores were greater in the control group at

TABLE 1 | Summary of study design.

References	Study period	Design	*N*	Intervention group	Intervention group	Protocol for intervention group	Control group	Follow up		Sexual outcomes
Chambers et al. (13)	May 2009 –May 2011	RCT	*N* = 189 patients and wife (74% recruited pre-surgery)	Peer support volunteers-delivered intervention (*n* = 63)	Nurse-delivered intervention (*n* = 62)	- 2 calls prior RP and 6 after for pre-surgery recruited patients - 5 calls post-RP for post-surgery recruited patients - + DVD support	Usual post-RP care	12 months	IIEF	- A scale assessing couples obtention of ED medical help - Psychological Impact of Erectile Dysfunction scale - Masculine Self-Esteem scale - Revised Dyadic Adjustment Scale to assess marital satisfaction - Supportive Care Needs Survey for couples
Santa Mina et al. (15)	February 2014–September 2015	RCT	*N* = 86	Preoperative total body exercise + PFMT (*n* = 44)	-	60 minutes of exercise 3-4 days per week + daily PFMT	Pre-RP PFMT	6 months	IIEF5	-
Lira (14)	March 2013 -December 2014	RCT	*N* = 31	Pre- and post-operative PFMT (*n* = 16)	-	2 preoperative sessions guided by a physical therapist + pre-RP and post-RP PFMT 3/day	Usual post-RP care	3 months	IIEF5	-
Osadchiy et al. (17)	January 2016 - December 2017.	Retrospective comparative study	*N* = 131	Oral therapy + lifestyle counseling before RP + Vacuum post-RP (*n* = 106)	-	5mg tadalafil daily and 1500 mg L-citrulline twice daily + lifestyle counseling 2 weeks before RP and vacuum daily initiated 1-month post-RP	Oral therapy and vacuum initiated 1-month post-RP	12 months	SEP: Q2 and Q3	-
Milios et al. (16)	2016-2018	RCT	*N* = 97	Intensive PFMT pre- and post-RP	-	5 weeks prior and 12 weeks post-RP, intensive PFMT (120 contractions/day instead of 30)	"Standard" PFMT pre- and post-RP	3 months	IIEF5	EF domain of EPIC-CP

RCT, randomized control trial; N, number of subjects; RP, radical prostatectomy, IIEF, international index of erectile function; ED, erectile dysfunction; PFMT, pelvic floor muscle training; IIEF 5, simplified IIEF 5 items; SEP, sexual encounter profile; EF domain of EPIC-CP, erectile function domain of the expanded prostate cancer index composite for clinical practice.

TABLE 2 | Summary of study results.

References		Results		Limitations	Risk of bias (MINORS)	Risk of bias (Jadad score)
Chambers et al. (13)	participants in the peer and the nurse groups were 3.14 times and 3.67 times more likely to use medical treatment for ED respectively than those in the usual care group ($p = 0.016$ and $p = 0.008$)	Men and their partner reported greater therapeutic alliance in the nurse group	Significant higher IIEF ($p < 0.0001$) and greater sexual self-confidence ($p < 0.05$) were associated with patients recruited before RP	Heterosexual couples only included		1
Santa Mina et al. (15)	EF scores were greater in control group at 4-weeks post-RP (3.83 $\pm$ 1.33, $p = 0.004$) but not at any other time point			No control group with usual care and short follow up		2
Lira (14)	Tendency toward lower scores of IIEF5 in the Control Group (58.3%) than in the Physical Therapy Group (52.7%) (p = 0.745)			Short follow up, small population		2
Osadchiy et al. (17)	At 12 months, a higher percentage of men in the prehabilitation group reported return of EF compared with the post-RP rehabilitation group (56% [59/106] vs. 24% [6/25], $p = 0.007$)	Patients were more likely to report return of EF if : - they were in the prehabilitation group (OR 4.89, $P = 0.012$) - they underwent bilateral NS-RARP (OR 3.53, $P = 0.032$) - they had more follow-up visits (OR 4–5 visits: 12.19, $p = 0.002$)		Retrospective nonrandomized study, only nerve sparing surgery	10	
Milios et al. (16)	Rates of improvement, supported by reductions in EPIC-CP EF scores and increases in IIEF-5 scores, at 2, 6 and 12 weeks, occurred for patients in both groups with no significant differences between the two groups			No control group with usual care and short follow up		1

ED, erectile dysfunction; p, probability value; IIEF, international index of erectile function; MINORS, non-random study methodology index; EF, erectile function; RP, radical prostatectomy; p, probability value; IIEF5, simplified IIEF 5 items; NS-RALP, nerve sparing robotic assisted radical prostatectomy; OR, odd ratio; EPIC-CP EF score, erectile function score of the expanded prostate cancer index composite for clinical practice.

4-weeks post-RP (3.83 + 1.33, $p = 0.004$) but not at any other time point (15). The RCT study by Lira et al. showed a tendency toward lower scores of IIEF5 in the control group (58.3%) than in the physical therapy group (52.7%) ($p = 0.745$) (14). The RCT study by Milios et al. concluded that rates of improvement, supported by reductions in EPIC-CP EF scores and increases in IIEF-5 scores at 2, 6, and 12 weeks, occurred for patients in both groups with no significant differences between the two groups (16). The retrospective comparative study of Osadchiy et al. showed that at 12 months, a higher percentage of men in the prehabilitation group reported the return of EF compared with the post-RP rehabilitation group [56% (59/106) vs. 24% (6/25), $p = 0.007$] (17). This study also showed that patients were more likely to report the return of EF if: they were in the prehabilitation group (OR 4.89, $P = 0.012$) and if they had more follow-up visits (OR 4–5 visits vs. one visit: 12.19, $p = 0.002$).

The four RCTs presented a Jadad score <3 and the retrospective comparative study a MINOR score of 10.

Regarding the study based on counseling, participants in the peer and the nurse groups were 3.14 times and 3.67 times more likely to use medical treatment for ED, respectively, than those in the usual care group ($p = 0.016$ and $p = 0.008$). In this study, 74% were recruited before RP and a significantly higher IIEF ($p < 0.0001$) and greater sexual self-confidence ($p < 0.05$) were associated with those patients recruited before surgery.

Regarding the three studies using PFMT, none showed significant results but two showed tendencies to a better IIEF5 in the intervention group.

Regarding the study based on oral medication, vacuum, and counseling, a higher percentage of men in the prehabilitation group reported the return of EF compared with the control group [56% (59/106) vs. 24% (6/25), $p = 0.007$].

DISCUSSION

Guidelines for perioperative care after radical cystectomy for bladder cancer are already published, and strongly recommend that patients should receive routine dedicated preoperative counseling and education (18). Prehabilitation programs have also been proven to be effective in terms of a faster functional recovery (5). No guidelines are available for RP yet but there is a need for patients to be better prepared prior to surgery in order to minimize side effects especially at the time of minimally invasive surgery and ERAS. To the best of our knowledge, this review is the first one focussed on sexual prehabilitation before RP. We highlighted two important aspects: (1) three of the five papers showed better EF recovery post-RP if patients received a pre-surgical care; (2) self-confidence, therapeutic alliance, and adherence to treatment were stronger for patients with preoperative consultations and EF recovery was better in cases of a higher number of follow-up visits.

Age and preoperative EF are the most important predictors for better postoperative sexual outcomes (19). Preservation of the neurovascular bundles during RP may spare EF (20). Nerve-sparing (NS) surgery does not impact oncological outcomes if patients are carefully selected (21, 22). According to the current European Association of Urology (EAU) guidelines, it can be proposed in patients at low risk of extracapsular extension (based on cT stage, ISUP grade, nomogram, and multiparametric MRI) (23). Harris et al. found that the NS technique resulted in better sexual function in most men except in those with a low baseline of sexual function (24). Regarding the surgical technique, (extra-, inter-, and intra-fascial approaches), dissections closer to the prostate and performed bilaterally appear to be associated with better functional outcomes (sexual function and continence) (25–27). Novara et al. demonstrated that age $\leq$60 years, Charlson score of 0, and baseline IIEF-6 score $>$21 were predictors of EF recovery after NS surgery (28). In view of these results, we can suggest that ensuring a good preoperative sexual potency could improve postoperative sexual recovery and support the fact that prehabilitation should be developed and encouraged.

Despite the introduction and improvement of the NS techniques, ED is still commonly reported after RP (between 14 and 69% of cases) (29). Although a meticulous surgical procedure can be performed to avoid direct injury to the cavernous nerves, ED can occur as a consequence of neuropraxia due to traction, compression, or coagulation (30). In 4–75% of men, an accessory pudendal artery (APA) can run parallel to the dorsal vascular complex. Ligation of APA during RP could have a role in penile hypoxia independent from denervation (30). Promptly after the nerve injury, regardless of the severity and extent, a neuroinflammatory cascade is triggered, which ultimately results in the apoptosis of neurons and degeneration of axons in a process known as the Wallerian degeneration (31). The subsequent denervation of the corpora cavernosa leads to the worsening or loss of daily and nocturnal erections, inducing a persistent state of hypoxia. Penile hypoxia results in fibrosis and smooth muscle cell apoptosis (32). These events lead to a veno-occlusive dysfunction and consequent ED (33). The autonomic nervous system has an inherent capacity to regenerate after nerve injury, mediated by the secretion of neurotrophic factors in response to damage. Nonetheless, this mechanism is generally insufficient to prevent the organ's functional failure (34). Even if nerve sparing (NS) surgery is associated with a better post-operative EF, it is not the only factor to take into account to preserve sexual function.

Only three of the five studies included mentioned the RP surgical technique. A majority of NS-RALP was performed and none of the studies analyzed the impact of surgical technique on sexual outcomes. Unfortunately, we did not have enough data in our review to analyze the implication of RP modalities on the sexual prehabilitation results.

To date, different post-operative sexual rehabilitation strategies are published. Actual treatment options for ED management following RP are: oral therapy with phosphodiesterase type 5 inhibitors (PDE5-I) (35), vacuum devices (36), intra-urethral instillation (37) or intracavernous injections (ICI) of prostaglandin (38), and penile implant (39). The International Consultation for Sexual Medicine (ICSM) 2015 recommendations attest that there are conflicting data as to whether penile rehabilitation with PDE5i improves recovery of spontaneous erections. These recommendations also highlight that the data are inadequate to support any specific regimen as optimal for penile rehabilitation (40). PDE5i inhibit the PDE5 which prolongs action of cyclic guanylate monophosphate (cGMP) which leads to smooth muscle relaxation and erection, but nerve activation is required to initiate cGMP synthesis (41). This explains why only 0 to 15% of men treated by non-NSRP responded to PDE5i vs. 35 to 75% among those treated by NSRP (42). Many studies analyzed the effect of on-demand vs. daily vs. scheduled use of PDE5i, but rehabilitation strategies using PDE5i following RP do not increase self-reported potency and EF compared to on-demand use (9). A recent meta-analysis suggests that the early use of vacuum therapy appears to have a good therapeutic effect on post-RP patients and no serious side effects. Due to the overall limited quality of the included studies, this result needs to be confirmed (43). Intra-urethral alprostadil also appears to be a successful ED treatment after RP (37) and a good alternative in cases of patient refusing oral medication and injection. Despite ICI and penile implant are considered second- and third-line therapies for ED after RP, in the prospective analysis on EF after RP for high risk PCa published by Sridhar et al. 48 patients of the non-NSRP received ICI or penile implant and 94% of men on these treatments returned to baseline IIEF-5 scores. This highlights that men who undergo non-NSRP and consider EF a high priority after surgery should be commenced on immediate second- or third-line therapies because of the low rate of PDE5i efficacy (44). EAU guidelines confirm that data is inadequate to support the use of any specific regimen for penile rehabilitation after RP (35).

New approaches were recently proposed for sexual rehabilitation following pelvic surgery: low intensity extracorporeal shockwave therapy (Li-ESWT) and PFMT. Preliminary studies showed, on rat models, that Li-ESWT resulted in angiogenesis, tissue restoration, and nerve regeneration which facilitated a more complete reinnervation of penile tissue (45). There is no published study on early Li-ESWT

after RP for sexual rehabilitation, but positive results were obtained in patients with organic ED (46) and this treatment should be evaluated as an option of sexual pre- and post-RP rehabilitation. Many studies have demonstrated the benefits of PFMT for treating urinary incontinence in men following RP but literature reviews published in 2017 and 2020 also showed its efficacy for post-RP sexual rehabilitation (47, 48). Most studies of these reviews demonstrated improvements in EF with PFMT; however, a lack of methodological rigor and variability among protocols limited the interpretation of results.

Just as there is still no ideal and unambiguous protocol suggested for post-surgical sexual rehabilitation, there is absolutely no evidence regarding the best pre-surgery approach.

Our review showed that PFMT, oral medication, and vacuum started before surgery could be effective on EF recovery but also that information of patient and wife and a closer follow-up seems to be really important in sexual recovery (4). Our study is not devoid of limitations that primarily include the low number of studies, heterogenous protocols with high risk of bias (RCTs with a JADAD score <3 are of poor quality). At the same time, it highlights the need of further research on sexual rehabilitation started before RP. This is why two multimodal sexual prehabilitation protocols have been published and results should be the subject of future publications (49, 50).

The limits of this review are the small number of studies included and heterogeneity of methodology which highlights the lack of literature data on this really important topic and the need to improve our knowledge on sexual RP side effects management.

In conclusion, to try to briefly answer the clinical question of our review today, we do not have a solid scientific evidence to state with certainty what and when it is best to do sexual rehabilitation to obtain the best restoration of sexual function in the patient who undergoes RP. However, we have a few general principles that should be followed in the clinical management of patients and which include: (1) the correct selection of the patient who can really benefit from a NS approach, and that primarily cannot be separated from an optimal erection before surgery; (2) start a therapeutic protocol as soon as possible after the surgery, why not even before the surgery?; (3) use the most effective treatment modality to which the patient adheres best [PFMT seems to be a good treatment option in our review and in reviews already published (47, 48)]; and (4) involve the patient and his or her partner as much as possible in the rehabilitation program, because it is the concrete motivation to do everything possible the prelude to the optimal result. Preoperative and post-operative patient and partner information on sexual side effects and preoperative and postoperative PFMT rehabilitation protocol should be a good way to improve sexual recovery in clinical practice.

CONCLUSION

ED remains a frequent side effect after RP and really impact the patients' quality of life. Starting sexual rehabilitation prior to surgery seems to ensure a better post-operative EF recovery. This prehabilitation should include information of the patient and his or her partner, with a closer follow up (possibly with digital information supports), and the use of a multimodal treatment approach (oral medication, PFMT, vacuum devices, Li-ESWT). These protocols need to be tested and validated in a large RCT for stronger evidence.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

NS, GC, and PV performed title and abstract screening and full text review. NS wrote the manuscript, and prepared the tables, and figure. GC, CM, JR-O, FC, IO, J-FH, EX, and PV helped with redaction. All authors contributed to the article and approved the submitted version.

REFERENCES

1. Donovan JL, Hamdy FC, Lane JA, Mason M, Metcalfe C, Walsh E, et al. Patient-reported outcomes after monitoring, surgery, or radiotherapy for prostate cancer. *N Engl J Med.* (2016) 375:1425–37. doi: 10.1056/NEJMoa1606221
2. Mooney CD, Mooney AN. Trop proches pour être bien: les effets de la prostatectomie radicale sur l'intimité: L'expérience d'un couple de professionnels. *Can Fam Physician.* (2011) 57:e37–8.
3. Tang CY, Turczyniak M, Sayner A, Haines K, Butzkueven S, O'Connell HE. Adopting a collaborative approach in developing a prehabilitation program for patients with prostate cancer utilising experience-based co-design methodology. *Support Care Cancer.* (2020) 28:5195–202. doi: 10.1007/s00520-020-05341-z
4. Paich K, Dunn R, Skolarus T, Montie J, Hollenbeck B, Palapattu G, et al. Preparing patients and partners for recovery from the side effects of prostate cancer surgery: a group approach. *Urology.* (2016) 88:36–42. doi: 10.1016/j.urology.2015.07.064
5. Ploussard G, Almeras C, Beauval J, Gautier J, Garnault V, Frémont N, et al. A combination of enhanced recovery after surgery and prehabilitation pathways improves perioperative outcomes and costs for robotic radical prostatectomy. *Cancer.* (2020) 126:4148–55. doi: 10.1002/cncr.33061
6. Minnella EM, Awasthi R, Bousquet-Dion G, Ferreira V, Austin B, Audi C, et al. Multimodal prehabilitation to enhance functional capacity following radical cystectomy: a randomized controlled trial. *Eur Urol Focus.* (2019) 7:132–8. doi: 10.1016/j.euf.2019.05.016
7. Goonewardene SS, Gillatt D, Persad R. A systematic review of PFE pre-prostatectomy. *J Robot Surg.* (2018) 12:397–400. doi: 10.1007/s11701-018-0803-8
8. Ficarra V, Novara G, Ahlering TE, Costello A, Eastham JA, Graefen M, et al. Systematic review and meta-analysis of studies reporting potency rates after robot-assisted radical prostatectomy. *Eur Urol.* (2012) 62:418–30. doi: 10.1016/j.eururo.2012.05.046
9. Philippou YA, Jung JH, Steggall MJ, O'Driscoll ST, Bakker CJ, et al. Penile rehabilitation for postprostatectomy erectile dysfunction. *Cochrane Database Syst Rev.* (2018) 10:CD012414. doi: 10.1002/14651858.CD012414.pub2
10. Knoll T, Omar MI, Maclennan S, Hernández V, Canfield S, Yuan Y, et al. Key Steps in Conducting Systematic Reviews for Underpinning Clinical Practice Guidelines: methodology of the European Association of Urology. *Eur Urol.* (2018) 73:290–300. doi: 10.1016/j.eururo.2017.08.016
11. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials.* (1996) 17:1–12. doi: 10.1016/0197-2456(95)00134-4

12. Slim K, Nini E, Forestier D, Kwiatkowski F, Panis Y, Chipponi J. Methodological index for non-randomized studies (minors): development and validation of a new instrument. *ANZ J Surg.* (2003) 73:712–6. doi: 10.1046/j.1445-2197.2003.02748.x
13. Chambers SK, Occhipinti S, Schover L, Nielsen L, Zajdlewicz L, Clutton S, et al. A randomised controlled trial of a couples-based sexuality intervention for men with localised prostate cancer and their female partners: a couples-based sexuality intervention for men with prostate cancer. *Psychooncology.* (2015) 24:748–56. doi: 10.1002/pon.3726
14. Lira GHS de, Fornari A, Cardoso LF, Aranchipe M, Kretiska C, Rhoden EL. Effects of perioperative pelvic floor muscle training on early recovery of urinary continence and erectile function in men undergoing radical prostatectomy: a randomized clinical trial. *Int Braz J Urol.* (2019) 45:1196–203. doi: 10.1590/s1677-5538.ibju.2019.0238
15. Santa Mina D, Hilton WJ, Matthew AG, Awasthi R, Bousquet-Dion G, Alibhai SMH, et al. Prehabilitation for radical prostatectomy: a multicentre randomized controlled trial. *Surg Oncol.* (2018) 27:289–98. doi: 10.1016/j.suronc.2018.05.010
16. Milios JE, Ackland TR, Green DJ. Pelvic floor muscle training and erectile dysfunction in radical prostatectomy: a randomized controlled trial investigating a non-invasive addition to penile rehabilitation. *Sex Med.* (2020) 8:414–21. doi: 10.1016/j.esxm.2020.03.005
17. Osadchiy V, Eleswarapu SV, Mills SA, Pollard ME, Reiter RE, Mills JN. Efficacy of a preprostatectomy multi-modal penile rehabilitation regimen on recovery of postoperative erectile function. *Int J Impot Res.* (2020) 32:323–8. doi: 10.1038/s41443-019-0187-y
18. Cerantola Y, Valerio M, Persson B, Jichlinski P, Ljungqvist O, Hubner M, et al. Guidelines for perioperative care after radical cystectomy for bladder cancer: enhanced Recovery After Surgery (ERAS®) society recommendations. *Clin Nutr.* (2013) 32:879–87. doi: 10.1016/j.clnu.2013.09.014
19. Mulhall JP, Kattan MW, Bennett NE, Stasi J, Nascimento B, Eastham J, et al. Development of nomograms to predict the recovery of erectile function following radical prostatectomy. *J Sex Med.* (2019) 16:1796–802. doi: 10.1016/j.jsxm.2019.08.003
20. Walz J, Epstein JI, Ganzer R, Graefen M, Guazzoni G, Kaouk J, et al. A Critical Analysis of the current knowledge of surgical anatomy of the prostate related to optimisation of cancer control and preservation of continence and erection in candidates for radical prostatectomy: an update. *Eur Urol.* (2016) 70:301–11. doi: 10.1016/j.eururo.2016.01.026
21. Ward JF, Zincke H, Bergstralh EJ, Slezak JM, Myers RP, Blute ML. The impact of surgical approach (nerve bundle preservation versus wide local excision) on surgical margins and biochemical recurrence following radical prostatectomy. *J Urol.* (2004) 172:1328–32. doi: 10.1097/01.ju.0000138681.64035.dc
22. Neill MG, Louie-Johnsun M, Chabert C, Eden C. Does intrafascial dissection during nerve-sparing laparoscopic radical prostatectomy compromise cancer control? *BJU Int.* (2009) 104:1730–3. doi: 10.1111/j.1464-410x.2009.08670.x
23. Mottet N, van den Bergh RCN, Briers E, Van den Broeck T, Cumberbatch MG, De Santis M, et al. EAU-EANM-ESTRO-ESUR-SIOG Guidelines on Prostate Cancer-2020 Update. Part 1: screening, diagnosis, and local treatment with curative intent. *Eur Urol.* (2020) 79:243–62. doi: 10.1016/j.eururo.2020.09.042
24. Harris CR, Punnen S, Carroll PR. Men with low preoperative sexual function may benefit from nerve sparing radical prostatectomy. *J Urol.* (2013) 190:981–6. doi: 10.1016/j.juro.2013.02.008
25. Stolzenburg J-U, Kallidonis P, Do M, Dietel A, Häfner T, Rabenalt R, et al. A comparison of outcomes for interfascial and intrafascial nerve-sparing radical prostatectomy. *Urology.* (2010) 76:743–8. doi: 10.1016/j.urology.2010.03.089
26. Steineck G, Bjartell A, Hugosson J, Axén E, Carlsson S, Stranne J, et al. Degree of preservation of the neurovascular bundles during radical prostatectomy and urinary continence 1 year after surgery. *Eur Urol.* (2015) 67:559–68. doi: 10.1016/j.eururo.2014.10.011
27. Tewari AK, Srivastava A, Huang MW, Robinson BD, Shevchuk MM, Durand M, et al. Anatomical grades of nerve sparing: a risk-stratified approach to neural-hammock sparing during robot-assisted radical prostatectomy (RARP). *BJU Int.* (2011) 108:984–92. doi: 10.1111/j.1464-410X.2011.10565.x
28. Novara G, Ficarra V, D'Elia C, Secco S, De Gobbi A, Cavalleri S, et al. Preoperative criteria to select patients for bilateral nerve-sparing robotic-assisted radical prostatectomy. *J Sex Med.* (2010) 7:839–45. doi: 10.1111/j.1743-6109.2009.01589.x
29. Boorjian SA, Eastham JA, Graefen M, Guillonneau B, Karnes RJ, Moul JW, et al. A critical analysis of the long-term impact of radical prostatectomy on cancer control and function outcomes. *Eur Urol.* (2012) 61:664–75. doi: 10.1016/j.eururo.2011.11.053
30. Weyne E, Castiglione F, Van der Aa F, Bivalacqua TJ, Albersen M. Landmarks in erectile function recovery after radical prostatectomy. *Nat Rev Urol.* (2015) 12:289–97. doi: 10.1038/nrurol.2015.72
31. Gold BG. FK506 and the role of immunophilins in nerve regeneration. *Mol Neurobiol.* (1997) 15:285–306. doi: 10.1007/BF02740664
32. Leungwattanakij S, Bivalacqua TJ, Usta MF, Yang D-Y, Hyun J-S, Champion HC, et al. Cavernous neurotomy causes hypoxia and fibrosis in rat corpus cavernosum. *J Androl.* (2003) 24:239–45. doi: 10.1002/j.1939-4640.2003.tb02668.x
33. Mulhall JP, Slovick R, Hotaling J, Aviv N, Valenzuela R, Waters WB, et al. Erectile dysfunction after radical prostatectomy: hemodynamic profiles and their correlation with the recovery of erectile function. *J Urol.* (2002) 167:1371–5. doi: 10.1016/s0022-5347(05)65303-7
34. Bella AJ, Lin G, Cagiannos I, Lue TF. Emerging neuromodulatory molecules for the treatment of neurogenic erectile dysfunction caused by cavernous nerve injury. *Asian J Androl.* (2008) 10:54–9. doi: 10.1111/j.1745-7262.2008.00368.x
35. Salonia A, Bettocchi C, Carvalho J, Corona G, Jones TH, Kadioglu A, et al. *EAU Guidelines on Sexual and Reproductive Health*. Arnhem: EAU Guidelines Office. Available online at: http://uroweb.org/guidelines/compilations-of-all-guidelines/
36. Raina R, Agarwal A, Ausmundson S, Lakin M, Nandipati KC, Montague DK, et al. Early use of vacuum constriction device following radical prostatectomy facilitates early sexual activity and potentially earlier return of erectile function. *Int J Impot Res.* (2006) 18:77–81. doi: 10.1038/sj.ijir.3901380
37. Raina R, Pahlajani G, Agarwal A, Zippe CD. The early use of transurethral alprostadil after radical prostatectomy potentially facilitates an earlier return of erectile function and successful sexual activity. *BJU Int.* (2007) 100:1317–21. doi: 10.1111/j.1464-410X.2007.07124.x
38. Montorsi F, Guazzoni G, Strambi LF, Da Pozzo LF, Nava L, Barbieri L, et al. Recovery of spontaneous erectile function after nerve-sparing radical retropubic prostatectomy with and without early intracavernous injections of alprostadil: results of a prospective, randomized trial. *J Urol.* (1997) 158:1408–10.
39. Tal R, Jacks LM, Elkin E, Mulhall JP. Penile implant utilization following treatment for prostate cancer: analysis of the SEER-Medicare database. *J Sex Med.* (2011) 8:1797–804. doi: 10.1111/j.1743-6109.2011.02240.x
40. Salonia A, Adaikan G, Buvat J, Carrier S, El-Meliegy A, Hatzimouratidis K, et al. Sexual rehabilitation after treatment for prostate cancer-part 2: recommendations from the fourth international consultation for sexual medicine (ICSM 2015). *J Sex Med.* (2017) 14:297–315. doi: 10.1016/j.jsxm.2016.11.324
41. Dean RC, Lue TF. Physiology of penile erection and pathophysiology of erectile dysfunction. *Urol Clin North Am.* (2005) 32:379–95, v. doi: 10.1016/j.ucl.2005.08.007
42. Salonia A, Burnett AL, Graefen M, Hatzimouratidis K, Montorsi F, Mulhall JP, et al. Prevention and management of postprostatectomy sexual dysfunctions part 2: recovery and preservation of erectile function, sexual desire, and orgasmic function. *Eur Urol.* (2012) 62:273–86. doi: 10.1016/j.eururo.2012.04.047
43. Qin F, Wang S, Li J, Wu C, Yuan J. The early use of vacuum therapy for penile rehabilitation after radical prostatectomy: systematic review and meta-analysis. *Am J Mens Health.* (2018) 12:2136–43. doi: 10.1177/1557988318797409
44. Sridhar AN, Cathcart PJ, Yap T, Hines J, Nathan S, Briggs TP, et al. Recovery of Baseline erectile function in men following radical prostatectomy for high-risk prostate cancer: a prospective analysis using validated measures. *J Sex Med.* (2016) 13:435–43. doi: 10.1016/j.jsxm.2016.01.005
45. Li H, Matheu MP, Sun F, Wang L, Sanford MT, Ning H, et al. Low-energy shock wave therapy ameliorates erectile dysfunction in a pelvic neurovascular injuries rat model. *J Sex Med.* (2016) 13:22–32. doi: 10.1016/j.jsxm.2015.11.008
46. Porst H. Review of the current status of low intensity extracorporeal shockwave therapy (Li-ESWT) in erectile dysfunction (ED),

peyronie's disease (pd), and sexual rehabilitation after radical prostatectomy with special focus on technical aspects of the different marketed ESWT devices including personal experiences in 350 patients. *Sex Med Rev.* (2020) 9:93–122. doi: 10.1016/j.sxmr.2020.01.006

47. Rival T, Clapeau L. [Effectiveness of pelvic floor rehabilitation in erectile dysfunction: A literature review]. *Progres En Urol J Assoc Francaise Urol Soc Francaise Urol.* (2017) 27:1069–75. doi: 10.1016/j.purol.2017.09.004
48. Wong C, Louie DR, Beach C. A Systematic review of pelvic floor muscle training for erectile dysfunction after prostatectomy and recommendations to guide further research. *J Sex Med.* (2020) 17:737–48. doi: 10.1016/j.jsxm.2020.01.008
49. Paterson C, Roberts C, Toohey K, McKie A. Prostate cancer prehabilitation and the importance of multimodal interventions for person-centred care and recovery. *Semin Oncol Nurs.* (2020) 36:151048. doi: 10.1016/j.soncn.2020.151048
50. Wittmann D, Mehta A, Northouse L, Dunn R, Braun T, Duby A, et al. TrueNTH sexual recovery study protocol: a multi-institutional collaborative approach to developing and testing a web-based intervention for couples coping with the side-effects of prostate cancer treatment in a randomized controlled trial. *BMC Cancer.* (2017) 17:664. doi: 10.1186/s12885-017-3652-3

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REVIEW
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Radiation Therapy After Radical Prostatectomy: What Has Changed Over Time?

Fabio Zattoni[1], Isabel Heidegger[2], Veeru Kasivisvanathan[3,4], Alexander Kretschmer[5], Giancarlo Marra[6], Alessandro Magli[7], Felix Preisser[8], Derya Tilki[9,10], Igor Tsaur[11], Massimo Valerio[12], Roderick van den Bergh[13], Claudia Kesch[14], Francesco Ceci[15], Christian Fankhauser[16] and Giorgio Gandaglia[17] on behalf of the YAU Prostate cancer (PCa) working*

[1] Urology Unit, Azienda Sanitaria Universitaria Integrata di Udine, Udine, Italy, [2] Department of Urology, Medical University Innsbruck, Innsbruck, Austria, [3] Division of Surgery and Interventional Science, University College London, London, United Kingdom, [4] Department of Urology, University College London Hospital, London, United Kingdom, [5] Department of Urology, Ludwig-Maximilians-University of Munich, Munich, Germany, [6] Department of Urology, San Giovanni Battista Hospital, University of Turin, Turin, Italy, [7] Department of Radiation Oncology, Udine General Hospital, Udine, Italy, [8] Department of Urology, University Hospital Frankfurt, Frankfurt, Germany, [9] Martini-Klinik Prostate Cancer Center, University Hospital Hamburg-Eppendorf, Hamburg, Germany, [10] Department of Urology, University Hospital Hamburg-Eppendorf, Hamburg, Germany, [11] Department of Urology and Pediatric Urology, Mainz University Medicine, Mainz, Germany, [12] Department of Urology, CHUV Lausanne, Lausanne, Switzerland, [13] Department of Urology, Antonius Hospital, Utrecht, Netherlands, [14] Department of Urology, University Hospital Essen, Essen, Germany, [15] Division of Nuclear Medicine, IEO European Institute of Oncology IRCCS, Milan, Italy, [16] University Hospital Zürich, Zurich, Switzerland, [17] Division of Oncology/Unit of Urology, Urological Research Institute, IRCCS Ospedale San Raffaele, Milan, Italy

The role and timing of radiotherapy (RT) in prostate cancer (PCa) patients treated with radical prostatectomy (RP) remains controversial. While recent trials support the oncological safety of early salvage RT (SRT) compared to adjuvant RT (ART) in selected patients, previous randomized studies demonstrated that ART might improve recurrence-free survival in patients at high risk for local recurrence based on adverse pathology. Although ART might improve survival, this approach is characterized by a risk of overtreatment in up to 40% of cases. SRT is defined as the administration of RT to the prostatic bed and to the surrounding tissues in the patient with PSA recurrence after surgery but no evidence of distant metastatic disease. The delivery of salvage therapies exclusively in men who experience biochemical recurrence (BCR) has the potential advantage of reducing the risk of side effects without theoretically compromising outcomes. However, how to select patients at risk of progression who are more likely to benefit from a more aggressive treatment after RP, the exact timing of RT after RP, and the use of hormone therapy and its duration at the time of RT are still open issues. Moreover, what the role of novel imaging techniques and genomic classifiers are in identifying the most optimal post-operative management of PCa patients treated with RP is yet to be clarified. This narrative review summarizes most relevant published data to guide a multidisciplinary team in selecting appropriate candidates for post-prostatectomy radiation therapy.

Keywords: prostate cancer, adjuvant radiotherapy, salvage radiotherapy, biochemical recurrence, hormonal therapy, genomic classifiers

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Luis Alex Kluth,
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Petros Sountoulides,
Aristotle University of Thessaloniki, Greece
Simone Albisinni,
Université libre de Bruxelles, Belgium

****Correspondence:***
Fabio Zattoni
fabiozattoni@gmail.com
orcid.org/0000-0002-4178-373X

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INTRODUCTION

The most common primary treatment for localized prostate cancer (PCa) is radical prostatectomy (RP) (1). Approximately one third of men managed with RP will experience biochemical recurrence (BCR) over a 10-year period (2), and the majority of these patients will eventually develop distant metastases and/or will die of PCa over time if left untreated (3). Postoperative radiotherapy (RT) represents an option in a multimodal setting in order to reduce the risk of experiencing distant metastases at follow-up. Of note, RT might be administered in an adjuvant (i.e., immediately after surgery in the absence of signs of recurrence) or salvage setting (i.e., at the time of biochemical recurrence, BCR). However, there has been poor consensus regarding the timing of post-operative RT. Previous prospective, randomized clinical trials showed that ART was associated with a reduced risk of recurrence in patients at risk (i.e., positive surgical margins, pT3 disease, pathologic grade group 4–5). However, their generalizability is limited by either late use of SRT or no use of post-RP prostate-specific antigen (PSA) monitoring or both (4–7). More recent randomized studies compared ART with early SRT for patients with an increasing PSA level after RP (early SRT) and provide data which might be applied to contemporary patients (8–10). However, how to select patient at risk of progression who more likely will benefit from a more aggressive treatment after RP in a multimodal setting, the exact timing of RT after RP, and the use of hormone therapy and its duration at the time of RT are still open issues. This is particularly true when considering the poor sensitivity of imaging techniques (transrectal US, CT, pelvic MRI, PET/CT, and PET/MRI with different radiopharmaceuticals) in asymptomatic patients with early BCR after RP. Moreover, molecular biomarkers in this setting have been poorly addressed so far and their use in the clinical practice is still limited (11).

This narrative review summarizes most relevant published data to guide a multidisciplinary team in selecting appropriate candidates for post-prostatectomy radiation therapy after the availably of new landmarks randomized studies.

EVIDENCE ACQUISITION

A collaborative non-systematic literature review identified recently published randomized and non-randomized studies where outcome data were collected (cut-off date February 6th 2021). The medical electronic data base PubMed was used. The identified studies represented the basis for a narrative review of the literature analyzing role of ART and SRT for BCR/PSA persistence (BCP) after RP.

EVIDENCE SYNTHESIS

Defining Patients at Risk After Radical Prostatectomy

Accurate risk characterization could result in an appropriate management of post-RP patients. However, the optimal post-operative approach to these patients is a subject of continuous debate because the risk definition after RP relies on clinical, pathological features and PSA kinetics. Furthermore, the choice of treatment (initial observation, ART, and/or ADT) should be tailored according to prognostic factors and/or risk stratification.

Up to one-third of patients treated with RP may have adverse pathologic features (12), defined as positive surgical margins, extra-prostatic extension, seminal vesicle invasion, and/or lymph node invasion and high Gleason score.

Only patients with at least two of the following pathologic features are at higher risk of cancer specific mortality and may significantly benefit from adjuvant treatment after RP: pathologic Gleason score $\geq$8, pT3/pT4 disease, and the presence of nodal disease ($\geq$1) (13).

In the study of Abdollah et al. men with low-volume nodal disease ($<$ 3 LNs), ISUP grade 2–5 and pT3–4 or R1, as well as men with 3 to 4 positive nodes were more likely to benefit from RT after surgery, while the other subgroups did not (14).

However, the level of evidence for the management of pN1 patients is still low (15).

The most sensitive and the only validated biomarker for disease persistence and recurrence remains PSA and PSA-based parameters (PSA doubling time and interval to PSA failure). Persistent PSA is defined in the majority of studies as detectable post-RP PSA of $\geq$0.1 ng/mL within 4 to 8 weeks of surgery and occurs in 5–20% of men after RP (16, 17).

It is likely the expression of persistent local disease or pre-existing metastases and reflect in worse outcomes when compared to men experiencing BCR (18). In highly selected patients with favorable pathologic characteristics PSA persistence might also indicate the presence of benign tissue left *in situ* during the procedure (19). On the other hand, persistent PSA represents one of the worst prognostic factors for risk of metastasis and death (18, 20) when associated with adverse pathologic features (21). In these patients, the use of SRT may improve survival, although available data from number of study does not allow yet to make any clear treatment decision (20, 22).

When considering BCR after RP, the threshold that best predicts further metastases is a PSA level of $>$0.4 ng/mL and rising (4). However, this value should not be considered as the best cut-off to start further treatments. With access to ultrasensitive PSA testing, a rising PSA level below this level might be a cause for concern. So far, several studies report different cutoffs for defining BCR after RP. Currently the most common BCR definition in studies and guidelines is based on two consecutive PSA values $\geq$0.2 ng/mL and rising, representing a more sensitive threshold to PSA progression. However, a first rise in PSA levels should not be used as the only landmark to start treatments. Although better oncologic outcomes were noticed when salvage treatment was delivered at lower PSA levels, the accurate timing of its administration depends on pathologic features, functional status, quality of life effects and patient's preferences (23–25). Based on the idea that the patient group experiencing BCR is a heterogeneous group, the EAU guidelines suggested a new stratification which accounts for the factors previously described (excluded PSA persistence). This allows to stratify patients in two risk groups: the EAU low-risk BCR (PSA-DT $>$1 yr and pathological ISUP grade $<$4) and EAU high-risk BCR (PSA-DT $<$1 yr or pathological ISUP grade 4–5) group (26).

This novel BCR risk categories could be easily implemented in daily practice and could be precious in the decision-making for post-operative RT.

Timing of Radiotherapy After Radical Prostatectomy

The optimal timing of RT after RP is still debatable (27). Adjuvant treatment has the aim of decreasing the risk of relapse in men without evidence of disease persistence or recurrence after primary treatment when adverse pathologic features are present. On the contrary, SRT consists of the administration of additional therapies at the time of recurrence and represent a curative approach in men experiencing BCR or PSA persistence. The supporters of ART consider the prompt treatment to be more efficient with reduced risk of BCR and clinical recurrence, with acceptable toxicity. On the other hand, SRT may reduce exposure to unnecessary risks and toxicity (**Figure 1**). In addition, the impact of ART on survival remains controversial.

Seven randomized controlled trials have assessed the outcomes of ART after RP. These trials can be subdivided into two groups: (1) older trials such as the SWOG 8794 (5), EORTC 22911 (4), ARO 96-02 (6) and the FinnProstate Group trial (7) where timely SRT was not always used in the control arm; (2) modern trials such as RADICALS-RT (8), RAVES (9) and GETUG-17 (10) which mandated early SRT for PSA failure in the control arm (**Table 1**). Randomized trials testing the role of ART [SWOG 8794 (5), EORTC 22911(4), ARO 96–02 (6), FinnProstate Group trial (7)] provided level I evidence regarding the improvement of biochemical control (bPFS), however with no clear advantage in terms of metastasis-free survival (MFS) and overall survival (OS). A recent metanalysis of published randomized trials evaluating ART detected a significant improvement over a 10-year period in clinical progression and presentation of metastases, especially in patients with positive margins (28). However, there is no evidence of improved OS. The toxicity deriving from immediate radiotherapy proved acceptable with only mild increase of genitourinary toxicity (urethral stenosis and urinary incontinence) and rectal toxicity (28). However, it should be emphasized that none of the above-mentioned studies was conducted to confront ART and SRT, the studies had small sample size cohorts for OS analysis and ∼30% of the enrolled patients in the SWOG and EORTC trial have received SRT after initial radiotherapy and PSA persistence. On the contrary, there is an evidence that approximately 50% of patients enrolled in these studies did not experience BCR. Thus, the administration of ART in up to half of patients with adverse pathologic characteristics at RP would represent an overtreatment and would expose patients to treatment-related side effects without oncologic benefits.

The FinnProstate Group trial (7) was conducted using higher radiation dose, modern technique and adequate follow-up on one hand, but on the other hand the study had a small sample size with about 50% of patients enrolled in both arms of the trial who had initial PSA< 0.2 ng/ml. The trial included patients with pT2 positive surgical margins or pT3a (no pT3b) and showed that 40% of the patients developed biochemical progression. The main advantage of ART in terms of BCR was observed in patients with pT2 or positive surgical margins. Most patients who did not receive ART developed metastatic disease; ART was associated with negligible genitourinary toxicity. The most interesting fact is that patients with BCR who did not undergo ART received SRT at a median PSA of 0.7 ng/ml (late SRT) and 75% of these patients had no evidence of disease at last follow-up. This might confirm a certain effectiveness of late SRT in patients with low-risk factors.

The probability of success of SRT is conditioned by several risk factors for disease progression: pre-SRT PSA values, GS>7, seminal vesicles invasion, PSA-DT<10–12 months, and negative surgical margins. As for PSA values, an increase of 0.1 ng/ml is followed by a loss of 2.6% of bPFS, with a level 2a evidence for initiating SRT at the lowest possible PSA (29). The authors of the study also suggest that a rising post-operative PSA > 0.05 ng/mL might be a reliable indicator of biochemical failure, which justifies the initiation of SRT before PSA reaches a level of >0.2 ng/mL. A very early administration of SRT (PSA < 0.2 ng/ml) seem to be more efficient than the early SRT (eSRT) (0.2 ng/ml < PSA < 0.5 ng/ml) or late SRT (PSA < 0.5-1 ng/ml), particularly in presence of multiple risk factors (pT3b-T4, negative surgical margins, GS>7) (23). All studies that retrospectively confronted ART vs. SRT, showing benefit of ART, present several biases, such as "lead-time bias," difficult to remove even with sophisticated statistical techniques. Another limitation of the studies, both randomized and non-randomized, is that they refer to data gathered in an era where conventional imaging was not able to assess the presence of disease. Furthermore, there are other points that need to be clarified in order to optimize the use of post-operative RT: total radiation dose, pelvic lymph-node irradiation, combination with hormone therapy.

The three more recent randomized trials (RADICALS-RT, GETUG-AFU 17, and RAVES) evaluated the optimal timing between surgery and start of post-operative RT. Despite some differences such as patient selection, trigger PSA levels for SRT (PSA 0.1 ng/ml in RADICALS; PSA 0.2 ng/ml for other two studies), study design and primary endpoint, their objective was to compare ART and eSRT. RADICALS-RT (8) randomly assigned 1,396 patients at risk for progression to ART or SRT for PSA progression. The primary outcome of the study was freedom from distant metastases. The RADICALS-RT authors reported 5-year biochemical progression-free survival of 85% for patients in the ART group and 88% for those in the SRT group [hazard ratio (HR) 1.10, 95% CI 0.81–1.49; $p = 0.56$] after a median follow-up of 4.9 years. Thus, the authors concluded that an observation policy with PSA controls and SRT in case of PSA progression should be the standard of care after RP. However, this study might be underpowered for patients with a high risk for progression, and a potential benefit of ART may be underestimated by including many patients with favorable risk disease. Interestingly, the presence of lymph node invasion at final pathology represented an exclusion criterion (8). GETUG-AFU 1710 (10) randomized trial aimed to compare ART vs. eSRT after RP combined with short-term ADT in nearly all men. The results of the study suggest that there is no benefit for event-free survival in patients assigned to ART compared with patients assigned to SRT. However, ART can delay time to progression and fewer men had undergone SRT compared with ART. The RAVES study (9) was designed to assess whether freedom from

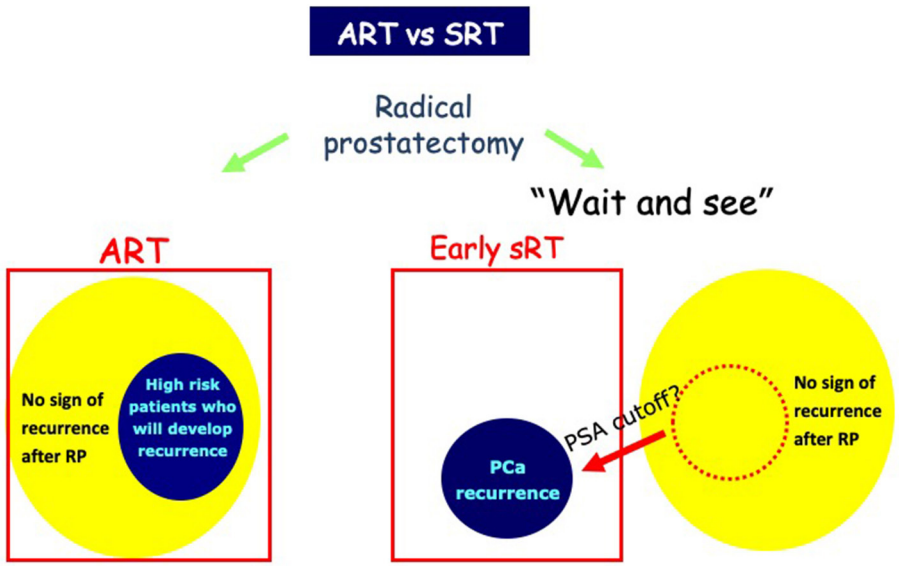

FIGURE 1 | Use of adjuvant RT (ART) and salvage radiotherapy (SRT). Early treatment with ART might be more effective than SRT for biochemical progression. SRT avoids unnecessary treatment of those cured by surgery alone and results in less treatment-related morbidity.

biochemical progression with SRT was non-inferior to ART in patients with extra-prostatic extension, seminal vesicle invasion, or positive surgical margins. HRs favoring SRT in the high-risk subgroups including seminal vesicle invasion and Gleason score of 8–10 in the RAVES study can be explained by a later time observation of PSA progression in the SRT group than in the ART group.

The ARTISTIC collaborative meta-analysis and systematic review (30) was prospectively designed before the results from the three randomized clinical trials were known. It included 2,153 men from the three recent randomized trials and showed no evidence that event-free survival, which was driven by PSA progression, was improved with use of ART compared to SRT in men with localized or locally advanced PCa. Unfortunately, a final recommendation for the use of ART or SRT cannot be made yet. Several limitations of the available literature regarding the use of RT after RP, including lack of group uniformity in pathological risk factors; variability in PSA assay sensitivity and failure criteria; heterogeneity of RT dose and techniques; lack of studies with long follow-up duration; and the use of BCR as an outcome surrogate. Less information was available regarding metastatic recurrence, cancer-specific survival, and overall survival. The patient eligibility criteria for RADICALS-RT included patients who would not receive ART in typical clinical practice because of the low risk of recurrence. Observation of PSA progression in the salvage radiotherapy group occurs at a later time than in the adjuvant radiotherapy group, which can explain a better survivorship favoring SRT in the RADICALS-RT study and in the high-risk subgroups including seminal vesicle invasion and Gleason score $\geq$8 in the RAVES study. Finally, androgen-deprivation therapy (ADT) can delay time to progression and fewer men had undergone salvage compared with adjuvant radiotherapy in the RADICALS-RT and GETUG-AFU 17 trials—concurrent androgen-deprivation therapy with radiotherapy was used in some men in RADICALS-RT and nearly all men in GETUG-AFU 17 (27).

Postoperative RT may have a detrimental effect on functional outcomes, such as urinary continence and erectile function (31, 32). As such, the identification of the appropriate timing to initiate early SRT is of utmost importance to maximize cancer control and to avoid overtreatment. Recovery from urinary incontinence after RP occurs at a lower rate in patients after ART compared with SRT (31, 33). Concordant data from recent randomized studies showed worse late urinary incontinence or grade $\geq$3 urinary complications in patients in the SRT group (**Table 1**).

An algorithm try to summarize the treatment recommendations for the use of ART and SRT after RP (**Figure 2**). A final recommendation cannot be made yet because several questions are still open.

ADT Plus Radiotherapy

The use of ADT in conjunction with RT in the post-RP patient remains controversial. The main questions are whether, when, for how long and in what form ADT should be administered. Available literature has methodological weaknesses since there is a large difference in ADT protocols including when it was administered (e.g., pre-RP, pre-RT, during RT, post-RT), for how long (e.g., months vs. years), differences in RT techniques, targets, total dose administered and study oncologic outcomes.

There are some observational studies which compare RT with or without some form of hormone therapy or antiandrogenic

TABLE 1 | Summary of recently published randomized trials for ART.

	Radicals-RT	GETUG-AFU 17	Raves
Trial design	Superiority	Superiority	Non-inferiority
Patients randomized	Adjuvant: 697 Early salvage: 699	Adjuvant:212 Early salvage: 212	Adjuvant: 166 Early salvage: 167
Key eligibility criteria	One or more of: - Positive margins - pT3a, pT3b, or pT4 - or Gleason 7–10	- pT3a, pT3b, or pT4a (with bladder neck invasion); - Positive margins; - Extracapsular extension	- pT2, pT3a, or pT3b AND - Either positive margins - Or extracapsular extension
Trigger for early salvage radiotherapy	PSA >0.1 ng/mL and rising or three consecutive rising PSA levels still below 0.1 ng/mL	PSA ≥ 0.20 ng/mL and rising	PSA ≥ 0.20 ng/mL
Early salvage radiotherapy timing	≤2 months of trigger PSA	As soon as possible after PSA relapse and before PSA of 1 ng/mL	≤4 months of trigger PSA
Adjuvant radiotherapy timing	≤6 months of radical prostatectomy ≤2	≤6 months of radical prostatectomy As	≤6 months of radical prostatectomy ≤4
Use of hormone therapy	Participants could choose to enter a second randomisation to no hormones or hormones for 6 or 24 months' duration; participants not randomized could receive hormone therapy off protocol	Yes, all patients	No
Primary endpoint	Freedom from distant metastases	Event-free survival	Freedom from biochemical progression
Urinary incontinence	Self-reported urinary incontinence was worse at 1 year for those in the adjuvant radiotherapy group (mean score 4.8 vs. 4.0; $p = 0.0023$)	Adjuvant: 116/212 (55%) Early salvage: 35/212 (17%)	N/A
Urinary disorder	Urethral stricture: Grade 3–4 within 2 years in 6% in the adjuvant radiotherapy group vs. 4% in the salvage radiotherapy group ($p = 0.020$)	- Urinary retention: Adjuvant: 6/212 (3%) Early salvage: 5/212 (2%) - Micturition disorder Adjuvant: 2/212 (1%) Early salvage: 0	≥grade 2 genitourinary toxicity rate (CTCAE*) Salvage radiotherapy (90/167 (54%) Adjuvant (116/166 (70%) OR mixed 0.34, (95% CI 0.17–0.68; $p = 0.0022$)

CTCAE, Adverse events were scored by clinicians per National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 3.0.14. The CTCAE genitourinary domains included cystitis, urinary incontinence, urethral stricture or stenosis, urinary frequency or urgency, urinary retention, and haemorrhage (genitourinary). Gastrointestinal domains included diarrhoea, proctitis, haemorrhage (rectal), and incontinence (anal).*

therapy (34–38). Four studies reported findings suggesting that patients who received ADT in combination with ART had better outcomes (bRFS), however only one study reported a statistically significant difference between the two groups. Specifically, Bastide et al. (34) reported that adjuvant ADT combined with RT after RP in patients with SVI resulted in a substantial benefit in 5 year bRFS.

In the retrospective study by Ost et al. (35) the addition of ADT to high dose ART showed significantly improved bRFS and clinical recurrence-free survival (cRFS). Around 30% of patients in RADICALS-RT reported receiving ADT with their post-operative radiotherapy. Although greater use of ADT might have improved outcomes, there is no evidence that it would have had a differential effect on the two arms of the trial. There are several observational studies evaluating post RP patients who received SRT alone compared to those who received SRT in combination with some type of ADT. Most of these suggest better outcomes for patients selected for SRT in combination with ADT.

Evidence from previous trials suggest that men receiving SRT benefit from the addition of ADT: RTOG 9601 showed an advantage in both, cancer-specific survival (CSS) and OS, for the use of 2 years bicalutamide (for all PSA values and for PSA > 1.5 ng/ml) and GETUG-AFU 16 showed an advantage in progression free survival and metastasis-free survival, for the use of 6 months Goserelin (39, 40). However, the offering of hormone therapy should be accompanied by a thorough discussion of the potential benefits and risks/burdens associated with its use in the SRT setting.

In a retrospective multicenter study including 525 patients reported that only in patients with more aggressive disease characteristics (pT3b/4 and ISUP grade >4, or pT3b/4 and a PSA level at early SRT of >0.4 ng/mL), the administration of concomitant ADT for more that 12 months resulted in a reduction in distant metastases (41). Likewise, in a retrospective study of 1,125 patients, three risk factors (stage ≥pT3b, Gleason score ≥8, and a PSA level at SRT of >5 ng/mL) for clinical recurrence were evaluated to determine which patients may benefit from long-term concomitant hormonal therapy (median ADT duration of 9 months). Their data suggest a significant effect of long-term ADT for patients with two or more adverse features.

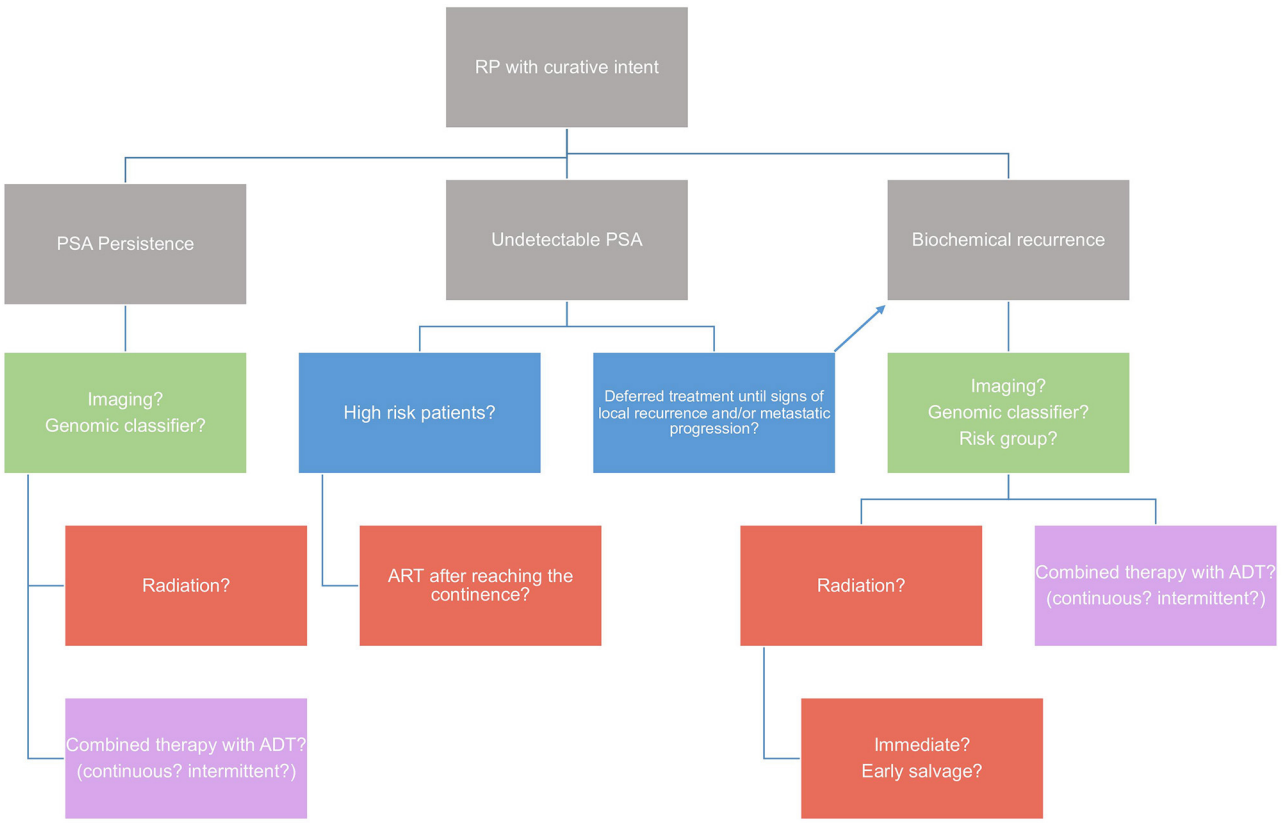

FIGURE 2 | Algorithm on treatment recommendations for the use of ART and SRT after radical prostatectomy. A final recommendation cannot be made yet because several questions are still open.

For patients with a single risk factor, short-term ADT (<12 mo) was slightly beneficial whereas patients without risk factors did not show a benefit from concomitant ADT (42). As a limitation of the study, the indication for concomitant ADT, the type of drug administered, and the treatment duration were left at the discretion of the treating physician on the basis of individual patient characteristics.

Imaging and Genetic Testing Before ART/SRT

The decision to offer RT in recurrent PCa can be challenging. A proper patient selection is essential to ensure favorable outcomes. Patients usually undergo SRT without local imaging because SRT is usually delivered because of PSA values (ideally when the PSA level < 0.5 ng/mL), without histological conformation of local recurrence. In addition, the dose delivered to the prostatic fossa tends to be uniform since it has not been demonstrated that stereotaxic boost to the recurrence site during SRT improves the oncologic outcome with comparable patient reported genitourinary symptom burden (26, 43).

Modern imaging modalities may provide earlier and accurate identification of sites of recurrences in the pelvic area and thus result in change in RT planning of the irradiation field and improvement in oncological outcomes. In certain cases, PSA levels have limited correlation with tumor burden, and patients with poorly differentiated tumors may have metastatic disease in the absence of significantly elevated PSA levels.

Multiparametric MRI of the pelvis is accurate to correctly identify local recurrence in patients with BCR after RP (44, 45). However, its sensitivity in patients with PSA level < 0.5 ng/mL remains controversial (45–47). To promote standardization and reduce variations in the acquisition, interpretation, and reporting of local PCa recurrence recently has been proposed a codified method for image acquisition and assessment of PCa local recurrence using MRI after RP (PI-RR) (48). At the moment, whole-body MRI in detecting occult bone or LN metastases in the case of BCR requires further assessment.

After RP, transrectal ultrasound can occasionally show local recurrence as a hypoechoic nodular mass identified in the perianastomotic area. The detection rates in a subgroup of patients with rising PSA ≤0.5 ng/ml are ranging between 28.1 and 73.0% (49, 50). The sensitivity however of anastomotic biopsies is low, especially for PSA levels <1 ng/mL (51). The prostatic fossa is notoriously difficult to biopsy and MR-TRUS fusion-guidance may aid in the localization of targets compared to TRUS-guidance alone (52). One implication of accurately localizing recurrences is that it enables targeted boost radiotherapy to confirmed lesions which is thought to improve response (53).

At the moment, prostate-specific membrane antigen PET/CT has shown good potential in patients with BCR, even with PSA levels <0.5 ng/mL (54) with a detection rate around 33–45% (55). Promising results for PET/CT are coming from not only retrospective studies but also from recent prospective trials.

68Ga-PSMA-11 PET accuracy in a prospective multicenter trial have showed 84 to 92% positive predictive value, 75% overall detection rate increasing with PSA values (38% for <0.001, 57% for 0.5 to <1.0 ng/mL, 84% for 1.0 to <2.0 ng/mL, 86% for 2.0 to <5.0 ng/mL, and 97% for 5.0 ng/mL), a good inter-reader reproducibility and safety (56).

According to a systematic review and metanalysis (57), for PSA categories 0–0.19, 0.2–0.49, 0.5–0.99,1–1.99, and >2 ng/ml, the percentages of positive scans are 33, 46, 57, 82, and 97%, respectively.

In OSPREY prospective trial, the diagnostic performance of PSMA PET/CT was assed to determine sites of metastatic PCa. In post-therapy men with suspected recurrent or metastatic disease, PSMA PET/CT demonstrated high sensitivity (>88%) and PPV (≥75%) in all sites of disease and across all PSA ranges (58). The use of a histopathologic biopsy as gold standard for all patients and a blinded, independent reader paradigm is a distinct feature of OSPREY study in establishing diagnostic performance.

In 208 patients with BCR (PSA ranging between 0.2 and 98.4 ng/mL) and negative standard imaging the performance of PSMA PET/CT (CONDOR study) was found to determine a correct localization rate of 84.8–87.0%. Interestingly 63.9% of evaluable patients had a change in intended management after PSMA PET/CT (59).

However, men with recurrent/persistent disease reflect different clinical settings and highly heterogeneous population, carrying different prognosis and different profiles of disease aggressiveness. Therefore, selecting the most suitable candidates for PSMA PET/CT is critical to optimize its use and to spare lower-risk patients by expensive and potentially unnecessary staging procedures. By identifying patients with high probability to result in positive PSMA PET/CT, suspicious PCa recurrence could be identified and treatment strategies adjusted accordingly. Nomogram might represent a comprehensive and useful tool in guiding physicians in the most appropriate use of PSMA PET/CT. Models include pathologic parameters (ISUP grade), biochemical characteristics (PSA, PSAdt, ongoing ADT, and time to relapse) and the clinical settings of PSA relapse. Nomogram may allows a smoother patient selection by the clinician, prior to imaging referral in comparison to the use of the PSA values only (60–62).

Sites of recurrence can be clarified by PSMA PET and disease localization may translate into management changes in >50% of patients with BCR (63). Thus, SRT may represent a future strategy in case of BCR where PSMA PET rules out metastatic disease.

In a recent systematic review and meta-analysis (64), PET/MRI seems to have a pooled detection rate of 80.9% (95% CI 73.0–86.9%). However, heterogeneity among the studies was very high. Interestingly, both Grubmuller et al. (65) and Hope et al. (66) reported a high detection rate for recurrent PCa even at very low PSA levels (<0.5 ng/mL). This may prompt changes in RT planning. It is worth noting that the term "PSMA PET" refers to several different radiopharmaceuticals and at present there are no conclusive data about comparison of such tracers. Little difference in terms of detection rate was revealed between the three most commonly used PSMA-radiotracers (68Ga-PSMA11, 18F-PSMA-1007, 18F-DCFPyl), which in turn showed clear superiority to choline and fluciclovine. In a network meta-analysis, 18F-PSMA-1007 is favored in all pairwise comparisons. However, there is currently insufficient evidence to favor any routinely used PSMA-radioligands over another owing to the limited evidence base and risk of publication bias (67).

For the future, new PET tracers and the extraction and quantification of MRI imaging features (radiomics) (68, 69) may guide future research in patients stratification into high potential responder (negative findings or recurrence confined to the prostate) and poor potential responder (positive nodes or distant disease) to SRT.

Genomic markers have been proposed as a complementary tool for risk stratification in patients with PCa. These markers capture genomic information specific to each patient's tumor which is beyond routinely available clinical and pathologic characteristics (tumor stage, grade, PSA value). In the last decade, there has been heightened interest in exploring the utility of different genomic signatures that serve as prognostic markers of cancer control in patients newly diagnosed with localized PCa as well as in patients who have undergone RP. Several novel biomarkers have been introduced for the diagnostic (PHI®, 4K score, SelectMDx®, ConfirmMDx®, PCA3, MiPS, ExoDX®, mpMRI) and prognostic purpose (OncotypeDX GPS®, Prolaris®, ProMark®, DNA-ploidy, Decipher®) (70).

The most utilized test in the real world practice is Decipher, which has been shown to correlate with increased cumulative incidence of BCR, metastasis and PCa-specific mortality (70, 71).

A recent systematic review (11) evaluated the clinical effectiveness of the Decipher genomic classifier (GC) for men with PCa. The authors found consistent evidence that the test may help to identify which cancers are more or less aggressive.

Decipher GC is prognostic for long-term metastasis/survival and changes management of PCa in the post-RP setting. Results have been demonstrated in prospective and *post-hoc* analysis of randomized clinical trials. Furthermore, GC results predict benefit from receipt of treatment which in turn supports personalized treatment decision-making in post-RP patients.

In this particular setting, Decipher GC may guide ART or SRT after RP based on a discrete cut-off score. Moreover, in patients who have already harbored BCR, it can guide decisions regarding the need for early/multimodal SRT vs. SRT alone. Interestingly, patients with higher Decipher GC scores were found to have more metastatic lymph node involvement on PSMA PET-imaging in a study population with 48% of prostatectomy patients. These suggests that patients with GC high risk might benefit from more nodal imaging and treatment intensification (72).

The Decipher GC met high level evidence in post-prostatectomy setting for both Simon and AUA criteria (11). This said, the evidence supports a routine use in clinical situations that will change patient management.

CONCLUSION

The three most recent randomized trials RADICALS-RT, GETUG-AFU 17, and RAVES and the ARTISTIC metanalysis all conclude that SRT may offer the opportunity to avoid, or at least postpone, radiotherapy and its associated side effects for many men with no obvious disadvantage to event-free survival.

However, in daily practice ART should be proposed to patients with PSA persistence, EAU high-risk group or to patients with undetectable PSA values but with multiple high-risk factors (seminal vesicle invasion, GS $>$ 7). Whereas, in patients with undetectable PSA values, EAU low-risk group and no high-risk factors (e.g., pT2/SM + or pT3a/ SM + or GS$<$8 and nerve sparing surgery) SRT should be considered in cases when PSA levels rise ($>$0.2 ng/ml).

In the nearer future, molecular biomarkers, clinical and histopathological features and imaging diagnostics will have to be used in a complementary fashion in order to provide the best possible patient selection. Further prospective studies are needed to confirm these conclusions.

AUTHOR CONTRIBUTIONS

FZ and GG: conceived the study. FZ and AM: collected the data. FZ, GG, IH, VK, and AK: wrote the manuscript. GM, FP, CK, FC, and CF: interpretation of results. DT, IT, MV, and RB: supervision. All authors reviewed the results and approved the final version of the manuscript.

REFERENCES

1. Miller DC, Gruber SB, Hollenbeck BK, Montie JE, Wei JT. Incidence of initial local therapy among men with lower-risk prostate cancer in the United States. *J Natl Cancer Inst.* (2006) 98:1826. doi: 10.1093/jnci/djj491
2. Han M, Partin AW, Pound CR, Epstein JI, Walsh PC. Long-term biochemical disease-free and cancer-specific survival following anatomic radical retropubic prostatectomy: the 15-year johns hopkins experience. *Urol Clin North Am.* (2001) 28:555–65. doi: 10.1016/S0094-0143(05)70163-4
3. Pound CR, Partin AW, Eisenberger MA, Chan DW, Pearson JD, Walsh PC. Natural history of progression after PSA elevation following radical prostatectomy. *JAMA.* (1999) 281:1591–7. doi: 10.1001/jama.281.17.1591
4. Thompson IM, Tangen CM, Paradelo J, Lucia MS, Miller G, Troyer D, et al. Adjuvant radiotherapy for pathological T3N0M0 prostate cancer significantly reduces risk of metastases and improves survival: long-term followup of a randomized clinical trial. *J Urol.* (2009) 181:956–62. doi: 10.1016/j.juro.2008.11.032
5. Bolla M, Van Poppel H, Tombal B, Vekemans K, Da Pozzo L, De Reijke TM, et al. Postoperative radiotherapy after radical prostatectomy for high-risk prostate cancer: Long-term results of a randomised controlled trial (EORTC trial 22911). *Lancet.* (2012) 380:2018–27. doi: 10.1016/S0140-6736(12)61253-7
6. Wiegel T, Bartkowiak D, Bottke D, Bronner C, Steiner U, Siegmann A, et al. Adjuvant radiotherapy versus wait-and-see after radical prostatectomy: 10-year follow-up of the ARO 96-02/AUO AP 09/95 trial. *Eur Urol.* (2014) 66:243–50. doi: 10.1016/j.eururo.2014.03.011
7. Hackman G, Taari K, Tammela TL, Matikainen M, Kouri M, Joensuu T, et al. Randomised trial of adjuvant radiotherapy following radical prostatectomy versus radical prostatectomy alone in prostate cancer patients with positive margins or extracapsular extension. *Eur Urol.* (2019) 76:586–95. doi: 10.1016/j.eururo.2019.07.001
8. Parker CC, Clarke NW, Cook AD, Kynaston HG, Petersen PM, Catton C, et al. Timing of radiotherapy after radical prostatectomy (RADICALS-RT): a randomised, controlled phase 3 trial. *Lancet.* (2020) 396:1413–21. doi: 10.1016/S0140-6736(20)31553-1
9. Kneebone A, Fraser-Browne C, Duchesne GM, Fisher R, Frydenberg M, Herschtal A, et al. Adjuvant radiotherapy versus early salvage radiotherapy following radical prostatectomy (TROG 08.03/ANZUP RAVES): a randomised, controlled, phase 3, non-inferiority trial. *Lancet Oncol.* (2020) 21:1331–40. doi: 10.1016/S1470-2045(20)30456-3
10. Sargos P, Chabaud S, Latorzeff I, Magné N, Benyoucef A, Supiot S, et al.. Adjuvant radiotherapy versus early salvage radiotherapy plus short-term androgen deprivation therapy in men with localised prostate cancer after radical prostatectomy (GETUG-AFU 17): a randomised, phase 3 trial. *Lancet Oncol.* (2020) 21:1341–52. doi: 10.1016/S1470-2045(20)30454-X
11. Jairath NK, Dal Pra A, Vince R, Dess RT, Jackson WC, Tosoian JJ, et al. A systematic review of the evidence for the decipher genomic classifier in prostate cancer. *Eur Urol.* (2021) 79:374–83. doi: 10.1016/j.eururo.2020.11.021
12. Adamis S, Varkarakis IM. Defining prostate cancer risk after radical prostatectomy. *Eur J Surg Oncol.* (2014) 40:496–504. doi: 10.1016/j.ejso.2014.02.221
13. Abdollah F, Suardi N, Cozzarini C, Gallina A, Capitanio U, Bianchi M, et al. Selecting the optimal candidate for adjuvant radiotherapy after radical prostatectomy for prostate cancer: a long-term survival analysis. *Eur Urol.* (2013) 63:998–1008. doi: 10.1016/j.eururo.2012.10.036
14. Abdollah F, Karnes RJ, Suardi N, Cozzarini C, Gandaglia G, Fossati N, et al. Impact of adjuvant radiotherapy on survival of patients with node-positive prostate cancer. *J Clin Oncol.* (2014) 32:3939–7. doi: 10.1200/JCO.2013.54.7893
15. Marra G, Valerio M, Heidegger I, Tsaur I, Mathieu R, Ceci F, et al. Management of patients with node-positive prostate cancer at radical prostatectomy and pelvic lymph node dissection: a systematic review. *Eur Urol Oncol.* (2020) 3:565–81. doi: 10.1016/j.euo.2020.08.005
16. Wiegel T, Bartkowiak D, Bottke D, Thamm R, Hinke A, Stöckle M, et al. Prostate-specific antigen persistence after radical prostatectomy as a predictive factor of clinical relapse-free survival and overall survival: 10-year data of the ARO 96-02 trial. *Int J Radiat Oncol Biol Phys.* (2015) 91:288–94. doi: 10.1016/j.ijrobp.2014.09.039
17. Ploussard G, Staerman F, Pierrevelcin J, Saad R, Beauval JB, Roupret M, et al. Predictive factors of oncologic outcomes in patients who do not achieve undetectable prostate specific antigen after radical prostatectomy. *J Urol.* (2013) 190:1750–6. doi: 10.1016/j.juro.2013.04.073
18. Spratt DE, Dai DLY, Den RB, Troncoso P, Yousefi K, Ross AE, et al. Performance of a prostate cancer genomic classifier in predicting metastasis in men with prostate-specific antigen persistence postprostatectomy. *Eur Urol.* (2018) 74:107–14. doi: 10.1016/j.eururo.2017.11.024
19. Gandaglia G, Briganti A, Clarke N, Karnes RJ, Graefen M, Ost P, et al. Adjuvant and salvage radiotherapy after radical prostatectomy in prostate cancer patients. *Eur Urol.* (2017) 72:689–709. doi: 10.1016/j.eururo.2017.01.039
20. Preisser F, Chun FKH, Pompe RS, Heinze A, Salomon G, Graefen M, et al. Persistent prostate-specific antigen after radical prostatectomy and its impact on oncologic outcomes. *Eur Urol.* (2019) 18:e874. doi: 10.1016/S1569-9056(19)30638-4
21. Rogers CG, Khan MA, Miller MC, Veltri RW, Partin AW. Natural history of disease progression in patients who fail to achieve an undetectable prostate-specific antigen level after undergoing radical prostatectomy. *Cancer.* (2004) 101:2549–56. doi: 10.1002/cncr.20637
22. Fossati N, Karnes RJ, Colicchia M, Boorjian SA, Bossi A, Seisen T, et al. Impact of early salvage radiation therapy in patients with persistently elevated or rising prostate-specific antigen after radical prostatectomy. *Eur Urol.* (2018) 73:436–44. doi: 10.1016/j.eururo.2017.07.026
23. Fossati N, Karnes RJ, Cozzarini C, Fiorino C, Gandaglia G, Joniau S, et al. Assessing the optimal timing for early salvage radiation therapy in patients

with prostate-specific antigen rise after radical prostatectomy. *Eur Urol.* (2016) 69:728–33. doi: 10.1016/j.eururo.2015.10.009
24. Stephenson AJ, Shariat SF, Zelefsky MJ, Kattan MW, Butler EB, Teh BS, et al. Salvage radiotherapy for recurrent prostate cancer after radical prostatectomy. *J Am Med Assoc.* (2004) 291:1325–32. doi: 10.1001/jama.291.11.1325
25. D'Amico AV. Adjuvant versus salvage post-prostatectomy radiation therapy: a critical review of the evidence. *J Urol.* (2013) 190:450–1. doi: 10.1016/j.juro.2013.05.028
26. Cornford P, van den Bergh RCN, Briers E, Van den Broeck T, Cumberbatch MG, De Santis M, et al. EAU-EANM-ESTRO-ESUR-SIOG guidelines on prostate cancer. Part II–2020 update: treatment of relapsing and metastatic prostate cancer[formula presented]. *Eur Urol.* (2021) 79:263–82. doi: 10.1016/j.eururo.2020.09.046
27. Tilki D, D'Amico AV. Timing of radiotherapy after radical prostatectomy. *Lancet.* (2020) 396:1374–5. doi: 10.1016/S0140-6736(20)31957-7
28. Bhindi B, Lokeshwar SD, Klaassen Z, Klotz L, Christopher, Wallis JD. CUAJ-Original research bhindi et al. adjuvant radiation vs. observation for improved overall survival in PCa Systematic review and meta-analysis of trials evaluating the role of adjuvant radiation after radical prostatectomy for prostate cancer: implications for early salvage. *Can Urol Assoc J.* (2020) 14:30. doi: 10.5489/cuaj.6440
29. King CR. The timing of salvage radiotherapy after radical prostatectomy: a systematic review. *Int J Radiat Oncol Biol Phys.* (2012) 84:104–11. doi: 10.1016/j.ijrobp.2011.10.069
30. Vale CL, Fisher D, Kneebone A, Parker C, Pearse M, Richaud P, et al. Adjuvant or early salvage radiotherapy for the treatment of localised and locally advanced prostate cancer: a prospectively planned systematic review and meta-analysis of aggregate data. *Lancet.* (2020) 396:1422–31. doi: 10.1016/S0140-6736(20)31952-8
31. Suardi N, Gallina A, Lista G, Gandaglia G, Abdollah F, Capitanio U, et al. Impact of adjuvant radiation therapy on urinary continence recovery after radical prostatectomy. *Eur Urol.* (2014) 65:546–51. doi: 10.1016/j.eururo.2013.01.027
32. Pearce A, Choo R, Danjoux C, Morton G, Loblaw DA, Szumacher E, et al. Effect of combined treatment with salvage radiotherapy plus androgen suppression on quality of life in patients with recurrent prostate cancer after radical prostatectomy. *Int J Radiat Oncol Biol Phys.* (2006) 65:78–83. doi: 10.1016/j.ijrobp.2005.11.041
33. van Stam MA, Aaronson NK, Pos FJ, Bosch JLHR, Kieffer JM, Tillier CN, et al. The effect of salvage radiotherapy and its timing on the health-related quality of life of prostate cancer patients. *Eur Urol.* (2016) 70:751–7. doi: 10.1016/j.eururo.2016.03.010
34. Bastide C, Rossi D, Lechevallier E, Bladou F, Barriol D, Bretheau D, et al. Seminal vesicle invasion: what is the best adjuvant treatment after radical prostatectomy? *BJU Int.* (2012) 109:525–30. doi: 10.1111/j.1464-410X.2011.10332.x
35. Ost P, Fonteyne V, Villeirs G, Lumen N, Oosterlinck W, De Meerleer G. Adjuvant high-dose intensity-modulated radiotherapy after radical prostatectomy for prostate cancer: clinical results in 104 patients. *Eur Urol.* (2009) 56:669–77. doi: 10.1016/j.eururo.2009.05.041
36. Ost P, De Troyer B, Fonteyne V, Oosterlinck W, De Meerleer G. A matched control analysis of adjuvant and salvage high-dose postoperative intensity-modulated radiotherapy for prostate cancer. *Int J Radiat Oncol Biol Phys.* (2011) 80:1316–22. doi: 10.1016/j.ijrobp.2010.04.039
37. Pai HH, Eldridge B, Bishop D, Alexander A, Lesperance M, Blood P, et al. Does neoadjuvant hormone therapy improve outcome in prostate cancer patients receiving radiotherapy after radical prostatectomy? *Can J Urol.* (2009) 16:4541–52.
38. Ost P, Cozzarini C, De Meerleer G, Fiorino C, De Potter B, Briganti A, et al. High-dose adjuvant radiotherapy after radical prostatectomy with or without androgen deprivation therapy. *Int J Radiat Oncol Biol Phys.* (2012) 83:960–5. doi: 10.1016/j.ijrobp.2011.09.007
39. Shipley WU, Seiferheld W, Lukka HR, Major PP, Heney NM, Grignon DJ, et al. Radiation with or without antiandrogen therapy in recurrent prostate cancer. *N Engl J Med.* (2017) 376:417–28. doi: 10.1056/NEJMoa1607529
40. Carrie C, Magné N, Burban-Provost P, Sargos P, Latorzeff I, Lagrange JL, et al. Short-term androgen deprivation therapy combined with radiotherapy as salvage treatment after radical prostatectomy for prostate cancer (GETUG-AFU 16): a 112-month follow-up of a phase 3, randomised trial. *Lancet Oncol.* (2019) 20:1740–9. doi: 10.1016/S1470-2045(19)30486-3
41. Gandaglia G, Fossati N, Karnes RJ, Boorjian SA, Colicchia M, Bossi A, et al. Use of concomitant androgen deprivation therapy in patients treated with early salvage radiotherapy for biochemical recurrence after radical prostatectomy: long-term results from a large, multi-institutional series. *Eur Urol.* (2018) 73:512–8. doi: 10.1016/j.eururo.2017.11.020
42. Fossati N, Robesti D, Karnes RJ, Soligo M, Boorjian SA, Bossi A, et al. Assessing the role and optimal duration of hormonal treatment in association with salvage radiation therapy after radical prostatectomy: results from a multi-institutional study. *Eur Urol.* (2019) 76:443–9. doi: 10.1016/j.eururo.2019.02.004
43. Beck M, Wust P, Barelkowski T, Kaul D, Thieme AH, Wecker S, et al. Risk adapted dose-intensified postoperative radiation therapy in prostate cancer patients using a simultaneous integrated boost technique applied with helical tomotherapy. *Radiat Oncol.* (2017) 12:125. doi: 10.1186/s13014-017-0862-4
44. Panebianco V, Barchetti F, Sciarra A, Musio D, Forte V, Gentile V, et al. Prostate cancer recurrence after radical prostatectomy: the role of 3-T diffusion imaging in multi-parametric magnetic resonance imaging. *Eur Radiol.* (2013) 23:1745–52. doi: 10.1007/s00330-013-2768-3
45. De Visschere PJL, Standaert C, Fütterer JJ, Villeirs GM, Panebianco V, Walz J, et al. A systematic review on the role of imaging in early recurrent prostate cancer. *Eur Urol Oncol.* (2019) 2:47–76. doi: 10.1016/j.euo.2018.09.010
46. Mertan F V., Greer MD, Borofsky S, Kabakus IM, Merino MJ, Wood BJ, et al. Multiparametric magnetic resonance imaging of recurrent prostate cancer. *Top Magn Reson Imaging.* (2016) 25:139–47. doi: 10.1097/RMR.0000000000000088
47. Coppola A, Platania G, Ticca C, De Mattia C, Bortolato B, Palazzi MF, et al. Sensitivity of CE-MRI in detecting local recurrence after radical prostatectomy. *Radiol Med.* (2020) 125:683–90. doi: 10.1007/s11547-020-01149-3
48. Panebianco V, Villeirs G, Weinreb JC, Turkbey BI, Margolis DJ, Richenberg J, et al. Prostate magnetic resonance imaging for local recurrence reporting (PI-RR): international consensus -based guidelines on multiparametric magnetic resonance imaging for prostate cancer recurrence after radiation therapy and radical prostatectomy. *Eur Urol Oncol.* (2021). doi: 10.1016/j.euo.2021.01.003. [Epub ahead of print].
49. Connolly JA, Shinohara K, Presti JC, Carroll PR. Local recurrence after radical prostatectomy: characteristics in size, location, and relationship to prostate-specific antigen and surgical margins. *Urology.* (1996) 47:225–31. doi: 10.1016/S0090-4295(99)80421-X
50. Scattoni V, Roscigno M, Raber M, Montorsi F, Da Pozzo L, Guazzoni G, et al. Multiple vesico-urethral biopsies following radical prostatectomy: the predictive roles of TRUS, DRE, PSA and the pathological stage. *Eur Urol.* (2003) 44:407–14. doi: 10.1016/S0302-2838(03)00320-8
51. Rouvière O, Vitry T, Lyonnet D. Imaging of prostate cancer local recurrences: why and how? *Eur Radiol.* (2010) 20:1254–66. doi: 10.1007/s00330-009-1647-4
52. Muller BG, Kaushal A, Sankineni S, Lita E, Hoang AN, George AK, et al. Multiparametric magnetic resonance imaging-transrectal ultrasound fusion-assisted biopsy for the diagnosis of local recurrence after radical prostatectomy. *Urol Oncol Semin Orig Investig.* (2015) 33:425.e1–6. doi: 10.1016/j.urolonc.2015.05.021
53. Zilli T, Jorcano S, Peguret N, Caparrotti F, Hidalgo A, Khan HG, et al. Dose-adapted salvage radiotherapy after radical prostatectomy based on an erMRI target definition model: toxicity analysis. *Acta Oncol.* (2014) 96–102. doi: 10.3109/0284186X.2013.837584
54. Wondergem M, van der Zant FM, Broos WAM, Knol RJJ. Clinical impact of PSMA PET in biochemically recurrent prostate cancer; a review of the literature. *Tijdschr Voor Urol.* (2020) 10:109–21. doi: 10.1007/s13629-020-00296-6
55. Farolfi A, Ceci F, Castellucci P, Graziani T, Siepe G, Lambertini A, et al. 68Ga-PSMA-11 PET/CT in prostate cancer patients with biochemical recurrence after radical prostatectomy and PSA <0.5 ng/ml. Efficacy and impact on treatment strategy. *Eur J Nucl Med Mol Imaging.* (2019). 46:11–9. doi: 10.1007/s00259-018-4066-4

56. Fendler WP, Calais J, Eiber M, Flavell RR, Mishoe A, Feng FY, et al. Assessment of 68 Ga-PSMA-11 PET accuracy in localizing recurrent prostate cancer. *JAMA Oncol.* (2019) 5:856. doi: 10.1001/jamaoncol.2019.0096
57. Perera M, Papa N, Roberts M, Williams M, Udovicich C, Vela I, et al. Gallium-68 prostate-specific membrane antigen positron emission tomography in advanced prostate cancer—updated diagnostic utility, sensitivity, specificity, and distribution of prostate-specific membrane antigen-avid lesions: a systematic review and meta-analysis. *Eur Urol.* (2020) 77:403–17. doi: 10.1016/j.eururo.2019.01.049
58. Pienta KJ, Gorin MA, Rowe SP, Carroll PR, Pouliot F, Probst S, et al. A phase 2/3 prospective multicenter study of the diagnostic accuracy of prostate-specific membrane antigen PET/CT with 18 F-DCFPyL in prostate cancer patients (OSPREY). *J Urol.* (2021) 206:52–61. doi: 10.1097/JU.0000000000001698
59. Morris MJ, Rowe SP, Gorin MA, Saperstein L, Pouliot F, Josephson DY, et al. Diagnostic performance of 18 F-DCFPyL-PET/CT in men with biochemically recurrent prostate cancer: results from the CONDOR Phase 3, multicenter study. *Clin Cancer Res.* (2021). doi: 10.1158/1078-0432.CCR-20-4573. [Epub ahead of print].
60. Ceci F, Bianchi L, Borghesi M, Polverari G, Farolfi A, Briganti A, et al. Prediction nomogram for 68Ga-PSMA-11 PET/CT in different clinical settings of PSA failure after radical treatment for prostate cancer. *Eur J Nucl Med Mol Imaging.* (2020) 47:136–46. doi: 10.1007/s00259-019-04505-2
61. Bianchi L, Borghesi M, Schiavina R, Castellucci P, Ercolino A, Bianchi FM, et al. Predictive accuracy and clinical benefit of a nomogram aimed to predict 68Ga-PSMA PET/CT positivity in patients with prostate cancer recurrence and PSA $<$ 1 ng/ml external validation on a single institution database. *Eur J Nucl Med Mol Imaging.* (2020) 47:2100–5. doi: 10.1007/s00259-020-04696-z
62. Rauscher I, Düwel C, Haller B, Rischpler C, Heck MM, Gschwend JE, et al. Efficacy, predictive factors, and prediction nomograms for 68Ga-labeled prostate-specific membrane antigen–ligand positron-emission tomography/computed tomography in early biochemical recurrent prostate cancer after radical prostatectomy. *Eur Urol.* (2018) 73:656–61. doi: 10.1016/j.eururo.2018.01.006
63. Fendler WP, Ferdinandus J, Czernin J, Eiber M, Flavell RR, Behr SC, et al. Impact of 68Ga-PSMA-11 PET on the management of recurrent prostate cancer in a prospective single-arm clinical trial. *J Nucl Med.* (2020) 61:1793–9. doi: 10.2967/jnumed.120.242180
64. Evangelista L, Zattoni F, Cassarino G, Artioli P, Cecchin D, dal Moro F, et al. PET/MRI in prostate cancer: a systematic review and meta-analysis. *Eur J Nucl Med Mol Imaging.* (2020) 48:859–73. doi: 10.1007/s00259-020-05025-0
65. Grubmuller B, Baltzer P, Hartenbach S, D'Andrea D, Helbich TH, Haug AR, et al. PSMA ligand PET/MRI for primary prostate cancer: staging performance and clinical impact. *Clin Cancer Res.* (2018) 24:6300–7. doi: 10.1158/1078-0432.CCR-18-0768
66. Hope TA, Aggarwal R, Chee B, Tao D, Greene KL, Cooperberg MR, et al. Impact of 68Ga-PSMA-11 PET on management in patients with biochemically recurrent prostate cancer. *J Nucl Med.* (2017) 58:1956–61. doi: 10.2967/jnumed.117.192476
67. Alberts IL, Seide SE, Mingels C, Bohn KP, Shi K, Zacho HD, et al. Comparing the diagnostic performance of radiotracers in recurrent prostate cancer: a systematic review and network meta-analysis. *Eur J Nucl Med Mol Imaging.* (2021). doi: 10.1007/s00259-021-05210-9. [Epub ahead of print].
68. Li L, Shiradkar R, Leo P, Algohary A, Fu P, Tirumani SH, et al. A novel imaging based nomogram for predicting post-surgical biochemical recurrence and adverse pathology of prostate cancer from pre-operative bi-parametric MRI. *EBioMedicine.* (2021) 63:103163. doi: 10.1016/j.ebiom.2020.103163
69. Yao S, Jiang H, Song B. Radiomics in prostate cancer: basic concepts and current state-of-the-art. *Chin J Acad Radiol*, (2020) 2, 47–55. doi: 10.1007/s42058-019-00020-3
70. Kretschmer A, Tilki D. Biomarkers in prostate cancer – current clinical utility and future perspectives. *Crit Rev Oncol Hematol.* (2017) 120:180–93. doi: 10.1016/j.critrevonc.2017.11.007
71. Ross A, Johnson MH, Yousefi K, Davicioni E, Fedor HL, Glavaris S, et al. Tissue-based genomics augments post-prostatectomy risk stratification in a natural history cohort of intermediate- and high-risk men. *Eur Urol.* (2016) 69:157–65. doi: 10.1016/j.eururo.2015.05.042
72. Xu MJ, Kornberg Z, Gadzinski AJ, Diao D, Cowan JE, Wu SY, et al. Genomic risk predicts molecular imaging-detected metastatic nodal disease in prostate cancer. *Eur Urol Oncol.* (2019) 2:685–90. doi: 10.1016/j.euo.2018.11.002

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Focal Therapy for Prostate Cancer: Complications and Their Treatment

Arnas Rakauskas[1], Giancarlo Marra[2], Isabel Heidegger[3], Veeru Kasivisvanathan[4,5], Alexander Kretschmer[6], Fabio Zattoni[7], Felix Preisser[8], Derya Tilki[9,10], Igor Tsaur[11], Roderick van den Bergh[12], Claudia Kesch[13], Francesco Ceci[14], Christian Fankhauser[15], Giorgio Gandaglia[16] and Massimo Valerio[1] on behalf of the EAU-YAU Prostate Cancer (PCa) Working Party*

[1] Department of Urology, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland, [2] Department of Urology, San Giovanni Battista Hospital, University of Turin, Turin, Italy, [3] Department of Urology, Medical University Innsbruck, Innsbruck, Austria, [4] Division of Surgery and Interventional Science, University College London, London, United Kingdom, [5] Department of Urology, University College London Hospital, London, United Kingdom, [6] Department of Urology, Ludwig-Maximilians-University of Munich, Munich, Germany, [7] Urology Unit, Azienda Sanitaria Universitaria Integrata di Udine, Udine, Italy, [8] Department of Urology, University Hospital Frankfurt, Frankfurt, Germany, [9] Martini-Klinik Prostate Cancer Center, University Hospital Hamburg-Eppendorf, Hamburg, Germany, [10] Department of Urology, University Hospital Hamburg-Eppendorf, Hamburg, Germany, [11] Department of Urology and Pediatric Urology, Mainz University Medicine, Mainz, Germany, [12] Department of Urology, Antonius Hospital, Utrecht, Netherlands, [13] Department of Urology, University Hospital Essen, Essen, Germany, [14] Division of Nuclear Medicine, IEO European Institute of Oncology Scientific Institute for Research, Hospitalization and Healthcare (IRCCS), Milan, Italy, [15] Department of Urology, University Hospital Zürich, Zurich, Switzerland, [16] Division of Oncology/Unit of Urology, Urological Research Institute, Scientific Institute for Research, Hospitalization and Healthcare (IRCCS) Ospedale San Raffaele, Milan, Italy

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***Correspondence:**
Derya Tilki
dtilki@me.com

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Focal therapy is a modern alternative to selectively treat a specific part of the prostate harboring clinically significant disease while preserving the rest of the gland. The aim of this therapeutic approach is to retain the oncological benefit of active treatment and to minimize the side-effects of common radical treatments. The oncological effectiveness of focal therapy is yet to be proven in long-term robust trials. In contrast, the toxicity profile is well-established in randomized controlled trials and multiple robust prospective cohort studies. This narrative review summarizes the relevant evidence on complications and their management after focal therapy. When compared to whole gland treatments, focal therapy provides a substantial benefit in terms of adverse events reduction and preservation of genito-urinary function. The most common complications occur in the peri-operative period. Urinary tract infection and acute urinary retention can occur in up to 17% of patients, while dysuria and haematuria are more common. Urinary incontinence following focal therapy is very rare (0–5%), and the vast majority of patients recover in few weeks. Erectile dysfunction can occur after focal therapy in 0–46%: the baseline function and the ablation template are the most important factors predicting post-operative erectile dysfunction. Focal therapy in the salvage setting after external beam radiotherapy has a significantly higher rate of complications. Up to one man in 10 will present a severe complication.

Keywords: prostate cancer, focal therapy, HIFU, cryotherapy, photodynamic therapy, complications

INTRODUCTION

Prostate cancer is the second most commonly diagnosed cancer in men. Almost 1.3 million patients are diagnosed worldwide annually, and 360,000 deaths were related to prostate cancer in 2018 (3.8% of all deaths caused by cancer in men) (1). The prevalence of prostate cancer increases with age; screening is generally recommended in well-informed men with prolonged life expectancy. The incidence of prostate cancer diagnosis varies widely between different geographical areas, largely due to different habits in screening policies by mean of prostate-specific antigen (PSA) testing, and life expectancy (2). Decision making in men with localized disease is driven by risk classification, patient's comorbidities and preferences. At present, men with low-risk disease are usually offered active surveillance whereas men with intermediate to high-risk disease are offered radical treatment in the form of surgery or radiation therapy.

Radical prostatectomy and external beam radiotherapy (ERBT) are the two established treatment modalities for intermediate and high-risk localized prostate cancer. Both treatments lead to improved progression-free survival, but the competitive advantage against active surveillance is confined to men with aggressive features and/or very long life expectancy. On the other hand, the risk of genito-urinary toxicity, and rectal toxicity in case of ERBT, is substantial (3, 4). Consequently, tissue-preserving strategies have been developed to improve the therapeutic (risk to benefit) ratio of active treatment.

Focal therapy is an alternative strategy aiming to treat only the part of the prostate harboring clinically significant prostate cancer while preserving the rest of the gland. The objective is to retain the benefits of treating clinically significant cancer while minimizing the damage caused to the adjacent structures of the prostate by whole-gland treatments. Focal therapy, initially seen as an alternative to active surveillance, is now arguably seen as an alternative treatment modality for patients diagnosed with intermediate risk localized prostate cancer who would otherwise undergo radical therapy (5–8).

Recent advances in magnetic resonance imaging (MRI) and fusion targeted biopsy have allowed an accurate spatial localization of clinically significant lesions within the prostate (9–11). This revolution of the diagnostic paradigm shifting from a random to a targeted approach makes the case for an evolution in the therapeutic paradigm. Currently, each patient considered for focal therapy is required to undergo a rigorous diagnostic work-up. Prostate MRI followed by targeted and systematic prostate biopsy or mapping biopsy allow an accurate determination of the margins of the index lesion and rules out with high reliability non MRI visible clinically significant lesions (10, 11). The rationale of focal therapy is deemed reasonable by most; however, the protracted natural history observed in prostate cancer requires long-term evaluation in order to determine the oncological effectiveness of a novel treatment strategy.

Growing evidence in focal therapy has partly clarified its comparative effectiveness as compared to radical treatment options. Mid-term oncological effectiveness is promising; long-term outcomes are awaited. The largest systematic review reporting on different focal therapy outcomes in more than 2,000 patients was published by Valerio et al. (12). The biochemical recurrence ranged from 60 to 86% with the need for secondary focal or salvage treatments after primary treatment failure measured at 0–34%. The progression to metastatic disease was very low (0–0.3%) and cancer-specific survival was extremely high in this review. However, most of the studies had a retrospective design, a short follow-up time and a certain heterogeneity in defining outcome measures. A more recent systematic review including only comparative studies evaluating focal therapy against any standard treatment strategy has highlighted the lack of robust explanatory trials in the target population—men with clinically significant disease (13).

In contrast, the toxicity profile is well-established in randomized controlled trials and multiple prospective cohort studies employing validated patient-reported outcome measures (PROMs). The aim of this review was to summarize current available literature on complications following focal therapy.

METHODS

This narrative review is based on studies reporting on focal therapy short term and/or long-term functional outcomes (e.g., erectile dysfunction, incontinence) and/ or complications (infection, haematuria, bladder outlet obstruction, rectal toxicity etc.). The review was integrated by the experience of the authors in areas in which there is a lack of published evidence.

RESULTS

Factors Influencing Toxicity

There are some factors influencing the toxicity after focal therapy. These include patient specific factors, cancer location, the amount of the tissue treated, and the source of the energy used.

Relevant patient related factors having an impact on postoperative toxicity are the size of the prostate, previous pelvic and prostate surgery, and predisposing conditions (pre-existing erectile dysfunction, lower tract urinary symptoms and neurological comorbidities) (8). The size of the prostate should always be precisely estimated prior to the treatment. Particularly large prostates might not be suitable for some energy sources or treatment templates; in such cases, patients are more at risk to develop significant lower urinary tract symptoms (LUTS) after treatment. Patient sexual and urinary functions should be well-documented with validated PROM prior to focal therapy. The most important determinant of erectile dysfunction after tissue preserving therapy is the preoperative erectile function status (14).

Cancer location is a key factor predicting the type and frequency of complications. Cancers located near the urethra, the bladder neck and the apical end are more difficult to be treated, and patients are more prone to develop postoperative irritative and obstructive LUTS. Cancers located close to the neurovascular bundles with capsule contact require extended ablation which may have an impact on erectile function recovery (15).

The amount of treated tissue has a significant impact on the toxicity: the more prostatic tissue is treated the more likely is to have postoperative complications. This has been clearly observed

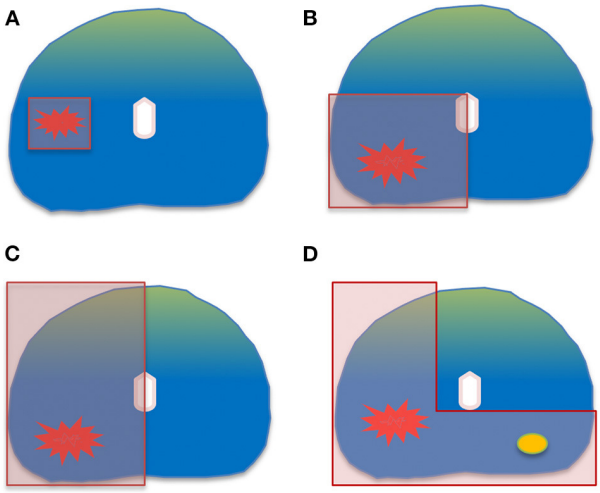

FIGURE 1 | Common ablation templates: **(A)** focal ablation. **(B)** quadrant ablation. **(C)** hemi-ablation. **(D)** "hockey-stick" ablation.

in studies comparing whole-gland to focal therapy strategies using the same treatment modalities (16).

The size and the location of the index lesion dictates the focal therapy strategy; coverage with a minimum of 1 cm margins around the index lesion is the priority in order to achieve local control (17–19). Treatment of a small unilateral cancer by a focal ablation will result in much less genito-urinary toxicity than treating a large portion of the gland. The following ablation templates are commonly used according to the cancer location, volume and extension on imaging and biopsy: focal ablation, zonal ablation, quadrant ablation, hemi-ablation and "hockey-stick" ablation (**Figure 1**) (20). The choice of the ablation template has a two-sided impact. From an oncological point of view, insufficient surgical margin is more likely to expose the patient to a higher risk of recurrence while from a functional perspective, the opposite is assumed.

Finally, different sources of energy have different side effect profiles (21). Available energies can be generally classified in thermal and non-thermal energies according to their main ablation mechanism. Among thermal sources of energy, the most used ones are: HIFU, cryotherapy, focal laser ablation and radiofrequency ablation. Among non-thermal sources of energy, the most used ones are: irreversible electroporation, PDT and brachytherapy. While it is possible to modulate for each energy the ablation template, thermal energies generally lead to a slightly wider ablation field as there is a progressive temperature gradient of thermal dispersion around the ablation target; non-thermal energy have usually a more demarcated boundary between the treated and the untreated tissue which limit the damage to the surrounding area. However, the choice of energy source should rely on patients' characteristics, intrinsic features and stage of assessment rather than on a theoretical lower side effect profile. Moreover, the field of focal therapy is rapidly evolving and novel sources of energy are constantly emerging. The potential advantages on novel technologies is yet to be confirmed in acceptable comparative studies.

TABLE 1 | Complications and their rates in the primary focal therapy setting.

Type of complication	Rate
Infectious (urinary tract infection, epididymo-orchitis)	0–17%
Haematuria	Very frequent; not reported
Acute urinary retention	0–17%
Urethral sloughing	Frequent; not reported
Urinary incontinence	0–5%
Erectile dysfunction	0–46%
Orgasmic/ejaculatory dysfunction	Not reported
Recto-urethral fistula	0–1%

Type of Complications

Specialists performing focal therapy should be well aware of possible complications and their management. While the risk profile is more favorable than for whole gland treatments, genito-urinary toxicity and complications can occur after treatment (16). This includes peri-operative, short-term, mid-term and late complications. The types of complications and their reported frequency are summarized in **Table 1** (12).

Peri-Operative Complications

The most common complications after focal therapy usually occur within the first 30 days after the intervention (22). These are often haematuria, infectious complications or catheter related issues such as pain, discomfort and urethral sloughing. Urine culture should be routinely performed prior to the treatment to rule out an ongoing infection. A 7-day antibiotic prophylaxis is usually recommended post operatively (23). Due to the swelling of the prostate induced by focal treatment, urinary catheter is recommended for 3–10 days, depending on the treatment protocol and the cancer location. Alpha-blockers are suggested prior to trial without the catheter (TWOC) and continued for 2 weeks after treatment. Usually, catheter induced discomfort and pain will be the most frequent symptom post-operatively (24). Therefore, painkillers, anti-inflammatory and anti-muscarinic drugs should be routinely prescribed. Finally, an information leaflet explaining in detail about the possible post-operative complications should be provided for all patients. A suggested protocol after focal therapy is summarized in **Table 2**. This might vary according to the energy source used, the treatment template and patients' characteristics.

Urinary tract infection and epididymo-orchitis after focal therapy can occur in 0–17% of patients (12). In two recent RCTs reporting on focal PDT and HIFU peri-operative urinary infection rates were 2 and 10%, respectively (25, 26). In recently published large cohort prospective studies on focal cryotherapy and HIFU the infection rates vary between 8.5 and 9% (27, 28). The sepsis rates are poorly reported in the available literature or not separately reported. In our experience sepsis after focal treatment is very rare. A recent prospective study has reported a single shot antibiotic prophylaxis prior to HIFU treatment with

TABLE 2 | Suggested protocol for perioperative care in focal therapy.

Treatment	Duration	Dose	Frequency
Urinary catheter	(3–10 days)*	x	x
Antibiotic	7 days	Depending on local guidelines	Depending on choice
Paracetamol	2 weeks	1,000 mg	PRN
Ibuprofen	2 weeks	400 mg	3 times a day
Alpha-blocker	2 weeks	Depending on treatment	Once a day
Antimuscarinic drug	Until TWOC	Depending on treatment	PRN
Information leaflet**	x	x	x

this may vary according to the energy sourced used.

***an information leaflet clearly explaining to the patient possible complications and actions to take after treatment.*

similar infectious rates as in the literature (29). A consensus on antibiotic prophylaxis choice and duration for focal treatments is yet to be achieved. In our opinion, due to global rise in antibiotic resistance, each center performing focal therapy should discuss the choice of antibiotic prophylaxis with the local preventive service to match the regional resistance patterns.

About 1 in 5 men will present a temporary LUTS following focal therapy (30) as shown in focal HIFU, while acute urinary retention is reported in 0–17% (12). Patients should also be warned about possible urethral sloughing following focal therapy. The frequency and amount of debris may vary between the energy sources and the ablation template (31). In some instances, urethral sloughing and debris might block the catheter causing acute urinary retention. Most men will respond to alpha-blocker treatment with symptoms gradually disappearing in the 1st month after the intervention. Patients failing the first TWOC should keep the indwelling catheter until the post-treatment inflammation and urethral sloughing is reduced. In case of a second failed TWOC a cystoscopy under general anesthesia is advised in order to rule-out the presence of obstructive necrotic tissue that would require a transurethral resection. The need for endoscopic interventions after focal treatments has become less frequent with the advent of more conservative ablation templates (22, 27).

Less commonly reported complication is penile numbness and penoscrotal swelling. It is most common in the peri-operative period following cryotherapy and in sources of energy delivered percutaneously through the perineum; it can occur in 10% of the cases (28).

Finally, haematuria is very common after any type of focal therapy. There are no studies that report the need of a blood transfusion following the treatment, although clot retention might occasionally, especially in patients using blood thinning agents.

Erectile Function and Sexual Satisfaction

The impact of active treatment on patients' sexual function can be a major factor contributing to the individual choice of therapy. Two large systematic reviews reported on erectile function in men following different types of focal therapy (12, 32); overall, 54–100% of patients had erections sufficient for penetration (with or without a phosphodiesterase type 5 inhibitor). The systematic review by Walker et al. concluded that most studies assessing the outcomes of focal therapy on sexual function are not of high quality and uses heterogenous outcomes to describe erectile dysfunction. Initial results of the PART randomized control trial that assigned 82 men to either radical prostatectomy or focal ablation by HIFU are now available. Although this was a pilot trial to prove the feasibility of a larger confirmatory trial, validated PROMs confirm a clear advantage in favor of HIFU (26): the HIFU group had a significantly better outcomes concerning sexual function (OR 12.5, 95% CI 4.5–18.5) and sexual quality of life as measured by the EPIC questionnaire (OR 10.9, 95% CI 4–17.8). There was no significant difference in sexual desire between the two groups. Another RCT randomizing patients between PDT and active surveillance has shown very low (1%) erectile dysfunction rates in both groups (25). Patients receiving PDT did present a transient erectile dysfunction, however at 2 years follow-up, the mean International Index of Erectile Function 15 (IIEF-15) scores were comparable between the groups (15 for PDT and 16.8 for active surveillance; *p*-value not reported).

A combined analysis of three prospective development trials evaluating erectile dysfunction post-focal HIFU demonstrated a complete return to baseline function at 1 year. A transient erectile dysfunction was observed at 1 month with a significant decline of the IIEF-15 score ($p < 0.01$). However, at 1 year there was no significant difference in the erectile function as compared to baseline score ($p = 0.3$). The number of men requiring phosphodiesterase type 5 inhibitor treatment went to 10% pre-operatively to 37% at 1 year (14).

Ejaculatory and orgasmic dysfunction are significant side effects following active treatment of prostate cancer, although probably underestimated and underreported (33). The rates of retrograde ejaculation/anejaculation and orgasmic dysfunction following focal therapy are poorly reported in the available literature. Patients undergoing any form of focal treatment should be warned about the risk of "dry orgasm" after treatment. This is not harmful and generally does not affect sexual pleasure.

It is important to highlight that ongoing trials are underway to evaluate sexual function after focal therapy. For instance, a trial in United Kingdom (34) will recruit patients undergoing different types of focal therapy. Patients' will fill in validated PROMs to explore ejaculation, orgasm, libido/sexual desire, masculinity/virility, penile morphology, pain or discomfort,

regret, shame, cancer-related stress, overall impact and partner satisfaction. This will help to council and manage expectations of prostate cancer patients undergoing focal therapy in the future.

Urinary Continence

Urinary incontinence is uncommon after focal therapy, regardless the source of energy used. Pad-free continence rate varies between 95 and 100%, while leak free continence is reported in 83–100% (12). In the PART randomized controlled trial, the overall urinary quality of life (OR 6.7, 95% CI 0.8–12.6), urinary function (OR 10.8, 95% CI 4.1–17.5) and urinary incontinence (OR 22.9 95% CI 13.6–32.2) were all in favor of focal HIFU when compared to radical prostatectomy (26). At 6 months no men in HIFU group reported the need to use pads as compared to around 60% in the radical prostatectomy group. In the focal PDT vs. active surveillance randomized trial the incontinence levels were also low (1%) (25). Incontinence was mostly related to urgency and usually occurred in the initial period after catheter withdrawal. Multiple prospective studies confirm low incontinence rates (12, 27, 35) with pad-free continence rates ranging between 95 and 100%. Patients presenting urinary incontinence after focal therapy rarely require more than one pad a day, thus social continence is maintained in most cases (27) as reported with focal HIFU.

The management of urinary incontinence following focal therapy should be adapted to the degree of incontinence. In most cases the recovery will be spontaneous while some men might need pelvic floor physiotherapy. We did not find any studies or case reports describing the need for artificial urinary sphincter or other invasive procedure following focal therapy for prostate cancer.

Rectal Toxicity

Recto-urethral fistula is a rare complication of focal therapy. An abnormal connection between the intestinal and the urinary systems is formed resulting in pneumaturia, fecaluria and urine leakage from the rectum. In the primary focal therapy setting, recto-urethral fistula is rare at 0–1% (12). Multiple RCT and prospective studies on different types of focal therapy confirm the low rates of this complication (22, 25–28). The risk is highest when treatment is performed in a salvage setting and when cancer is located in the posterior part of the prostate and extracapsular extension is present. Initial treatment is conservative in most cases with a long duration indwelling catheter. In case of conservative treatment failure, a temporary colostomy can be considered but, in most cases, a reconstructive procedure with excision of the fistulous tract, followed by closure and mobilization of an interposition graft or flap is necessary to definitively solve the problem.

Focal Therapy in the Salvage Setting

Focal salvage therapy after ERBT has a completely different toxicity profile than primary focal therapy: the rate of complications is significantly higher although much lower than in salvage radical prostatectomy.

A recent systematic review by Khoo et al. has summarized the complication rates for focal therapy strategies performed after ERBT treatment (36). Grade 3 toxicity adverse events were rare with all treatment modalities: recto-urethral fistula was reported in 0–5.5%, urethral stricture in 5–10% and pubic bone osteitis in 0.7–4.2%. Pad free continence rates were around 87%. Erectile function was reported in two studies and worsened from 18 to 13 points and from 15 to 13 points, respectively, as reported with IIEF−5 PROMs. The authors acknowledge significant limitations as most studies were single arm case series with a lack of standardization in patient selection, treatment protocols and outcome reporting. There are no RCTs comparing focal salvage treatment modalities to other treatments. Focal therapy in the post ERBT setting should be performed only by experienced units. Post-radiotherapy changes in the prostate and surrounding tissues make any procedure more challenging. The procedure needs to be adapted to each case, and some devices need to be adapted with specific parameters to avoid major complications.

CONCLUSION

Focal therapy has become an interesting treatment strategy for localized prostate cancer. Level 1 evidence shows its favorable toxicity profile and preservation of genito-urinary function. Most complications are mild and follow the 30-day period after treatment, these can be managed with medication and do not require invasive procedures in the majority of patients. Urinary incontinence is rare, and the risk of new onset erectile dysfunction is much lower than for whole gland treatments. The toxicity profile of focal therapy in the salvage setting has been less evaluated in robust studies, although the complication rate is higher with severe complications occurring in up to one man in 10.

AUTHOR CONTRIBUTIONS

AR and MV generated and produced first draft of the manuscript. GM, IH, VK, AK, FZ, FP, DT, IT, RB, CK, FC, CF, and GG revised the manuscript. All authors contributed to the article and approved the submitted version.

REFERENCES

1. World Cancer Research Fund. (2018). Available online at: https://www.wcrf.org/dietandcancer/prostate-cancer (accessed February 21, 2021).
2. Rawla P. Epidemiology of prostate cancer. *World J Oncol.* (2019) 10:63–89. doi: 10.14740/wjon1191
3. Resnick MJ, Koyama T, Fan K-H, Albertsen PC, Goodman M, Hamilton AS, et al. Long-term functional outcomes after treatment for localized prostate cancer. *N Engl J Med.* (2013) 368:436–45. doi: 10.1056/NEJMoa1209978
4. Zhang P, Qian B, Shi J, Xiao Y. Radical prostatectomy versus brachytherapy for clinically localized prostate cancer on oncological and functional outcomes: a meta-analysis. *Transl Androl Urol.* (2020) 9:332–43. doi: 10.21037/tau.2020.02.15
5. Tay KJ, Scheltema MJ, Ahmed HU, Barret E, Coleman JA, Dominguez-Escrig J, et al. Patient selection for prostate focal therapy in the era of active surveillance: an International Delphi Consensus Project. *Prostate Cancer Prostatic Dis.* (2017) 20:294–9. doi: 10.1038/pcan.2017.8

6. Muller BG, van den Bos W, Pinto PA, de la Rosette JJ. Imaging modalities in focal therapy: patient selection, treatment guidance, and follow-up. *Curr Opin Urol.* (2014) 24:218–24. doi: 10.1097/MOU.0000000000000041
7. Ouzzane A, Betrouni N, Valerio M, Rastinehad A, Colin P, Ploussard G. Focal therapy as primary treatment for localized prostate cancer: definition, needs and future. *Future Oncol.* (2017) 13:727–41. doi: 10.2217/fon-2016-0229
8. Donaldson IA, Alonzi R, Barratt D, Barret E, Berge V, Bott S, et al. Focal therapy: patients, interventions, and outcomes–a report from a consensus meeting. *Eur Urol.* (2015) 67:771–7. doi: 10.1016/j.eururo.2014.09.018
9. Kasivisvanathan V, Rannikko AS, Borghi M, Panebianco V, Mynderse LA, Vaarala MH, et al. MRI-targeted or standard biopsy for prostate-cancer diagnosis. *N Engl J Med.* (2018) 378:1767–77. doi: 10.1056/NEJMoa1801993
10. Ahmed HU, El-Shater Bosaily A, Brown LC, Gabe R, Kaplan R, Parmar MK, et al. Diagnostic accuracy of multi-parametric MRI and TRUS biopsy in prostate cancer (PROMIS): a paired validating confirmatory study. *Lancet.* (2017) 389:815–22. doi: 10.1016/S0140-6736(16)32401-1
11. Simmons LAM, Kanthabalan A, Arya M, Briggs T, Barratt D, Charman SC, et al. The PICTURE study: diagnostic accuracy of multiparametric MRI in men requiring a repeat prostate biopsy. *Br J Cancer.* (2017) 116:1159–65. doi: 10.1038/bjc.2017.57
12. Valerio M, Ahmed HU, Emberton M, Lawrentschuk N, Lazzeri M, Montironi R, et al. The role of focal therapy in the management of localised prostate cancer: a systematic review. *Eur Urol.* (2014) 66:732–51. doi: 10.1016/j.eururo.2013.05.048
13. Bates AS, Ayers J, Kostakopoulos N, Lumsden T, Schoots IG, Willemse P-PM, et al. A systematic review of focal ablative therapy for clinically localised prostate cancer in comparison with standard management options: limitations of the available evidence and recommendations for clinical practice and further research. *Eur Urol Oncol.* (2021) 4:405–23. doi: 10.1016/j.euo.2020.12.008
14. Yap T, Ahmed HU, Hindley RG, Guillaumier S, McCartan N, Dickinson L, et al. The effects of focal therapy for prostate cancer on sexual function: a combined analysis of three prospective trials. *Eur Urol.* (2016) 69:844–51. doi: 10.1016/j.eururo.2015.10.030
15. Sivaraman A, Barret E. Focal therapy for prostate cancer: an "À la Carte" approach. *Eur Urol.* (2016) 69:973–5. doi: 10.1016/j.eururo.2015.12.015
16. Borges RC, Tourinho-Barbosa RR, Glina S, Macek P, Mombet A, Sanchez-Salas R, et al. Impact of focal versus whole gland ablation for prostate cancer on sexual function and urinary continence. *J Urol.* (2021) 205:129–36. doi: 10.1097/JU.0000000000001327
17. Le Nobin J, Rosenkrantz AB, Villers A, Orczyk C, Deng F-M, Melamed J, et al. Image guided focal therapy of magnetic resonance imaging visible prostate cancer: defining a 3-dimensional treatment margin based on magnetic resonance imaging-histology co-registration analysis. *J Urol.* (2015) 194:364–70. doi: 10.1016/j.juro.2015.02.080
18. Pooli A, Johnson DC, Shirk J, Markovic D, Sadun TY, Sisk AE, et al. Predicting pathological tumor size in prostate cancer based on multiparametric prostate magnetic resonance imaging and preoperative findings. *J Urol.* (2021) 205:444–51. doi: 10.1097/JU.0000000000001389
19. Priester A, Natarajan S, Khoshnoodi P, Margolis DJ, Raman SS, Reiter RE, et al. Magnetic resonance imaging underestimation of prostate cancer geometry: use of patient specific molds to correlate images with whole mount pathology. *J Urol.* (2017) 197:320–6. doi: 10.1016/j.juro.2016.07.084
20. Lebastchi AH, George AK, Polascik TJ, Coleman J, de la Rosette J, Turkbey B, et al. Standardized nomenclature and surveillance methodologies after focal therapy and partial gland ablation for localized prostate cancer: an international multidisciplinary consensus. *Eur Urol.* (2020) 78:371–8. doi: 10.1016/j.eururo.2020.05.018
21. Emberton M. Has tailored, tissue-selective tumour ablation in men with prostate cancer come of age? *BJU Int.* (2018) 121:676–7. doi: 10.1111/bju.14088
22. Schmid FA, Schindele D, Mortezavi A, Spitznagel T, Sulser T, Schostak M, et al. Prospective multicentre study using high intensity focused ultrasound (HIFU) for the focal treatment of prostate cancer: safety outcomes and complications. *Urol Oncol.* (2020) 38:225–30. doi: 10.1016/j.urolonc.2019.09.001
23. Ahmed HU, Dickinson L, Charman S, Weir S, McCartan N, Hindley RG, et al. Focal ablation targeted to the index lesion in multifocal localised prostate cancer: a prospective development study. *Eur Urol.* (2015) 68:927–36. doi: 10.1016/j.eururo.2015.01.030
24. Bai Y, Wang X, Li X, Pu C, Yuan H, Tang Y, et al. Management of catheter-related bladder discomfort in patients who underwent elective surgery. *J Endourol.* (2015) 29:640–9. doi: 10.1089/end.2014.0670
25. Azzouzi A-R, Vincendeau S, Barret E, Cicco A, Kleinclauss F, van der Poel HG, et al. Padeliporfin vascular-targeted photodynamic therapy versus active surveillance in men with low-risk prostate cancer (CLIN1001 PCM301): an open-label, phase 3, randomised controlled trial. *Lancet Oncol.* (2017) 18:181–91. doi: 10.1016/S1470-2045(16)30661-1
26. Hamdy FC, Elliott D, le Conte S, Davies LC, Burns RM, Thomson C, et al. Partial ablation versus radical prostatectomy in intermediate-risk prostate cancer: the PART feasibility RCT. *Health Technol Assess.* (2018) 22:1–96. doi: 10.3310/hta22520
27. Guillaumier S, Peters M, Arya M, Afzal N, Charman S, Dudderidge T, et al. A Multicentre study of 5-year outcomes following focal therapy in treating clinically significant non-metastatic prostate cancer. *Eur Urol.* (2018) 74:422–9. doi: 10.1016/j.eururo.2018.06.006
28. Shah TT, Peters M, Eldred-Evans D, Miah S, Yap T, Faure-Walker NA, et al. Early-medium-term outcomes of primary focal cryotherapy to treat non-metastatic clinically significant prostate cancer from a prospective multicentre registry. *Eur Urol.* (2019) 76:98–105. doi: 10.1016/j.eururo.2018.12.030
29. Westhoff N, Ritter M, Maros M, Rassweiler-Seyfried M-C, Michel M-S, Honeck P, et al. Prospective feasibility study of single-shot antibiotic prophylaxis in transrectal focal ablation of prostate cancer. *UIN.* (2020) 104:378–85. doi: 10.1159/000507123
30. Ahmed HU, Hindley RG, Dickinson L, Freeman A, Kirkham AP, Sahu M, et al. Focal therapy for localised unifocal and multifocal prostate cancer: a prospective development study. *Lancet Oncol.* (2012) 13:622–32. doi: 10.1016/S1470-2045(12)70121-3
31. Bakavicius A, Sanchez-Salas R, Muttin F, Sivaraman A, Dell'Oglio P, Barret E, et al. Comprehensive evaluation of focal therapy complications in prostate cancer: a standardized methodology. *J Endourol.* (2019) 33:509–15. doi: 10.1089/end.2018.0809
32. Faure Walker NA, Norris JM, Shah TT, Yap T, Cathcart P, Moore CM, et al. A comparison of time taken to return to baseline erectile function following focal and whole gland ablative therapies for localized prostate cancer: A systematic review. *Urol Oncol.* (2018) 36:67–76. doi: 10.1016/j.urolonc.2017.12.002
33. Green TP, Saavedra-Belaunde J, Wang R. Ejaculatory and Orgasmic Dysfunction Following Prostate Cancer Therapy: Clinical Management. *Med Sci.* (2019) 7:109. doi: 10.3390/medsci7120109
34. Fiard G, Kelly D, Yap T, Emberton M. Detailing sexual outcomes after treatment of localised prostate cancer with focal therapy using various energy sources: protocol for a mixed-methods study. *BMJ Open.* (2020) 10:e045500. doi: 10.1136/bmjopen-2020-045500
35. Royce PL, Ooi JJY, Sothilingam S, Yao HH. Survival and quality of life outcomes of high-intensity focused ultrasound treatment of localized prostate cancer. *Prostate Int.* (2020) 8:85–90. doi: 10.1016/j.prnil.2019.12.002
36. Khoo CC, Miah S, Connor MJ, Tam J, Winkler M, Ahmed HU, et al. A systematic review of salvage focal therapies for localised non-metastatic radiorecurrent prostate cancer. *Transl Androl Urol.* (2020) 9:1535–45. doi: 10.21037/tau.2019.08.21

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REVIEW
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Management of Medium and Long Term Complications Following Prostate Cancer Treatment Resulting in Urinary Diversion – A Narrative Review

Benedikt Hoeh[1,2], Stefan C. Müller[1], Luis A. Kluth[1†] and Mike Wenzel[1,2] for the Trauma Reconstructive Urology Working Party of the European Association of Urology Young Academic Urologists[†]*

[1] Department of Urology, University Hospital Frankfurt, Goethe University Frankfurt am Main, Frankfurt am Main, Germany, [2] Cancer Prognostics and Health Outcomes Unit, Division of Urology, University of Montréal Health Center, Montréal, QC, Canada

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***Correspondence:**
Benedikt Hoeh
benedikt.hoeh@kgu.de

[†] Senior member of the Trauma Reconstructive Urology Working Party of the European Association of Urology Young Academic Urologists

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The purpose of this narrative review is to discuss and highlight recently published studies regarding the surgical management of patients suffering from prostate cancer treatment complications. Focus will be put on the recalcitrant and more complex cases which might lead to urinary diversion as a definite, last resort treatment. It is in the nature of every treatment, that complications will occur and be bothersome for both patients and physicians. A small percentage of patients following prostate cancer treatment (radical prostatectomy, radiation therapy, or other focal therapies) will suffer side effects and thus, will experience a loss of quality of life. These side effects can persist for months and even years. Often, conservative management strategies fail resulting in recalcitrant recurrences. Prostate cancer patients with "end-stage bladder," "devastated outlet," or a history of multiple failed interventions, are fortunately rare, but can be highly challenging for both patients and Urologists. In a state of multiple previous surgical procedures and an immense psychological strain for the patient, urinary diversion can offer a definite, last resort surgical solution for this small group of patients. Ideally, they should be transferred to centers with experience in this field and a careful patient selection is needed. As these cases are highly complex, a multidisciplinary approach is often necessary in order to guarantee an improvement of quality of life.

Keywords: prostate cancer, urinary diversion, radical prostatecomy, radiation theraphy, devastated bladder outlet

INTRODUCTION

Prostate cancer is the most commonly diagnosed cancer in men, with an estimated 1.3 million diagnoses worldwide in 2018, ranking as the fifth leading cause of cancer death in men (1). Radical prostatectomy and radiation therapy can be seen as equally accepted therapeutic approaches regarding oncological outcomes and play a crucial part in the curative active treatment strategies for prostate cancer (2). In the last decades, less invasive surgical approaches, as well as focal therapy concepts, e.g., high-intensity focused ultrasound (HIFU), brachytherapy and cryotherapy became frequently discussed treatment strategies of localized prostate cancer due to a trend to minimize morbidity while providing maximum of oncological tumor control (3, 4). Moreover, multimodal

therapy concepts such as combination of surgical/radiation approaches, salvage or cytoreductive treatments have shown improvement of the survival outcomes in settings of high-risk, locally advanced or even metastatic prostate cancer patients (2).

Regardless of the constant urge to improve treatment and minimize therapy-associated side effects, concomitant and late onset complications have to be carefully taken into account, when treatment decisions are made and should be carefully monitored and managed. Severity and time of appearance of persisting side effects differ regarding the underlying treatment and can result in a bothersome reduced quality of life for the patient (5).

The vast majority of complications following prostate cancer treatments across all stages can be successfully treated conservatively with a significant increase of patients' quality of life. Unfortunately, a small proportion of patients suffers of ongoing (chronic) complications, leaving patients, and Urologists in a bothersome and frustrating situation. Urinary diversion can be seen as an *ultima ratio* for this subgroup of complex cases. The recent literature consists of small case series and expert recommendations (6–8). However, no current clinical trials or guideline recommendation exist to provide an evidence-based approach for those patients with a persisting reduction of quality of life.

This review aims to highlight the preoperative diagnostic steps and provides an overview of the current medical literature according to different surgical approaches and possibly solutions for patients requiring a urinary diversion as an *ultima ratio* due to their prolonged ordeal after prostate cancer treatment.

Literature review was performed separately by two authors of the study (BH, MW). Inclusion criteria were articles published between 1994 and 2021, using "urinary diversion," "end stage bladder," "devastated bladder outlet," "complications prostate cancer" as search terms. Articles written in other language than English or German were excluded from further consideration.

Urinary diversion is defined as a surgically applied continent or incontinent mechanism for urine release after functional or disease-specific requirement of surgical intervention and removement of the natural anatomy of the urinary tract system. Foley catheterization and percutaneous nephrostomies are usually included in this definition (9). However, this review will mainly focus on long-lasting, definite types of urinary diversion.

Fundamental considerations regarding a continent vs. an incontinent-based urinary diversion have to be made in accordance with patient's age, comorbidities, manual dexterity, and cognitive ability (9). **Table 1** summarizes the most common types of urinary diversions and their functional outcomes in terms of postoperative expected continence.

Within continent urinary diversions, different surgical approaches are known concerning the type of bowel used and different types of continence-mechanisms, either based on a flap-valve principle (Mitrofanoff appendicovesicostomy, Yang-Monti-Channel) or nipple-valve principle (Intussuscepted ileal channel) (8, 10, 11). It is of note, that some findings are drawn from small case studies and derived partly from pediatric patients.

Prerequisites for quality of life are: a sufficient capacity (and if possible, well-contracted), reservoir (storage), a competent sphincteric mechanism and an unobstructed outlet (emptying). Especially radiation can damage all these three components without the tendency of healing over time. In this case urinary diversion remains as only solution. To avoid further complications of any surgical reconstructive procedure, one should take care not to use tissue which has been exposed to radiation, or use healthy vital tissue for interposition (e.g., greater omentum, pedunculated rectus or gracilis muscle flaps) (10, 12). Attention should be given to the bladder neck area. In any circumstances, surgical closure of the bladder neck should be performed in order to minimize risks of vesicourethral fistulae (13). Furthermore, following cases studies and experts opinions, tissue interposition should be performed to minimize complications such as vesicourethral fistulae (8, 9, 14). For example, the greater omentum or Musculus rectus abdominis/gracilis have been used as a vital tissue interposition with sufficient clinical results. Opposed to a bladder neck closure, a perineal closure of the distal urethra can be performed in a subgroup of patients, who are not eligible for a transabdominal approach and want to avoid an abdominal operation, especially after radiation therapy (6).

It is important to mention, that above mentioned general comments regarding surgical procedures must not be seen as a strict guideline. They should rather be considered as a pool of recommendations which can support decision making for both surgeons and patients. On behalf of the YAU Special edition "Sequelae of prostate Cancer Therapy: Avoidance Strategies and Management options," a detailed summarization of different complications, which can lead to a urinary diversion at the far end of conservative treatment, will be discussed here.

TABLE 1 | Outline of the most commonly used urinary diversion types divided by the postoperative expected continence type.

Urinary diversion	
Continent types	**Non-continent types**
- Suprapubic vesicostomy (minimal-invasive) - Appendicovesicostomy - Ileovesicostomy - Cystoplasty with simultaneous Ileocecal bladder-augmentation - Ureterosigmoidostomy - Colon-pouch (Mainz-pouch I/III, Indiana pouch)	- Ureterosigmoidostomy - Cystectomy followed by ureterocutaneostomies - Cystectomy followed by Ileum/colon-conduit

OSTEOMYELITIS OF THE SYMPHYSIS PUBIS/OSTEITIS PUBIS FOLLOWING UROSYMPHYSEAL FISTULA

Definition, Etiology, and Clinical Presentation

Osteomyelitis of the symphysis pubis and osteitis pubis are two rare complications following prostate cancer treatment

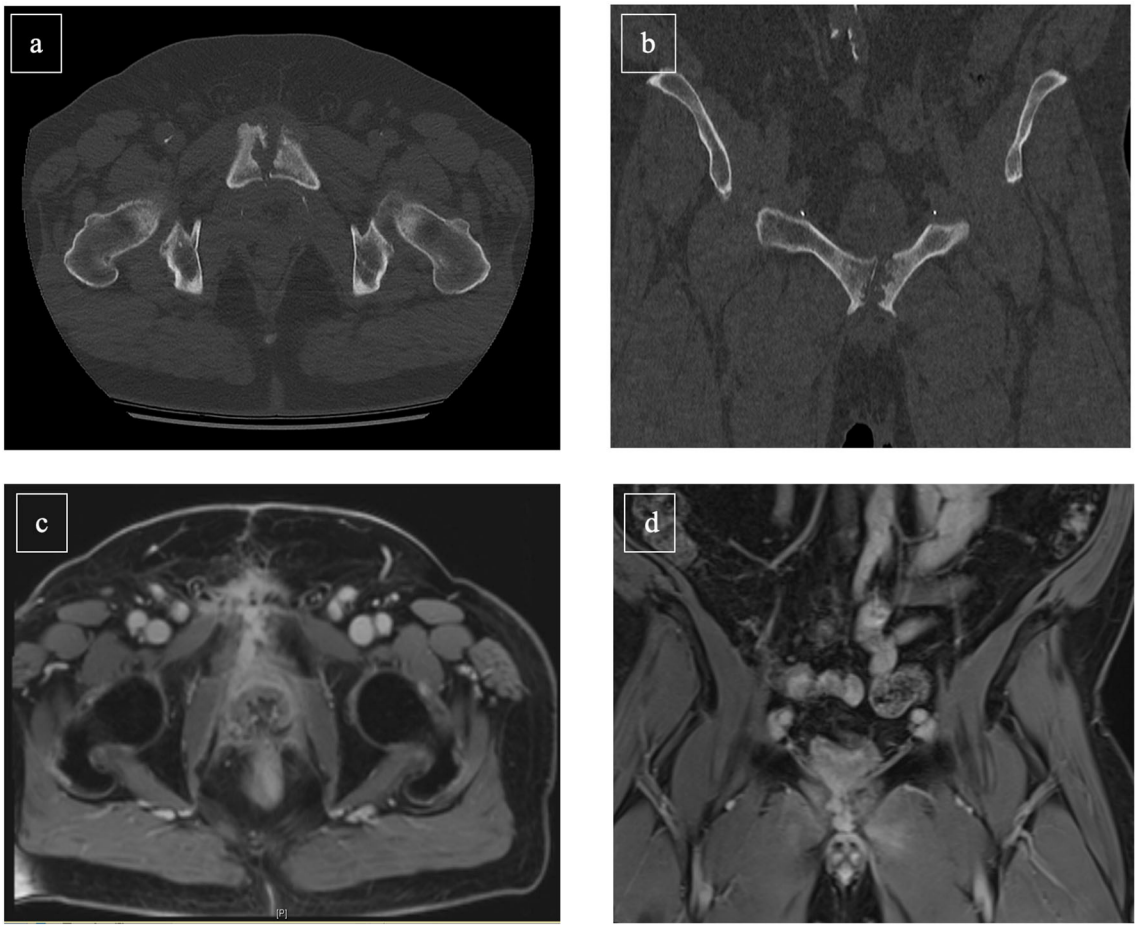

FIGURE 1 | Abdominal CT scan [**(a)**: transversal, **(b)**: frontal] and MR-Imaging [**(c)**: transversal, **(d)**: frontal] of a 56-year-old prostate cancer patient suffering osteomyelitis following photon-beam radiation therapy of the prostate (2017) and salvage radical prostatectomy with persistent insufficient anastomosis (2019). Cystectomy with Mainz-I pouch with appendix-nipple was successful performed. Furthermore, symphyseal resection and omentus major flap was simultaneously achieved.

(15). Since osteitis pubis is defined as a painful inflammatory process resulting in bone destruction of the symphysis margins, osteomyelitis of the symphysis is additionally associated with a detection of bacteria in bone cultures (16). In the vast majority of cases, urosymphyseal fistulae can be observed as the cause for this rare and debilitating diseases and complications after prostate cancer treatment (17).

Diagnosis of these progressive inflammation processes can be difficult and may prolong patients' suffering. Patients can also present with non-urological symptoms such as unspecific lower bowel/suprapubic pain, limitations in mobility, and generally reduced quality of life (18, 19). Chronic pubic pain is a common symptom following surgical and non-surgical prostate cancer treatment. However, prolonged episodes of pain should raise suspicion and physicians should consider the above-mentioned diseases as its origin for the patient's suffering. Furthermore, recurrent urinary tract infections and voiding discomfort can also occur as additional symptoms (17).

Diagnosis and Investigations

When osteomyelitis of the symphysis/pubis and urosymphyseal fistula is suspected, clinical assessments should include physical examination, ultrasound diagnostics, and blood testings. Additionally, urethrocystoscopy and urodynamics are important diagnostic tools to evaluate size and location of a fistula, its relationship to the orifices and a normal function of the urinary tract. Moreover, concomitant bladder neck contractures can be excluded by above-mentioned clinical assessments. Furthermore, bladder capacity and sphincteric competence should ideally be assessed within those diagnostic methods (14). Magnetic resonance imaging (MRI) with contrast agent provides currently the most accurate diagnostic modality for the confirmation or rejection of urosymphyseal fistula (20, 21). Conventional radiographs can be additionally performed, if involvement of bone structures cannot be sufficiently assessed by prior MRI (**Figure 1**). Moreover, it should be considered that a delay in diagnostics can cause a progress in inflammation and infection

and evade into the perineum, scrotum, groin, or thigh resulting in abscesses and chronically discharging sinuses (14).

Epidemiology

The current literature of body is scarce including only few sporadic case reports and small heterogenous studies about urosymphyseal fistula including 13–36 patients (14–16). It is noteworthy to mention, that the vast majority of patients suffering from osteomyelitis with concomitant urosymphyseal fistula had a history of definitive radiation therapy for initial prostate cancer treatment. In a case review by Kahokehr et al. (15) including 36 patients between 2012 and 2019 and addressing the prevalence of urosymphyseal fistula, solely three patients (8.3%) who underwent extirpative surgery for urosymphyseal fistula, were initially treated with a radical prostatectomy for primary prostate cancer. The vast majority of patients (91.7%) received either radiation therapy or combination of radiation therapy and radical prostatectomy (15). These findings are in an agreement with the results from a single-center case series by Bugeja et al. (14) ($n = 16$), where all urosymphyseal fistula patients (100%) were initially treated with radiation therapy for prostate cancer disease.

It is also of note that few cases of urosymphyseal fistula and concomitant osteomyelitis were observed in patients undergoing salvage focal therapy for prostate cancer treatment, such as HIFU, and palliative transurethral resection of the prostate following initial radiation therapy of prostate cancer treatment (19, 22, 23).

Management

The vast majority of patients fail to respond to conservative management for urosymphyseal fistula, including analgesia, antibiotics, and intermittent urine diversion by a urethral or suprapubic catheter (14). After failure of conservative management, a subsequent radical surgical management (urinary diversion and/or debridement) with periinterventional antibiotic therapy is mostly applied. Nosé et al. (24) demonstrated in a case series of 33 patients who underwent extirpative surgery with urinary diversion for urosymphyseal fistula that urine culture correlated in 63% with bone culture results in patients. In consequence, the radical surgical approach normally includes the resection of the pubic symphysis joint and all affected pubic bone in combination with fistula excision and interposition of healthy tissue (14, 24).

Following a retrospective review ($n = 36$) published by Kahokehr et al., (15) 89% of patients suffering from urosymphyseal fistula following initial prostate cancer treatment, harbored osteomyelitis in histological analysis. The majority of these patients had a history of radiation therapy (92%). Here, all patients underwent extirpative debridement of the pubic bone. Noteworthy, concurrent cystectomy with urinary diversion was performed in 92% and two patients had already undergone cystectomy prior to presentation. Conversely, the bladder could be preserved solely in one patient. Interestingly, this patient did not have a history of radiation (15). In contrast, Bugeja et al. presented a case series of 16 patients being treated for urosymphyseal fistula, in which reconstruction by salvage prostatectomy and substitution/augmentation cystoplasty was successful in seven patients (47%). Conversely, cystectomy and ileum conduit were the preferred urinary diversions for eight patients (53%). Mundy et al. stated, that the ability to successfully reconstruct the lower urinary tract is strongly related to bladder capacity and compliance, which are commonly significantly reduced after pelvic radiation (25). Both case series emphasized the importance of pubic bone resection, tissue interpositioning and, if applicable, bladder neck closure at time of urosymphyseal fistula surgery. **Table 2** outlines the most important characteristics which play a determining factor whether reconstructive surgery or cystectomy followed by a urinary diversion might represent the more suitable surgical approach. Moreover, it should be mentioned that in cases of bone involvement, interdisciplinary approaches including Urologists, Microbiologists, and Orthopedic surgeons should be targeted.

TABLE 2 | Important patient and anatomical characteristics determining reconstructive surgery vs. cystectomy including urinary diversion in patients with devasted bladder outlets after prostate cancer treatment.

Patient characteristics	Anatomical and functional characteristics
- Prostate cancer treatment (radical prostatectomy, external beam radiation therapy, high intensity focused ultrasound, focal therapy [cryo/brachytherapy]) - Prostate cancer status (cancer-free, local/distant recurrence, progressive disease) - Age - Comorbidities - Body habitus, Body Mass Index - Performance status - Mental capacity/motivation	- Status of bladder (bladder capacity, compliance) - Size and location of fistula - Prostate organ still *in situ* - Presence of concomitant bladder neck contracture - Presence of pre-sacral cavity - Concomitant fistula into the rectum - Length of proximal bulbar urethra available to anastomose bladder/neobladder onto

RADIATION THERAPY-ASSOCIATED BLADDER TOXICITY

Definition, Etiology, and Clinical Presentation

Radiation therapy of the pelvic structures is in general associated with bladder toxicity as a specific type of iatrogenic damage of the bladder. This holds especially true for prostate cancer treatment, which is usually performed with 74–80 Gy in primary prostate cancer treatment (2, 26). Besides urinary tract infections following radiation therapy, radiation-induced cystitis is a common challenging side effect of radiation therapy. This radiation therapy-induced cystitis is mainly related to DNA-damage associated endarteritis, including bladder hypoperfusion, which leads to mucosal atrophy, hypocellularity, and hypovascularity (27, 28). Patients suffering from hemorrhagic cystitis can present with mild intermittent hematuria. Conversely, also recurrent, progressive, and uncontrollable bleeding can end in life threatening situations.

Diagnosis and Investigations

Radiation therapy-induced cystitis is a chronic condition characterized by urinary frequency, dysuria, incontinence, and pelvic pain. Hemorrhagic cystitis is a subtype, referred to when hematuria is present and is usually described as a late toxicity effect (29). Reduced bladder capacity and compliance and occurrence of secondary bladder malignancy can be also observed (30, 31). The existence of all of these symptoms occurring simultaneously (reduced bladder capacity, pain persistence and recurrent hematuria) are marked as a so called *end-stage bladder*, demonstrating the maximum expression of radiation-associated bladder toxicity (6). Diagnostic work-up should contain the exclusion of other symptoms-related side effects (29). Besides clinical examination and urine analyses, diagnostic urethrocystoscopy should be performed for visual assessment and rule-out intravesical malignancies. In doubt, urological imaging (computed tomography or magnetic resonance Imaging) can additionally be performed (32).

Epidemiology

The reported incidence of radiation-induced cystitis varies from 23 to 80%, depending on the definition of cystitis, types, and dosage of radiation therapy and the studies observation period (32, 33). The median period for developing radiation-induced cystitis is given with 36 months after radiation therapy for prostate cancer treatment. Nonetheless, acute bladder toxicity symptoms can also occur in a shorter period of time (29, 34). Incidences of hemorrhagic cystitis range from 2.6 to 12.1% in prostate cancer patients primary treated with radiation therapy, depending on the duration of follow up (35–37). The median time to the appearance of hemorrhagic cystitis range from 48 to 79 months in the current literature (37, 38).

Management

Treatment of radiation-associated bladder toxicity depends on the severity and derogation of quality of life for patients. It has to be emphasized, that sufficient randomized trials are lacking and most treatment options are based on small sample size (29). Suggested treatment options comprise simple bladder irrigation, cystoscopic fulguration, intravesical treatment with alum or formalin, hydrodistention, or hyperbaric oxygen therapy (39). Internal iliacal artery embolization can be taken into consideration if hematuria is intractable and contraindication exist regarding a definite surgical solution with cystectomy. However, success rate vary widely and a non-neglectable amount of patients is prone to further interventions (40).

Cystectomy with urinary diversion can be seen as the last resort of *end-stage bladder* following radiation therapy and reduced quality of life due to persisting patients' suffering. Urinary diversions in form of (ileum)-conduit and ureterocutaneostomies were preferred types of urinary diversion in most studies (41–43). In a retrospective review by Faris et al. ($n = 30$), analyzing treatment patterns of patients undergoing urinary diversion following radiation therapy for prostate cancer, four out of five *end-stage bladder* patients (80%) underwent cystectomy with conduit diversion. Conversely, suprapubic catheter was placed in the remaining 20%. Similar distributions could be observed for patients suffering *devastated-bladder outlet* or a combination of both in this case series (41). In line with these findings, Sack et al. demonstrated in a case series of 15 patients undergoing urinary diversion following radiation therapy of prostate cancer, that cysto(-prostat)ectomy followed by a ileum conduit was the most frequently administered type of urinary diversion in this cohort (88%) (43). Ureteroileal stricture is more often seen in irradiated patients undergoing ileal conduit as a form of urinary diversion. Gontero et al. (44) demonstrated an ureteroileal stricture rate of 9.4%, whereas, non-irradiated control groups presented with significant less rates (45). One should bear in mind, that this was a case series of 643 patients receiving a cystectomy with a radiation therapy due to different oncological tumors (prostate cancer, bladder cancer, colon cancer).

It is of note that technical developments of radiation therapy took place within the recent years with respect to more precise delivery of the dosage and hypofraction was introduced for the treatment of prostate cancer. These developments may hopefully translate into less occurrence of end-stage bladders in the future and makes it crucial for reassessment of the radiation therapy-related data in the following years.

URORECTAL AND VESICOCUTANEOUS FISTULAE

Definition, Etiology, and Clinical Presentation

Urorectal fistula is a well-known, but fortunately, uncommon complication of the treatment for prostate cancer with radical prostatectomy or radiation therapy (46). Besides radiation therapy (47) and iatrogenic damage of the rectum during radical prostatectomy (48), salvage prostatectomies after failure of radiation therapy (49), and a transperitoneal radical prostatectomy approach (47) are described risk factors to develop urorectal fistula. Especially, post-prostatectomy fistula often involve a direct track from vesicourethral anastomosis into the rectum (14). Radiation therapy increases the complexity of urorectal fistula, leaving the surrounding tissue ischemic and scared, often combined with cavitation. In general, radiation therapy-associated fistula tend to have a larger diameter and longer fistula-tracks (50). Common symptoms in regards to urorectal fistulae are pneumaturia (75%), faecaluria (63%), und recurrent urinary tract infections (57%) (51). Severe rectal or pelvic pain can furthermore be among the leading symptom (52).

Diagnosis and Investigations

Diagnostic workup should include a thoroughly medical history taking and clinical examination. Furthermore, a retrograde urethrogram combined with a micturition-cystourography should be done. Standard, but mandatory, radiographical imaging must be performed in anterior-posterior and lateral recording in order to detect a potential fistula-track running dorsally (53). Additionally, diagnostic urethrocystoscopy seems essential to confirm and determine the size and location of the fistula and its relationship to the orifices and exclude concomitant

urethral anomalies. To elucidate the length, size, and precise location of the fistula, rectoscopy, and contrast-agent based imaging of the rectum- and colon should also be performed (54). By using MRI, uncertainties, including potential concomitant fistula cavities and quality of surrounding tissue, can be ruled out prior to decision making for surgical treatment (50, 55).

Epidemiology

The reported incidence of urorectal fistula is fairly uncommon and appears between 0.1 and 2% in recent literature (48, 56, 57). Patients undergoing salvage prostatectomy (58) or salvage HIFU-therapy (59) are at highest risk (1–3 and 5%, respectively) of developing an urorectal fistula. An extremely rare complication of fistula are vesicocutaneous fistulae following radiation therapy and reported solely in case reviews and are only included in this review for the sake of completeness (60, 61).

Management

Spontaneous healing of urorectal fistulae following a conservative treatment is unlikely and should be critically discussed with the patient (62). Nevertheless, an intermittent suprapubic catheter should be inserted to minimize local irritation (63). Radiation-associated fistula tend to have even less chances of a spontaneous healing within a conservative management, due to the above mentioned pathophysiology (57).

Excision is the first step in the surgical treatment of urorectal fistulae and can be performed *via* different surgical approaches: Transanorectal sphincter splitting (York/Mason approach), peri-anal rectal advancement flap (Park approach), transabdominal, and perineal are established surgical procedures. Especially the two latter approaches reported sufficient success rates between 60 and 100% in case series, including 18 and 37 patients (55, 62, 64, 65). If possible, interposition of vital tissue (as above stated, e.g., Omentum flap, M. gracilis flap) should be performed and contribute to lower rates of fistula recurrences (66).

The effect of prior radiation therapy on the surgical outcome for urorectal fistulae was remarkably demonstrated by Linder et al. In their retrospective cases series of 42 patients diagnosed between 1998 and 2010, 16 patients with urorectal fistula had no history of radiation. Conversely, 26 patients were exposed to radiation therapy following prostate cancer treatment. Noteworthy, a primary repair (defined as surgical fistula excision and restoration of the natural urine outlet) was more frequently administered (94 vs. 21%) and more successful in the cohort of non-radiated patients (87 vs. 17%). Management of patients with prior radiation and urorectal fistula resulted very often in a permanent urinary diversion (93%) with concomitant permanent colostomy (86%) (52).

Irrespective the high success rates for successful primary repair of urorectal fistula in non-radiated patients, those with a history of radiation therapy are at high risk to fail a repair attempt and should be managed with a urinary diversion with or without a (temporal) bowel diversion (52). Furthermore, for urorectal fistula, a multidisciplinary approach is necessary for best treatment results and patient's care. Specifically, urologists, general surgeons, and dietary therapists should work hand in hand.

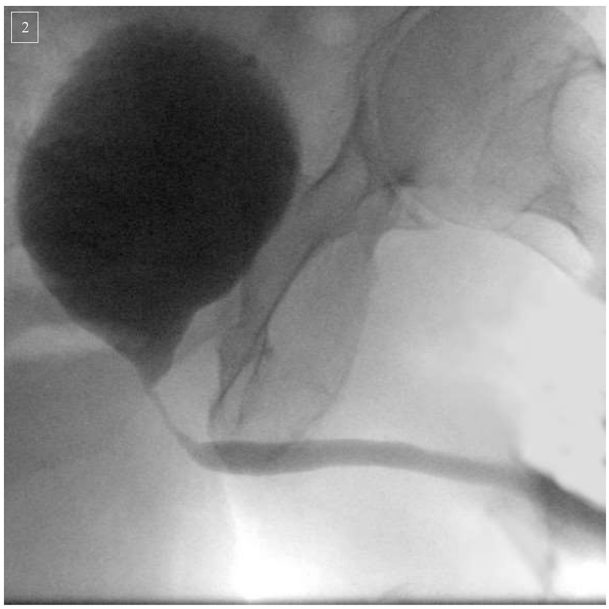

FIGURE 2 | Micturition-cystourography of a 74-year-old patient suffering of an infra/intersphincteric urethral stricture following robotic-assisted radical prostatectomy (2016) and adjuvant radiation (2017) therapy for prostate cancer. Urethroplasty with mucosal ventral-onlay graft was successfully performed.

VESICOURETHRAL ANASTOMOSIS STENOSIS, BLADDER NECK CONTRACTURE, AND URETHRAL STRICTURES

Definition, Etiology, and Clinical Presentation

Vesicourethral anastomosis stenosis, bladder neck contracture (or also described as bladder neck stenosis) and urethral strictures can be seen as complications following all types of prostate cancer treatment (67). All complications can be seen as a result of luminal constriction caused by tissue fibrosis (5). The term "stricture" – according to recent definitions — is used if the narrowing part of the urethra is surrounded by corpus spongiosum, including fossa navicularis, penile, and bulbar urethra. All other locations with narrowed diameter are defined as "stenosis" (5). Unfortunately, the past literature has not been differentiating between vesicourethral anastomosis stenosis and bladder neck contracture precisely. It should be highlighted, that a differentiation between bladder neck contracture, which can occur after surgical procedures for benign prostatic hyperplasia and vesicourethral anastomosis stenosis after radical prostatectomy, is inevitable, since anatomy, recurrence rates and functional outcomes differ significantly (68, 69). Since a small subgroup of PCa patients might receive a palliative endoscopic procedure, bladder neck contracture and urethral strictures are listed as

potential complications following PCa treatments, however, the majority of patients presenting with obstructive outlet following prostate cancer treatment will suffer of vesicourethral anastomosis stenosis. Patients suffering above mentioned post-prostate cancer treatment complications generally present with lower urinary tract symptoms, recurrent urinary tract infections, and slowing of the urinary stream in uroflowmetry (70). Furthermore, irritative symptoms with subjective residual urine are described (71).

Diagnosis and Investigations

The diagnostic work up begins with a thorough history and physical examination. The history should elicit prior (endoscopic) treatments, history of radiation therapy and presence of urinary incontinence. Laboratory evaluation consists of urine analysis to rule out hematuria or urinary tract infection (72). Additionally, uroflowmetry, measurement of post-void residual and evaluation of concomitant (in)continence should ideally be performed (63). More invasive diagnostic measurements should include diagnostic urethrocystoscopy and retrograde urethrogram combined with a micturition-cystourography (**Figure 2**). In certain instances, urodynamic testing can give further insight into the bladder capacity/compliance (13).

Epidemiology

Due to incongruent definitions and insufficient data, incidences for each localization can only vaguely be assessed. Based on the large-scale North American CaPSURE database, the overall incidence of urethral strictures and stenoses treatments following prostate cancer therapy, is 5.2% in the United States (73). However, no such large-scale databased analyses are currently available for European patients. In consequence, further, epidemiological research is needed to provide and improve information about the risk of the mentioned post-prostate cancer treatment related complications. The incidence of radiation therapy-induced urethral strictures and stenoses varies between 0 and 18% and is also affected by the delivered dosage and sort of radiation therapy (74). Specifically, in a review of more than 16,000 patients, the prevalence of strictures and stenoses was 2% after external beam radiation therapy (EBRT), 2% after brachytherapy and 5% after combination therapy with an median follow-up of 4 years (75). Other studies have reported an incidence rate of 12% urethral strictures or stenoses following a combined radiation therapy (EBRT plus brachytherapy) with an median follow up of 5 years (76). The main affected location of the male urethra seems to be the bulbomembranous urethra, followed by the bladder neck (77). Following a study by Msezane et al. (78), incidences of vesicourethral anastomosis stenosis after open radical prostatectomy and robot-assisted radical prostatectomy are given with 5.1 vs. 1.4%. Notably, initial incidence of stenosis occurred in ∼30% cases at the beginning era of radical prostatectomy several decades ago. Improvement of surgical techniques in the recent years have been translated into lower stenosis rates in the recent decades. Surgical-induced stenoses occur mostly within 12 months after radical prostatectomy. Conversely, radiation therapy-induced strictures and stenoses tend to occur later on and in a more insidious fashion, up to 2–3 years after radiation therapy for prostate cancer treatment (73). Those specific time information have to be taken into account by physicians, when stricture/stenosis is suspected.

Management

For the specific treatment of vesicourethral anastomosis stenosis after prostate cancer treatment, several different surgical approaches can be applied. Besides endoscopic dilatation, incision, or resection, open urethroplasty is a well-established surgical approach with satisfying clinical results and postoperative quality of life (79). It has to be mentioned, that results of urethroplasty in patients following radiation therapy tend to be less promising, but still remain the most favorable treatment option (71). Patients have to be informed prior to surgery, that by treating a stenosis a "hidden" incontinence can be demasked. Caused by the occurrence of the stenosis, patients can be classified as pseudo-continent after especially radical prostatectomy treatment of prostate cancer. In the first course of stenosis with endoscopic treatment, high rates of recurrences occur and increase with the number of redo endoscopic procedures. However, even the current gold standard of urethroplasties cannot always avoid recurrences. In combination with sphincteric damage, this state is often referred to as "devastated outlet" and is challenging for urologists, as well as patients (5).

Definite surgical solutions include bladder preservation with the closure of bladder neck and vesicostomy (continent vs. incontinent) with or without bladder augmentation. In a retrospective review by Faris et al. (41) evaluating 30 patients undergoing urinary diversion following radiation therapy for prostate cancer, *devastated outlet,* or a combination of *devastated outlet plus end-stage bladder* were the underlying cause for urinary diversion in almost the half of the cases (47%). Patients underwent 4 to 5 operative interventions aimed at salvage of lower urinary tract function, before receiving urinary diversion. The majority of patients (75%) suffering of devastated outlet received a cystectomy with conduit as a urinary diversion in this case series (41). In line with this single-center review, Bassett et al. confirmed in a multi-center case series of 100 patients undergoing urinary diversion following radiation therapy, vesicourethral anastomosis stenosis, and urethral strictures was in half of the patients (52%) the underlying cause of urinary diversion. A further differentiation regarding the exact location was not performed, however. Predominantly, patients underwent cystectomy (83%) with a conduit (84%) as urinary diversion. Noteworthy, Grade 3a or greater Clavien-Dindo complications occurred in 35% ($n = 31$) of these men, including four deaths (80). Complication rates for urinary diversion after irradiated prostate cancer patients are considerable, yet pros and cons must be carefully weighed up for each patient. Therefore older, multimorbid patients might benefit

using suprapubic urinary diversion with a permanent suprapubic catheter (81, 82).

URINARY INCONTINENCE

Definition, Etiology, and Clinical Presentation

Many patients prior to prostate cancer treatment decision making are concerned of post-treatment urinary incontinence. It is proven that urinary incontinence increases the risk of anxiety and depression and is associated with a lower healthcare related quality of life (83). Incontinence after prostate cancer treatment includes stress incontinence, urge incontinence and mixed incontinence (84). Especially, urinary incontinence after radical prostatectomy is mostly based on stress incontinence. However, patients can also simultaneously develop urge incontinence, which is related to a detrusor overactivity (85). Since surgical techniques improved in the recent years, stress urinary incontinence is less frequently observed after radical prostatectomy (86).

Following radiation therapy of the prostate for prostate cancer treatment, inflammatory changes can lead to a nociceptive response that may manifest as bladder detrusor overactivity, resulting in a urge incontinence (87). Definitions regarding incontinence following prostate cancer treatment, vary throughout the medical literature. Most commonly, continence is defined by no usage or usage of only one safety pad/24 h. Other definitions focus on the amount of urine loss, defining 2 g of urine loss/24 h or less as continent (88). Involuntary und uncontrollable leakage of urine is one of the bothersome symptoms of urinary incontinence. Furthermore, recurrent urinary tract infections and incontinence-associated dermatitis can additionally occur (83).

Diagnosis and Investigations

Diagnostic work-up should include the medical history with focus on potential pretreatment incontinence and risk-factors. Specifically, a thorough physical examination and evaluation of the severity and type of incontinence needs to be done. Besides a precise mictionary diary, validated tools such as questionnaires (ICIQ-UI SF, M-ISI) and pad-tests should be performed (89–91). Due to its replicability, the 24-h pad-test is stated to be the most accurate pad-test to quantify urinary incontinence (92). Additional urine analyses can also rule out the prevalence of urinary infection. Moreover, diagnostic urethrocystoscopy should be performed to visually examine the bulbomembraneous urethra, external sphincter, and vesicourethral anastomosis. Although, its routine adoption is controversial discussed, urodynamic investigations can be used to determine the maximum bladder capacity and degree of bladder overactivity (93), giving important insights into the underlying type of urinary incontinence. Due to continued recovery to continence up to 12 months following radical prostatectomy, urodynamics

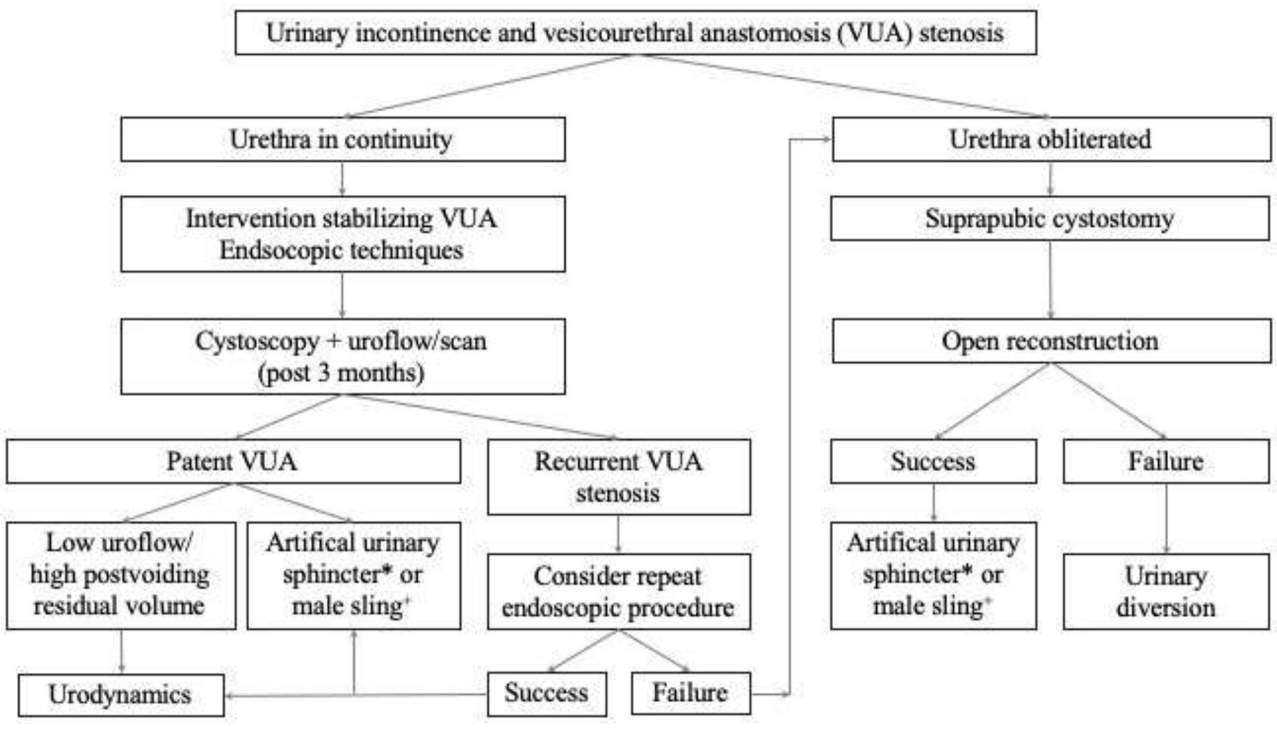

FIGURE 3 | Suggested algorithm for the management of the incontinent patient with a concomitant vesicourethral anastomosis stenosis following prostate cancer treatment. *Artificial urinary sphincter preferably for patients with a history of radiation therapy. +Male sling preferably for patients without a history of radiation therapy.

investigations probably should be performed not earlier than 12 months after surgery unless other urgent circumstances exist (93).

Epidemiology

Depending on stringency of definition, as well as the time point of its assessment, reported rates of stress incontinence after radical prostatectomy range widely from 2.9 and 87% (93). Recent data suggest an average long-term stress urinary incontinence rate after robot-assisted radical prostatectomy of 8–16% with above mentioned variability based on definition, surgical technique and skill level (88, 94). A study by Nam et al. (95) investigated, that ∼5% of radical prostatectomy (open and laparoscopic approach) will require artificial urinary sphincter or male sling within 15 years after prostate cancer treatment. Additionally, overactive bladder symptoms can be present in up to 77% of patients following radical prostatectomy. However, during the first year after prostate cancer treatment, most of these symptoms resolve spontaneously (96).

Following a study by Pinkawa et al. (97), radiation therapy-induced urinary incontinence (defined as usage of pads) ranges between 8 and 15% after 5 years of follow up. Due to different radiation therapy modalities, radiation dosage and differing follow-up periods, issuing a precise statement regarding incidence rates of urinary incontinence following radiation therapy, is difficult (98).

Management

Management options of urinary incontinence have a wide range and can be stratified into conservative and surgical treatment options. If conservative management fails to sufficiently improve the incontinence situation and quality of life, subsequent surgical procedures need to be applied (84). Prior to surgery, concomitant problems, such as predominant overactive/small capacity bladder, vesicourethral anastomosis stenosis, or urethral strictures, must be excluded (84). Surgical treatment mainly includes the implantation of male sling systems or artificial urinary sphincter devices, the latter being the gold standard for males suffering of stress incontinence (99). Incontinent patients with a concomitant vesicourethral anastomosis stenosis should be managed gradually, treating the stenosis first. **Figure 3** demonstrates a potential algorithm for this subgroup of patients. Success of an artificial urinary sphincter device is not only based on the expertise of the surgeon, but also on a precise and thorough selection of patients, who will be eligible and might benefit of it. Prior to sphincter implantation, concomitant vesicourethral anastomosis stenosis, and urethral stricture should be ruled out with a urethrocystoscopy which also helps to determine sphincteric damage (74). Furthermore, bladder detrusor overactivity must not be apparent during the first 300 ml of bladder filling in urodynamic investigations (99). Manual dexterity and mental ability for the usage of an artificial urinary sphincter must be ensured prior to device implantation (100). Due to clinical experience, a small, yet undeniable proportion of patients do not qualify for sphincteric implantation following above mentioned requirements. Some of them even present with a combination of urinary incontinence and vesicourethral anastomosis stenosis. Within this situation of a *devastated bladder outlet* urinary diversion can be seen as the final, yet definite treatment option. In different case series evaluating urinary diversions following prostate cancer treatment, *devastated bladder outlet* was among the major underlying causes to undergo urinary diversion. Cystectomy with ileum conduit was the preferred type of urinary diversion (80%) in a small case series of patients undergoing urinary diversion due to prostate cancer treatment complications (41). Cystectomy should usually be performed to prevent complications associated with leaving the bladder *in situ* with a closed bladder outlet (6).

RADIATION THERAPY AS A RISK FACTOR

Since a large body of evidence showed that pelvic surgery after radiation therapy is associated with a high risk of complications, we dedicated a specific paragraph on this important topic (44, 101–103). When it comes to the appropriate selection of tissue used for the urinary diversion, special caution needs to be administered in prostate cancer patient with an history of prior radiation therapy. In regards to the type of radiation therapy, collateral damage to the surrounding tissue is still often unavoidable and can cause progressive tissue ischemia, fibrosis and prolonged healing capabilities (104). From a urological point of view, usage of viable bowel outside the radiation field for urinary diversion, often referred as "stay away" principle, is elementary for a successful procedure (105). In line with published data, usage of non-irradiated intestine should be aimed at and preferably used in patients previously radiated in the pelvis, especially if a continent urinary diversion is seeked (41, 102, 106, 107).

Stolzenburg et al. (108) demonstrated in a case series of 24 female patients undergoing urinary diversion following radiation therapy, that usage of MAINZ-Pouch III can safely be performed with comparable outcomes to non-irradiated patients. As the MAINZ-Pouch III is in the upper abdomen, ureters can be cut at a very high level, thus ensuring an excellent blood supply. It has to be mentioned, that these patients were female patients mainly undergoing urinary diversion following a gynecological tumor treatment (108). By contrast, Wilkin et al. demonstrated in a long-time follow up of female patients with an INDIANA-Pouch following radiation therapy, feasibility of using both ileal and colon in irradiated patients. However, one has to highlight, that compared to non-irradiated patients, higher rates of complications and a significant increase in specific redo-surgery were observed (109). Above mentioned results can in general be transferred to prostate cancer patients undergoing urinary diversion strengthening the usage of non-irradiated tissue.

CONCLUSION

With regards to an increasing global population, aging society, and improving prostate cancer treatment options, urologists will fortunately see more prostate cancer survivors than the generations before. New multimodal and focal therapies are likely to improve this positive and encouraging trend, but will also

result in an increase of complications and side effects. Above painted scenarios of complications following prostate cancer treatment are statistically scarce, however, can be recalcitrant and frustrating for both patients and physicians. Decision-making should be performed in a multidisciplinary team and need to include the patient. Urinary diversion must be seen unarguably as a last resort. Even though, current literature lacks of reliable data regarding improvements in quality of life in form of PROMs, above mentioned case reports/study indicate beneficial improvements for patients' quality of life. Whenever possible, bowel for urinary diversion outside the field of prior radiation therapy should be used.

AUTHOR CONTRIBUTIONS

BH and MW: manuscript writing/editing, protocol/project development, and data analysis. SM: protocol/project development. LK: protocol/project development and manuscript writing/editing. All authors contributed to the article and approved the submitted version.

REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. (2018) 68:394–424. doi: 10.3322/caac.21492
2. Mottet N, Cornford P, van den Bergh RCN, Briers E, De Santis M, Fanti S, et al. *EAU Guidelines for Prostate Cancer*. Amsterdam: EAU Annual Congress. (2020).
3. Wenzel M, Borgmann H, Von Hardenberg J, Cash H, Welte MN, Bründl J, et al. Acceptance, indications, and chances of focal therapy in localized prostate cancer: a real-world perspective of urologists in Germany. *J Endourol*. (2020) 35:444–50. doi: 10.1089/end.2020.0774
4. Mohler JL, Antonarakis ES, Armstrong AJ, D'Amico AV, Davis BJ, Dorff T, et al. Prostate cancer, version 2.2019, NCCN clinical practice guidelines in oncology. *J Nat Comprehens Cancer Netw*. (2019) 17:479–505. doi: 10.6004/jnccn.2019.0023
5. Nicholson HL, Al-Hakeem Y, Maldonado JJ, Tse V. Management of bladder neck stenosis and urethral stricture and stenosis following treatment for prostate cancer. *Transl Androl Urol*. (2017) 6(Suppl. 2):S92–102. doi: 10.21037/tau.2017.04.33
6. Riedmiller H, Kocot A. The devastated bladder outlet: treatment options. *Curr Opin Urol*. (2015) 25:352–6. doi: 10.1097/MOU.0000000000000185
7. Kavanagh A, Afshar K, Scott H, MacNeily AE. Bladder neck closure in conjunction with enterocystoplasty and mitrofanoff diversion for complex incontinence: closing the door for good. *J Urol*. (2012) 188(Suppl. 4):1561–6. doi: 10.1016/j.juro.2012.02.027
8. Spahn M, Kocot A, Loeser A, Kneitz B, Riedmiller H. Last resort in devastated bladder outlet: bladder neck closure and continent vesicostomy—long-term results and comparison of different techniques. *Urology*. (2010) 75:1185–92. doi: 10.1016/j.urology.2009.11.070
9. Kocot A. Der zerstörte Blasenauslass ("devastated bladder outlet") – suprapubischer Katheter vs. Rekonstruktion. *Urologe*. (2020) 59:408–15. doi: 10.1007/s00120-020-01153-5
10. Hoebeke P, De Kuyper P, Goeminne H, Van Laecke E, Everaert K. Bladder neck closure for treating pediatric incontinence. *Eur Urol*. (2000) 38:453–6. doi: 10.1159/000020323
11. Shpall AI, Ginsberg DA. Bladder neck closure with lower urinary tract reconstruction: technique and long-term followup. *J Urol*. (2004) 172(6 Pt. 1):2296–9. doi: 10.1097/01.ju.0000144072.15735.32
12. Smith EA, Kaye JD, Lee JY, Kirsch AJ, Williams JK. Use of rectus abdominis muscle flap as adjunct to bladder neck closure in patients with neurogenic incontinence: preliminary experience. *J Urol*. (2010) 183:1556–60. doi: 10.1016/j.juro.2009.12.044
13. Mundy AR, Andrich DE. Posterior urethral complications of the treatment of prostate cancer. *BJU Int*. (2012) 110:304–25. doi: 10.1111/j.1464-410X.2011.10864.x
14. Bugeja S, Andrich DE, Mundy AR. Fistulation into the pubic symphysis after treatment of prostate cancer: an important and surgically correctable complication. *J Urol*. (2016) 195:391–8. doi: 10.1016/j.juro.2015.08.074
15. Kahokehr AA, Boysen WR, Schild MH, Nosé BD, Huang J, Eward W, et al. Urinary pubic symphysis fistula leads to histopathologic osteomyelitis in prostate cancer survivors. *Urology*. (2020) 148:297–301. doi: 10.1016/j.urology.2020.07.038
16. Degheili JA, Mansour MM, Nasr RW. Symphysis pubis osteomyelitis: an uncommon complication after robotic assisted radical prostatectomy—case description with literature review. *Case Rep Urol*. (2018) 2018:5648970. doi: 10.1155/2018/5648970
17. Gupta S, Zura RD, Hendershot EF, Peterson AC. Pubic symphysis osteomyelitis in the prostate cancer survivor: clinical presentation, evaluation, and management. *Urology*. (2015) 85:684–90. doi: 10.1016/j.urology.2014.11.020
18. Moore DC, Keegan KA, Resnick MJ, Eisenberg R, Holt GE, Cookson MS. A 57-year-old man with a history of prostatectomy and pelvic irradiation presents with recurrent urinary tract infections, hematuria, and pelvic pain. *Urology*. (2013) 81:221–5. doi: 10.1016/j.urology.2012.10.037
19. Davis NF, Torregiani W, Thornhill J. Osteitis pubis after standard bipolar TURP surgery: insight into aetiology, diagnosis, management and prevention of this rarity. *BMJ Case Rep*. (2016) 2016:bcr2015212420. doi: 10.1136/bcr-2015-212420
20. Sexton SJ, Lavien G, Said N, Eward W, Peterson AC, Gupta RT. Magnetic resonance imaging features of pubic symphysis urinary fistula with pubic bone osteomyelitis in the treated prostate cancer patient. *Abdom Radiol*. (2019) 44:1453–60. doi: 10.1007/s00261-018-1827-2
21. Matsushita K, Ginsburg L, Mian BM, De E, Chughtai BI, Bernstein M, et al. Pubovesical fistula: a rare complication after treatment of prostate cancer. *Urology*. (2012) 80:446–51. doi: 10.1016/j.urology.2012.04.036
22. Kanthabalan A, Peters M, Van Vulpen M, McCartan N, Hindley RG, Emara A, et al. Focal salvage high-intensity focused ultrasound in radiorecurrent prostate cancer. *BJU Int*. (2017) 120:246–56. doi: 10.1111/bju.13831
23. Kapogiannis F, Fasoulakis K, Tsiampa E, Triantafyllou S, Fasoulakis C. Prostatosymphyseal fistula after photoselective vaporization of the prostate: a very rare complication of a transurethral surgery. *Cureus*. (2020) 12:e7703. doi: 10.7759/cureus.7703
24. Nosé BD, Boysen WR, Kahokehr AA, Inouye BM, Eward WC, Hendershot EF, et al. Extirpative cultures reveal infectious pubic bone osteomyelitis in prostate cancer survivors with Urinary-Pubic Symphysis Fistulae (UPF). *Urology*. (2020). 142:221–5. doi: 10.1016/j.urology.2020.04.095
25. Mundy AR, Andrich DE. Urorectal fistulae following the treatment of prostate cancer: urorectal fistulae after prostate cancer treatment. *BJU International*. (2011) 107:1298–303. doi: 10.1111/j.1464-410X.2010.09686.x
26. Villeirs L, Tailly T, Ost P, Waterloos M, Decaestecker K, Fonteyne V, et al. Hyperbaric oxygen therapy for radiation cystitis after pelvic radiotherapy: Systematic review of the recent literature. *Int J Urol*. (2020). 27:98–107. doi: 10.1111/iju.14130
27. Manikandan R, Kumar S, Dorairajan LN. Hemorrhagic cystitis: a challenge to the urologist. *Indian J Urol*. (2010) 26:159–66. doi: 10.4103/0970-1591.65380
28. Liem X, Saad F, Delouya G. A practical approach to the management of radiation-induced hemorrhagic cystitis. *Drugs*. (2015) 75:1471–82. doi: 10.1007/s40265-015-0443-5
29. Mühlstädt S, Mohammed N, Weigand K, Schumann A, Kawan F, Göllert C, et al. [Radiation cystitis : Pathophysiology treatment]. *Urologe*. (2017) 56:301–5. doi: 10.1007/s00120-017-0319-2

30. Abern MR, Aronson WJ, Terris MK, Kane CJ, Presti JC, Amling CL, et al. Delayed radical prostatectomy for intermediate-risk prostate cancer is associated with biochemical recurrence: possible implications for active surveillance from the SEARCH database. *Prostate*. (2013) 73:409–17. doi: 10.1002/pros.22582
31. Shah SK, Lui PD, Baldwin DD, Ruckle HC. Urothelial carcinoma after external beam radiation therapy for prostate cancer. *J Urol*. (2006) 175:2063–6. doi: 10.1016/S0022-5347(06)00324-7
32. Browne C, Davis NF, Mac Craith E, Lennon GM, Mulvin DW, Quinlan DM, et al. A narrative review on the pathophysiology and management for radiation cystitis. *Adv Urol*. (2015) 2015:346812. doi: 10.1155/2015/346812
33. Marks LB, Carroll PR, Dugan TC, Anscher MS. The response of the urinary bladder, urethra, and ureter to radiation and chemotherapy. *Int J Radiat Oncol Biol Phys*. (1995) 31:1257–80. doi: 10.1016/0360-3016(94)00431-J
34. Rapariz-González M, Castro-Díaz D, Mejía-Rendón D, EURCIS. Evaluation of the impact of the urinary symptoms on quality of life of patients with painful bladder syndrome/chronic pelvic pain and radiation cystitis: EURCIS study. *Actas Urol Esp*. (2014) 38:224–31. doi: 10.1016/j.acuroe.2014.02.008
35. Afonso-João D, Pacheco-Figueiredo L, Antunes-Lopes T, Morgado LA, Azevedo V, Vendeira L, et al. Cumulative incidence and predictive factors of radiation cystitis in patients with localized prostate cancer. *Acta Urol Español*. (2018) 42:256–61. doi: 10.1016/j.acuroe.2018.03.006
36. Haldar S, Dru C, Bhowmick NA. Mechanisms of hemorrhagic cystitis. *Am J Clin Exp Urol*. (2014) 2:199–208.
37. Martin SE, Begun EM, Samir E, Azaiza MT, Allegro S, Abdelhady M. Incidence and morbidity of radiation-induced hemorrhagic cystitis in prostate cancer. *Urology*. (2019) 131:190–5. doi: 10.1016/j.urology.2019.05.034
38. Fergany AF, Moussa AS, Gill IS. Laparoscopic cystoprostatectomy for radiation-induced hemorrhagic cystitis. *J Endourol*. (2009) 23:275–8. doi: 10.1089/end.2008.0432
39. Dautruche A, Delouya G. A contemporary review about the management of radiation-induced hemorrhagic cystitis. *Curr Opin Support Palliat Care*. (2018) 12:344–50. doi: 10.1097/SPC.0000000000000375
40. Comploj E, Pycha A, Trenti E, Palermo S, Bonatti M, Krause P, et al. Transarterial embolization in the management of intractable haemorrhage. *Urol Int*. (2020) 105:95–9. doi: 10.1159/000511123
41. Faris SF, Milam DF, Dmochowski RR, Kaufman MR. Urinary diversions after radiation for prostate cancer: indications and treatment. *Urology*. (2014) 84:702–6. doi: 10.1016/j.urology.2014.04.023
42. Kocot A, Riedmiller H. [Treatment of long-term radiation injuries in the urinary tract]. Urologe. (2015) 54:1765–71. doi: 10.1007/s00120-015-4011-0
43. Sack BS, Langenstroer P, Guralnick ML, Jacobsohn KM, O'Connor RC. Cystectomy and urinary diversion for the management of a devastated lower urinary tract following prostatic cryotherapy and/or radiotherapy. *WMJ*. (2016) 115:70–3.
44. Gontero P, Pisano F, Palou J, Joniau S, Albersen M, Colombo R, et al. Complication rate after cystectomy following pelvic radiotherapy: an international, multicenter, retrospective series of 682 cases. *World J Urol*. (2020) 38:1959–68. doi: 10.1007/s00345-019-02982-6
45. Ramani VAC, Maddineni SB, Grey BR, Clarke NW. Differential complication rates following radical cystectomy in the irradiated and non-irradiated pelvis. *Eur Urol*. (2010) 57:1058–63. doi: 10.1016/j.eururo.2009.12.002
46. Venkatesan K, Zacharakis E, Andrich DE, Mundy AR. Conservative management of urorectal fistulae. *Urology*. (2013) 81:1352–6. doi: 10.1016/j.urology.2012.10.040
47. Thomas C, Jones J, Jäger W, Hampel C, Thüroff JW, Gillitzer R. Incidence, clinical symptoms and management of rectourethral fistulas after radical prostatectomy. *J Urol*. (2010) 183:608–12. doi: 10.1016/j.juro.2009.10.020
48. Mandel P, Linnemannstöns A, Chun F, Schlomm T, Pompe R, Budäus L, et al. Incidence, risk factors, management, and complications of rectal injuries during radical prostatectomy. *Eur Urol Focus*. (2018) 4:554–7. doi: 10.1016/j.euf.2017.01.008
49. Rabbani F, Yunis LH, Pinochet R, Nogueira L, Vora KC, Eastham JA, et al. Comprehensive standardized report of complications of retropubic and laparoscopic radical prostatectomy. *Eur Urol*. (2010) 57:371–86. doi: 10.1016/j.eururo.2009.11.034
50. Rosenbaum CM, Vetterlein MW, Fisch M. [Fistula surgery]. *Urologe*. (2020) 59:489–98. doi: 10.1007/s00120-020-01167-z
51. Daniels IR, Bekdash B, Scott HJ, Marks CG, Donaldson DR. Diagnostic lessons learnt from a series of enterovesical fistulae. *Colorectal Dis*. (2002) 4:459–62. doi: 10.1046/j.1463-1318.2002.00370.x
52. Linder BJ, Umbreit EC, Larson D, Dozois EJ, Thapa P, Elliott DS. Effect of prior radiotherapy and ablative therapy on surgical outcomes for the treatment of rectourethral fistulas. *J Urol*. (2013) 190:1287–91. doi: 10.1016/j.juro.2013.03.077
53. Kluth LA, Dahlem R. Komplexe Fisteln der hinteren Harnröhre. In: Michel MS, Thüroff JW, Janetschek G, Wirth M, Herausgeber, editors. *Die Urologie*. Heidelberg: Springer Berlin Heidelberg. (2015). p. 1–18. doi: 10.1007/978-3-642-41168-7_98-1
54. Borchers H, Pinkawa M, Donner A, Wolter TP, Pallua N, Eble MJ, et al. Rectourethral fistula following LDR brachytherapy. *Urol Int*. (2009) 82:365–6. doi: 10.1159/000209374
55. Hanna JM, Turley R, Castleberry A, Hopkins T, Peterson AC, Mantyh C, et al. Surgical management of complex rectourethral fistulas in irradiated and non-irradiated patients. *Dis Colon Rectum*. (2014) 57:1105–12. doi: 10.1097/DCR.0000000000000175
56. Igel TC, Barrett DM, Segura JW, Benson RC, Rife CC. Perioperative and postoperative complications from bilateral pelvic lymphadenectomy and radical retropubic prostatectomy. *J Urol*. (1987) 137:1189–91. doi: 10.1016/S0022-5347(17)44445-4
57. Lane BR, Stein DE, Remzi FH, Strong SA, Fazio VW, Angermeier KW. Management of radiotherapy induced rectourethral fistula. *J Urol*. (2006) 175:1382–7; discussion 1387–8. doi: 10.1016/S0022-5347(05)00687-7
58. Theodorescu D, Gillenwater JY, Koutrouvelis PG. Prostatourethral-rectal fistula after prostate brachytherapy. *Cancer*. (2000) 89:2085–91. doi: 10.1002/1097-0142(20001115)89:10<2085::AID-CNCR8>3.0.CO;2-Q
59. Gotto GT, Yunis LH, Vora K, Eastham JA, Scardino PT, Rabbani F. Impact of prior prostate radiation on complications after radical prostatectomy. *J Urol*. (2010) 184:136–42. doi: 10.1016/j.juro.2010.03.031
60. Hennessey DB, Bolton E, Thomas AZ, Lynch TH. Vesicocutaneous fistula following adjuvant radiotherapy for prostate cancer. *BMJ Case Rep*. (2013) 2013:bcr2013008986. doi: 10.1136/bcr-2013-008986
61. Moreira SG, Seigne JD, Ordorica RC, Marcet J, Pow-Sang JM, Lockhart JL. Devastating complications after brachytherapy in the treatment of prostate adenocarcinoma. *BJU Int*. (2004) 93:31–5. doi: 10.1111/j.1464-410X.2004.04550.x
62. Ghoniem G, Elmissiry M, Weiss E, Langford C, Abdelwahab H, Wexner S. Transperineal repair of complex rectourethral fistula using gracilis muscle flap interposition–can urinary and bowel functions be preserved? *J Urol*. (2008) 179:1882–6. doi: 10.1016/j.juro.2008.01.021
63. Rosenbaum CM, Reiss CP, Borgmann H, Salem J, Fisch M, Huber J, et al. Management of anterior urethral strictures in adults: a survey of contemporary practice in Germany. *Urol Int*. (2017) 99:43–50. doi: 10.1159/000471928
64. Pfalzgraf D, Kluth L, Reiss P, Fisch M, Dahlem R. Staged urethroplasty: comparison of early functional results and quality of life in mesh graft and buccal mucosa technique. *Can J Urol*. (2015) 22:7720–6.
65. Voelzke BB, McAninch JW, Breyer BN, Glass AS, Garcia-Aguilar J. Transperineal management for postoperative and radiation rectourethral fistulas. *J Urol*. (2013) 189:966–71. doi: 10.1016/j.juro.2012.08.238
66. Harris CR, McAninch JW, Mundy AR, Zinman LN, Jordan GH, Andrich D, et al. Rectourethral fistulas secondary to prostate cancer treatment: management and outcomes from a multi-institutional combined experience. *J Urol*. (2017) 197:191–4. doi: 10.1016/j.juro.2016.08.080
67. Matta R, Chapple CR, Fisch M, Heidenreich A, Herschorn S, Kodama RT, et al. Pelvic complications after prostate cancer radiation therapy and their management: an international collaborative narrative review. *Eur Urol*. (2019) 75:464–76. doi: 10.1016/j.eururo.2018.12.003
68. Rosenbaum CM, Fisch M, Vetterlein MW. Contemporary management of vesico-urethral anastomotic stenosis after radical prostatectomy. *Front Surg*. (2020) 7:587271. doi: 10.3389/fsurg.2020.587271

69. Branche B, Crocerossa F, Carbonara U, Klausner AP, Roseman JT, Hampton LJ, et al. Management of bladder neck contracture in the age of robotic prostatectomy: an evidence-based guide. *Eur Urol Focus*. (2021) S2405–4569. doi: 10.1016/j.euf.2021.01.007. [Epub ahead of print].
70. Kovell RC, Terlecki RP. Management strategies for post-prostatectomy bladder neck contractures. *Curr Urol Rep*. (2015) 16:65. doi: 10.1007/s11934-015-0536-4
71. Vetterlein MW, Kluth LA, Zumstein V, Meyer CP, Ludwig TA, Soave A, et al. Buccal mucosal graft urethroplasty for radiation-induced urethral strictures: an evaluation using the extended Urethral Stricture Surgery Patient-Reported Outcome Measure (USS PROM). *World J Urol*. (2020) 38:2863–72. doi: 10.1007/s00345-020-03102-5
72. Rocco NR, Zuckerman JM. An update on best practice in the diagnosis and management of post-prostatectomy anastomotic strictures. *Ther Adv Urol*. (2017) 9:99–110. doi: 10.1177/1756287217701391
73. Elliott SP, Meng MV, Elkin EP, McAninch JW, Duchane J, Carroll PR, et al. Incidence of urethral stricture after primary treatment for prostate cancer: data From CaPSURE. *J Urol*. (2007) 178:529–34; discussion 534. doi: 10.1016/j.juro.2007.03.126
74. Herschorn S, Elliott S, Coburn M, Wessells H, Zinman L. SIU/ICUD Consultation on Urethral Strictures: Posterior urethral stenosis after treatment of prostate cancer. *Urology*. (2014) 83(Suppl. 3):S59–70. doi: 10.1016/j.urology.2013.08.036
75. Awad MA, Gaither TW, Osterberg EC, Murphy GP, Baradaran N, Breyer BN. Prostate cancer radiation and urethral strictures: a systematic review and meta-analysis. *Prostate Cancer Prostatic Dis*. (2018) 21:168–74. doi: 10.1038/s41391-017-0028-3
76. Khor R, Duchesne G, Tai K-H, Foroudi F, Chander S, Van Dyk S, et al. Direct 2-arm comparison shows benefit of high-dose-rate brachytherapy boost vs external beam radiation therapy alone for prostate cancer. *Int J Radiat Oncol Biol Phys*. (2013) 85:679–85. doi: 10.1016/j.ijrobp.2012.07.006
77. Mohammed N, Kestin L, Ghilezan M, Krauss D, Vicini F, Brabbins D, et al. Comparison of acute and late toxicities for three modern high-dose radiation treatment techniques for localized prostate cancer. *Int J Radiat Oncol Biol Phys*. (2012) 82:204–12. doi: 10.1016/j.ijrobp.2010.10.009
78. Msezane LP, Reynolds WS, Gofrit ON, Shalhav AL, Zagaja GP, Zorn KC. Bladder neck contracture after robot-assisted laparoscopic radical prostatectomy: evaluation of incidence and risk factors and impact on urinary function. *J Endourol*. (2008) 22:97–104. doi: 10.1089/end.2006.0460
79. Wenzel M, Krimphove MJ, Lauer B, Hoeh B, Müller MJ, Mandel P, et al. Is standardization transferable? Initial experience of urethral surgery at the University Hospital Frankfurt. *Front Surg*. (2020) 7:600090. doi: 10.3389/fsurg.2020.600090
80. Bassett MR, Santiago-Lastra Y, Stoffel JT, Goldfarb R, Elliott SP, Pate SC, et al. Urinary diversion for severe urinary adverse events of prostate radiation: results from a multi-institutional study. *J Urol*. (2017) 197(3 Pt. 1):744–50. doi: 10.1016/j.juro.2016.10.091
81. Hensle TW, Kirsch AJ, Kennedy WA, Reiley EA. Bladder neck closure in association with continent urinary diversion. *J Urol*. (1995) 154(2 Pt. 2):883–5. doi: 10.1016/S0022-5347(01)67194-5
82. Ullrich NFE, Wessells H. A technique of bladder neck closure combining prostatectomy and intestinal interposition for unsalvageable urethral disease. *J Urol*. (2002) 167(2 Pt. 1):634–6. doi: 10.1016/S0022-5347(01)69101-8
83. Coyne KS, Kvasz M, Ireland AM, Milsom I, Kopp ZS, Chapple CR. Urinary incontinence and its relationship to mental health and health-related quality of life in men and women in Sweden, the United Kingdom, and the United States. *Eur Urol*. (2012) 61:88–95. doi: 10.1016/j.eururo.2011.07.049
84. Das AK, Kucherov V, Glick L, Chung P. Male urinary incontinence after prostate disease treatment. *Can J Urol*. (2020) 27:36–43.
85. Groutz A, Blaivas JG, Chaikin DC, Weiss JP, Verhaaren M. The pathophysiology of post-radical prostatectomy incontinence: a clinical and video urodynamic study. *J Urol*. (2000) 163:1767–70. doi: 10.1016/S0022-5347(05)67538-6
86. Theissen L, Preisser F, Wenzel M, Humke C, Roos FC, Kluth LA, et al. Very early continence after radical prostatectomy and its influencing factors. *Front Surg*. (2019) 6:60. doi: 10.3389/fsurg.2019.00060
87. Zwaans BMM, Nicolai HG, Chancellor MB, Lamb LE. Challenges and opportunities in radiation-induced hemorrhagic cystitis. *Rev Urol*. (2016) 18:57–65. doi: 10.3909/riu0700
88. Ficarra V, Novara G, Rosen RC, Artibani W, Carroll PR, Costello A, et al. Systematic review and meta-analysis of studies reporting urinary continence recovery after robot-assisted radical prostatectomy. *Eur Urol*. (2012) 62:405–17. doi: 10.1016/j.eururo.2012.05.045
89. Moore K, Allen M, Voaklander DC. Pad tests and self-reports of continence in men awaiting radical prostatectomy: establishing baseline norms for males. *Neurourol Urodyn*. (2004) 23:623–6. doi: 10.1002/nau.20067
90. Suskind AM, Dunn RL, Morgan DM, DeLancey JOL, McGuire EJ, Wei JT. The Michigan Incontinence Symptom Index (M-ISI): a clinical measure for type, severity, and bother related to urinary incontinence. *Neurourol Urodyn*. (2014) 33:1128–34. doi: 10.1002/nau.22468
91. Wein AJ. ICIQ: a brief and robust measure for evaluating the symptoms and impact of urinary incontinence. *J Urol*. (2005) 173:908–9. doi: 10.1016/S0022-5347(05)60382-5
92. Karantanis E, Fynes M, Moore KH, Stanton SL. Comparison of the ICIQ-SF and 24-hour pad test with other measures for evaluating the severity of urodynamic stress incontinence. *Int Urogynecol J Pelvic Floor Dysfunct*. (2004) 15:111–6; discussion 116. doi: 10.1007/s00192-004-1123-2
93. Arcila-Ruiz M, Brucker BM. The role of urodynamics in post-prostatectomy incontinence. *Curr Urol Rep*. (2018) 19:21. doi: 10.1007/s11934-018-0770-7
94. Kang SG, Shim JS, Onol F, Bhat KRS, Patel VR. Lessons learned from 12,000 robotic radical prostatectomies: is the journey as important as the outcome? *Investig Clin Urol*. (2020) 61:1–10. doi: 10.4111/icu.2020.61.1.1
95. Nam RK, Herschorn S, Loblaw DA, Liu Y, Klotz LH, Carr LK, et al. Population based study of long-term rates of surgery for urinary incontinence after radical prostatectomy for prostate cancer. *J Urol*. (2012) 188:502–6. doi: 10.1016/j.juro.2012.04.005
96. Porena M, Mearini E, Mearini L, Vianello A, Giannantoni A. Voiding dysfunction after radical retropubic prostatectomy: more than external urethral sphincter deficiency. *Eur Urol*. (2007) 52:38–45. doi: 10.1016/j.eururo.2007.03.051
97. Pinkawa M, Gharib A, Schlenter M, Timm L, Eble MJ. Quality of life more than 10 years after radiotherapy for localized prostate cancer-impact of time after treatment and prescription dose. *Qual Life Res*. (2020) 30:437–43. doi: 10.1007/s11136-020-02639-7
98. Budäus L, Bolla M, Bossi A, Cozzarini C, Crook J, Widmark A, et al. Functional outcomes and complications following radiation therapy for prostate cancer: a critical analysis of the literature. *Eur Urol*. (2012) 61:112–27. doi: 10.1016/j.eururo.2011.09.027
99. Ahyai SA, Ludwig TA, Dahlem R, Soave A, Rosenbaum C, Chun FK-H, et al. Outcomes of single- vs double-cuff artificial urinary sphincter insertion in low- and high-risk profile male patients with severe stress urinary incontinence. *BJU Int*. (2016) 118:625–32. doi: 10.1111/bju.13449
100. Anger JT, Raj GV, Delvecchio FC, Webster GD. Anastomotic contracture and incontinence after radical prostatectomy: a graded approach to management. *J Urol*. (2005) 173:1143–6. doi: 10.1097/01.ju.0000155624.48337.a5
101. Ravi R, Dewan AK, Pandey KK. Transverse colon conduit urinary diversion in patients treated with very high dose pelvic irradiation. *Br J Urol*. (1994) 73:51–4. doi: 10.1111/j.1464-410X.1994.tb07455.x
102. Wammack R, Wricke C, Hohenfellner R. Long-term results of ileocecal continent urinary diversion in patients treated with and without previous pelvic irradiation. *J Urol*. (2002) 167:2058–62. doi: 10.1016/S0022-5347(05)65083-5
103. Segreti EM, Morris M, Levenback C, Lucas KR, Gershenson DM, Burke TW. Transverse colon urinary diversion in gynecologic oncology. *Gynecol Oncol*. (1996) 63:66–70. doi: 10.1006/gyno.1996.0280
104. Toia B, Seth J, Ecclestone H, Pakzad M, Hamid R, Greenwell T, et al. Outcomes of reconstructive urinary tract surgery after pelvic radiotherapy. *Scand J Urol*. (2019) 53:156–60. doi: 10.1080/21681805.2019.1611631

105. Pycha A, Trenti E. Hohe harnableitung nach bestrahlung im kleinen becken. *Urologe*. (2020) 59:416–25. doi: 10.1007/s00120-020-01156-2
106. Leissner J, Black P, Fisch M, Höckel M, Hohenfellner R. Colon pouch (Mainz pouch III) for continent urinary diversion after pelvic irradiation. *Urology*. (2000) 56:798–802. doi: 10.1016/S0090-4295(00)00789-5
107. Kim HL, Steinberg GD. Complications of cystectomy in patients with a history of pelvic radiation. *Urology*. (2001) 58:557–60. doi: 10.1016/S0090-4295(01)01269-9
108. Stolzenburg J-U, Schwalenberg T, Liatsikos EN, Sakelaropoulos G, Rödder K, Hohenfellner R, et al. Colon pouch (Mainz III) for continent urinary diversion. *BJU Int*. (2007) 99:1473–7. doi: 10.1111/j.1464-410X.2007.06767.x
109. Wilkin M, Horwitz G, Seetharam A, Hartenbach E, Schink JC, Bruskewitz R, et al. Long-term complications associated with the Indiana pouch urinary diversion in patients with recurrent gynecologic cancers after high-dose radiation. Urol Oncol. (2005) 23:12–5. doi: 10.1016/j.urolonc.2004.07.018

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STUDY PROTOCOL
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Anaesthesia in PROstate Biopsy Pain Obstruction Study: A Study Protocol for a Multicentre Randomised Controlled Study Evaluating the Efficacy of Perineal Nerve Block in Controlling Pain in Patients Undergoing Transperineal Prostate Biopsy

Bi-Ming He†, Rong-Bing Li† and Hai-Feng Wang on behalf of the APROPOS Group*

Department of Urology, Shanghai East Hospital, School of Medicine, Tongji University, Shanghai, China

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Edited by:
Luis Alex Kluth,
University Hospital Frankfurt, Germany

Reviewed by:
Pietro Pepe,
Cannizzaro Hospital, Italy
Mark Taratkin,
I.M. Sechenov First Moscow State Medical University, Russia

***Correspondence:**
Hai-Feng Wang
446720864@qq.com

†These authors have contributed equally to this work

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Introduction: Transperineal prostate biopsy is as effective as the transrectal biopsy in detecting prostate cancer and has a lower risk of infection. However, concerning the procedural pain of the transperineal route, a higher level of anaesthesia is needed, which prevents this approach from being widely used. Although several methods of local anaesthesia to relieve pain during transperineal biopsy have been described, few well-designed trials have been conducted to assess the efficacy of local anaesthesia.

Methods: This is a prospective, multicentre, randomised controlled study in men suspected of having prostate cancer and planning to undergo transperineal prostate biopsy. The aim of this trial is to determine whether the perineal nerve block and periprostatic block relieve pain to different extents in men undergoing transperineal biopsy. The main inclusion criteria are men aged between 18 and 80 years old, a prostate-specific antigen (PSA) level of 4–20 ng/ml, or/and suspicious rectal examination findings. A sample size of 190 participants, accounting for a 10% loss, is required. All participants will be randomly allocated at a ratio of 1:1 to the perineal nerve block ($n = 95$) and periprostatic block groups ($n = 95$). The primary outcome will be the level of the worst pain experienced during the transperineal prostate biopsy procedure, which will be measured by a numerical rating scale (NRS). The key secondary outcomes will include the pain severity score at 1, 6, and 24 h after prostate biopsy.

Results: The primary outcome is the level of the worst pain experienced during the prostate biopsy procedure. The main secondary outcomes are as follows: (1) Post-biopsy pain severity score at 1, 6, and 24 h after the prostate biopsy; (2) Changes in blood pressure, heart rate and breathing rate during the biopsy procedure; (3) External manifestations of pain during biopsy; (4) Anaesthesia satisfaction; (5) The detection rate for clinically significant prostate cancer and any prostate cancer.

Conclusion: Anaesthesia in PROstate biopsy Pain Obstruction Study (APROPOS) is randomised controlled trial aiming to determine the efficacy of the perineal nerve block in controlling pain in patients undergoing prostate biopsy *via* the transperineal approach.

Clinical Trial Registration: www.ClinicalTrials.gov, identifier: NCT04501055.

Keywords: prostate biopsy, transperineal, perineal nerve block, randomised controlled trial (RCT), pain

INTRODUCTION

Prostate cancer (PCa) is the second most frequently diagnosed malignancy and the fifth leading cause of death among males worldwide (1). Men with an elevated serum prostate-specific antigen (PSA) level and abnormal findings on digital rectal examinations (DREs) or transrectal ultrasonography (TRUS) examinations are usually suspected of having of prostate cancer. In the clinic, males who are suspected of having PCa typically undergo a prostate biopsy to obtain specimens for pathological diagnosis.

Prostate biopsies are mainly performed by either the transrectal or transperineal approach. Although these two methods differ little in the overall cancer detection rate (2, 3), the transperineal approach has a lower incidence of infection because the instrument is inserted from the perineum to the prostate, which avoiding damage to the rectal wall (4).

While the transperineal approach has merits, the severe pain caused by this approach has prevented its widespread use for prostate biopsies. Compared with the transrectal approach, thetransperineal approach causes more pain (5). Hence, unlike the transrectal approach, which can be performed under local anaesthesia only, transperineal biopsies require general anaesthesia in some cases (6), which takes more time, is costlier, and is associated with more anaesthesia-related risks. To date, several local anaesthesia methods for transperineal biopsy have been described (7–10). The periprostatic block procedure is the recommended and accepted method for patients undergoing a transperineal biopsy (11), although it was first described for use for the transrectal approach (12).

We describe a local anaesthesia method, the perineal nerve block, to reduce the procedural pain of transperineal biopsies; the method was developed on the basis of an anatomical study, and then a single-centre randomizedtrial was conducted to preliminarily verify its efficacy and safety (13). This method showed a reasonable positive effect on pain measured using a visual analogue scale (VAS). Hence, we plan to conduct this multicentre randomised controlled trial to confirm the findings and ensure the results are generalizable.

The aim of this trial is to compare the perineal nerve block and periprostatic block in terms of pain control in patients undergoing a prostate biopsy *via* the transperineal approach. The primary objective is to assess whether the perineal nerve block is superior to the periprostatic block in relieving the procedural pain related to transperineal biopsies.

TRIAL DESIGN

In this prospective, multicentre, randomised controlled trial, we anticipate to enrol 190 patients who are scheduled to undergo a transperineal prostate biopsy. The participants will be randomised to the perineal nerve block or periprostatic block groups.

The trial flow chart is shown in **Figure 1**, and the details and timeframe are shown in **Table 1**. The primary objective of this study is to assess the efficacy of the perineal nerve block compared with that of the periprostatic block in relieving pain.

OUTCOMES

The primary outcome is the level of the worst pain experienced during the prostate biopsy procedure Pain will be measured by a numerical rating scale (NRS) ranging from 0 to 10, where 0 represents no pain and 10 represents the worst pain imaginable. Additionally, we will measure the pain experienced during the phlebotomizing procedure, with the pain experienced when the needle first touches the skin at the start of anaesthesia as the baseline or reference. Additionally, the adjusted NRS pain score (an adjusted score of 1 will be defined as the worst pain during the biopsy procedure minus the pain of phlebotomizing, and an adjusted of 2 will be defined as the worst pain during the biopsy procedure minus the pain of the needle first touching the skin at the start of anaesthesia) will be reported.

The main secondary outcomes are as follows:

- Post-biopsy pain severity score, for which pain will be evaluated by the NRS at 1, 6, and 24 h after the prostate biopsy.
- Changes in blood pressure, heart rate and breathing rate during the biopsy procedure, which will be measured and recorded by a multi-parameter monitor from 1 min prior to anaesthesia (initial value) to 1 min after the prostate biopsy. The change will be defined as the difference between the average value during the anaesthesia and biopsy procedures and the initial value. Additionally, the difference between the maximum value and the initial value will be assessed.
- External manifestations of pain during biopsy, which will be assessed by a research nurse who will be blinded to the block arm during the biopsy procedure. The pain assessment will be divided into five parts: the degree of facial expression (0 points for no particular expression or smile; 1 point for an occasional grimace or frown, a withdrawn expression, or a disinterested expression, 2 points for frequent or constant quivering chin or a clenched jaw), the degree of activity (0 points for lying quietly or being in a normal position, 1 point

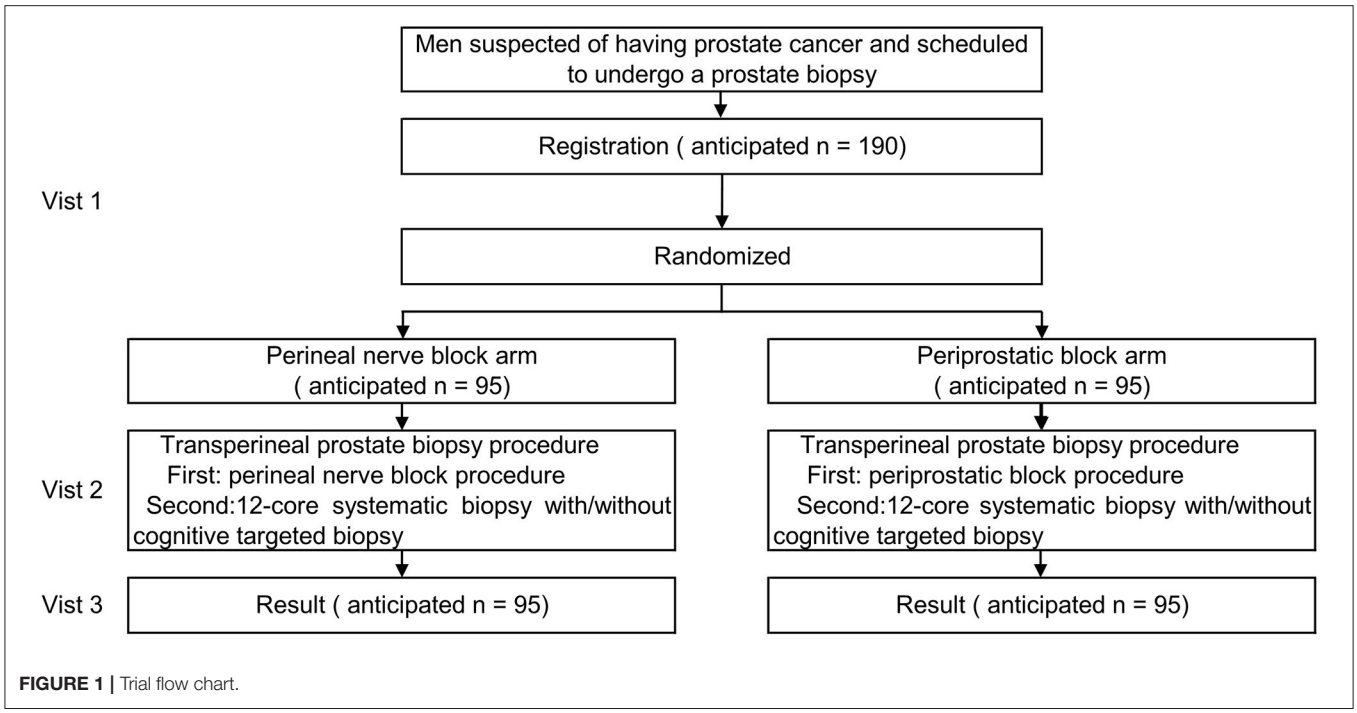


FIGURE 1 | Trial flow chart.

TABLE 1 | Timeline of the study protocol for participants.

	Contact with patient							
	Visit 1	Visit 2						Visit 3
	0	Pre-biopsy	Biopsy procedure	1-min post-biopsy	1-h post-biopsy	6 h post-biopsy	24 h post-biopsy	2 weeks post-biopsy
Consent	×							
Screening	×							
Baseline characteristic	×							
PSA	×							
MRI	×							
Randomisation	×							
Perineal nerve block (Perineal nerve block arm)		×						
Periprostatic block (Periprostatic block arm)		×						
Transperineal prostate biopsy (12-core systematic biopsy with/without cognitive targeted biopsy)			×					
Blood presure measurement		×	×	×				
Heart rate measurement		×	×	×				
Breath rate measurement		×	×	×				
External manifestations assessment			×					
NRS pain score assessment				×	×	×	×	
Anaesthesia satisfaction assessment							×	
Pathological assessment								×
Withdrawal	Complete as required at any time following registration							
SAE	Complete as required at any time following registration							

for slight contractions of the hip muscles or slight movements of hip, 2 points for severe contractions of the hip or lifting the hip out of the bed), the degree of voice expression (0 points for quiet or normal communication, 1 point for an occasional moan or weeping sound, 2 points for constant moaning or sobbing and screaming), the degree of pacification (0 points

for being peaceful and not requiring pacification, 1 point for being able to be comforted easily, 2 points for being difficult to comfort) and the degree of cooperation (0 points for being calm and cooperative, 1 point for language resistance, 2 points for body resistance).

- Anaesthesia satisfaction, or patient satisfaction with overall anaesthesia, which will be measured by a questionnaire at 24 h after the biopsy. Five items will be included to evaluate satisfaction: whether the pain during the biopsy was less severe than expected (scores from 0 to 10, where 0 represents far less severe, and 10 represents far more severe than expected); whether the pain after anaesthesia was less severe than the pain during anaesthesia (scores from 0 to 10, where 0 represents far less severe and 10 represent far more severe); weather the patient is satisfied with the overall feeling of the biopsy (scores from 0 to 10, where 0 represents the highest level of satisfaction, and 10 represents the lowest level of satisfaction); whether the patient would recommend this type of biopsy to other patients (scores from 0 to 10, where 0 represents they would highly recommend, and 10 represents they would definitely not recommend it); and whether the patient would still want to choose this way if they have to undergo another biopsy (scores 0 to 10, where 0 represents very willing to choose it and 10 represents extreme reluctance).
- The detection rate for prostate cancer, defined as the proportion of men with prostate cancer among those who undergo a prostate biopsy.
- The detection rate for clinically significant prostate cancer, defined as the proportion of men with prostate cancer of International Society of Urological Pathology (ISUP) grade 2 or higher, according to the 2014 ISUP classification, among men who undergo a prostate biopsy.
- Adverse events, which will be recorded 7 days after this trial. These events mainly include haematuria, vagal reflex, infection, urinary retention and other adverse events identified by the Common Terminology Criteria for Adverse Events (CTCAE).

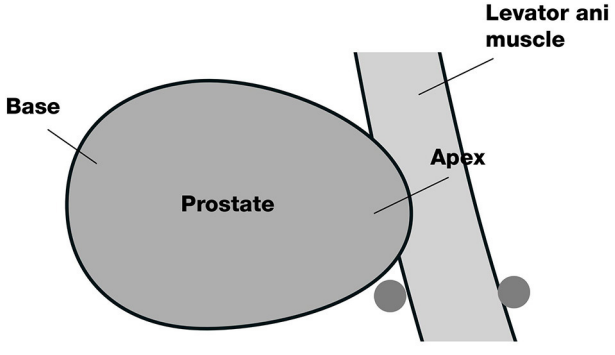


FIGURE 2 | Diagram of the location of the perineal nerve block: The 2 grey dots are the block sites.

METHODS AND ANALYSIS

Patient Population

Patients who fulfil all items of the inclusion criteria and exclusion criteria will be considered qualified to register for this trial. The inclusion criteria include an age between 18 and 80 years old, a PSA level of 4–20 ng/ml, and/or suspicious rectal examination findings. Volunteers will not be recruited if they have a history of an allergy to the study drug, symptomatic acute/chronic prostatitis or contraindications for a biopsy.

Randomisation

The participants who meet the criteria and sign the consent form will be allocated at a ratio of 1:1 to the perineal nerve block arm or periprostatic block arm by using block randomisation.

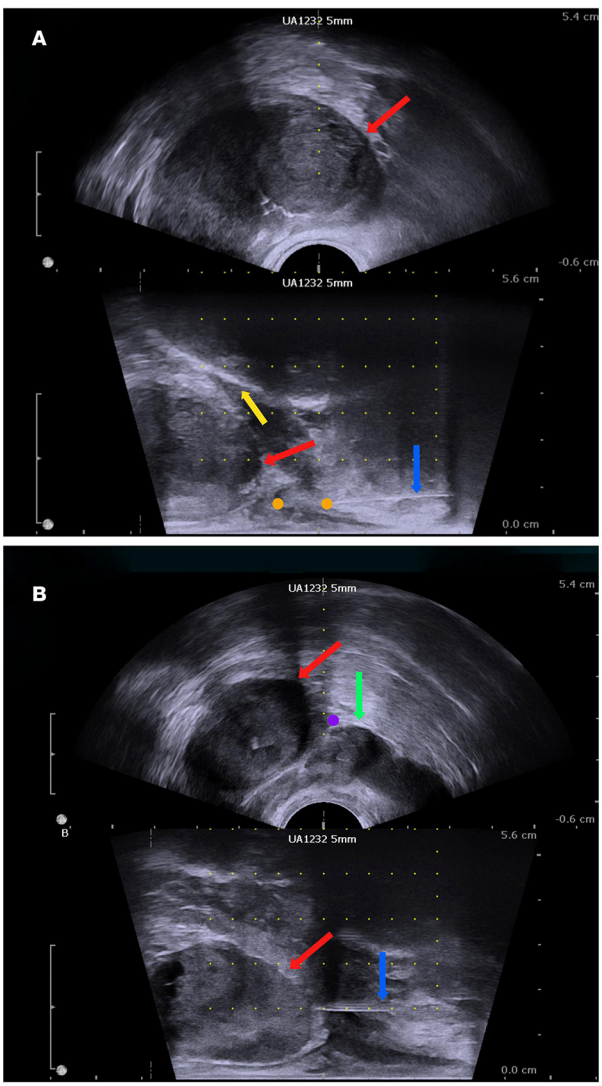


FIGURE 3 | The biplanar transrectal ultrasound image. **(A)** Perineal nerve block. **(B)** Periprostatic block: prostate (red arrow); pubis (yellow arrow); seminal vesicle (green arrow); anaesthesia needle (blue arrow); perineal nerve block site (orange dot); periprostatic site (purple dot).

The random sequence will be generated by the PROC PLAN statement of the SAS program and then sealed in envelopes. The randomised number will be known and kept by one research nurse and blinded to the others. The randomised number will be revealed to the urologist (the one who will perform anaesthesia) only when the participant has already entered the operation room for anaesthesia and the prostate biopsy.

INTERVENTIONS

Preparation Before the Block

All participants will be placed in the lithotomy position with a multi-parameter monitor. The participant's blood pressure, heart rate and breathing rate will be measured automatically every min, from 1 min before the anaesthesia procedure to 1 min after the prostate biopsy process. A urologist will be informed of which block method to perform on the spot after the research nurse open a sealed envelope.

Perineal Nerve Block Arm

The participants in this arm will undergo a perineal nerve block before a prostate biopsy. The insertion site on the skin will be located on the horizontal line of the anal canal at the upper margin, 20 mm beside the midline. First, the insertion site will be anaesthetized with 10 ml of 1% lidocaine with a 22-gauge 32 mm needle. Then, an advanced injection of perineal nerve block will be carried out with a 20-gauge and 80 mm needle. We will inject 5 ml of 1% lidocaine at each site of the perineal nerve bundle under the guidance of a biplanar ultrasound transducer (**Figures 2**, **3A**).

Periprostatic Block Arm

In this arm, the periprostatic block procedure will be performed *via* an 80 mm 20-gauge needle under the guidance of the ultrasound probe after the skin is anaesthetised by 10 ml of 1% lidocaine *via* a 22-gauge 32 mm needle. The block region will be located on the basal prostatic capsule, lateral to the location between the prostate and seminal vesicle (**Figure 3B**). Additionally, 5 ml of 1% lidocaine will be injected at each site.

TABLE 2 | Other side effects that may occur in this trial besides pain.

Side effect	Expected probability	Outcome
Hematuria	2 in 3 men	Self-resolving, 3–14 days
Hematospermia	3 in 10 men	Self-resolving, 1–2 months
Bleeding in perineal	1 in 10 men	Self-resolving, 1–12 hours
Bleeding in rectum	1 in 50 men	Self-resolving, 1–3 days
Lower urinary tract symptoms	1 in 10 men	Self-resolving, 1–7 days
Transient erectile dysfunction	1 in 10 men	Self-resolving, 2–3 weeks
Urinary retention	1 in 30 men	Indwelling catheter, 3–7 days
Discomfort when passing urine	2 in 3 men	Self-resolving, 1–3 days
Discomfort in the rectum	2 in 3 men	Self-resolving, 1–3 days
Urinary tract infection	1 in 100 men	Oral antibiotics, 3–7 days
Fever	None	Intravenous antibiotics 3–7 days
Vasovagal event	1 in 50 men	Self-resolving, 0.5–2 h
Anaesthetic allergy	None	Antiallergy treatment, 0.5–3 h

Prostate Biopsy

Another urologist who is blinded to the block method will perform the prostate biopsy. All patients will undergo a 12-core systematic transperineal prostate biopsy with or without a targeted biopsy. The 12-core systematic biopsy region will be taken as described previously (14). A targeted biopsy will be performed using the cognitive fusion method (15), only when there is at least one suspicious lesion [defined as a lesion with a score $\geq$3 according to the Prostate Imaging Reporting and Data System (PI-RADS) criteria (16)] shown by the MRI. Another research nurse who is also blinded to allocation will record the manifestations of the patients during the biopsy procedure.

Histology

The pathologic results will be reported within 14 days after the biopsy according to the ISUP guidelines (17). The pathologists who assess the biopsy samples will be blinded to all clinical data including the anaesthesia technique. The Gleason score, the length of the tumour, and the percentage of the tumour will be reported for each needle sample. Clinically significant cancer cases will be defined as those with a ISUP score of 2 or higher.

Sample Size

The prospective data in our previous study showed a mean maximal VAS score of 1.8 for patients who underwent a biopsy with a perineal nerve block and a mean maximal VAS score of 3.4 for those who received a periprostatic block. The standard eviations for these two methods were 1.02 and 0.96, respectively.

For the calculation of sample size, using a power of 90%, a two-sided α of 5%, and an allocation ratio of 1:1 and assuming an NRS score for the perineal nerve block of 2.0, an NRS score for the periprostatic block of 2.5, and the standard deviations for these two methods are equal to 1.0, 86 men per arm will be required. Accounting for a withdrawal/loss rate of 10%, a total of 190 participants are required for inclusion.

Statistical Analysis

The primary outcome in this trial will be analysed following the intention-to-treat principle as well as the per-protocol principle. The difference between the two groups will be evaluated with a 95% confidence interval (CI) using a generalised linear mixed model to express the precision of the estimate. In this model, the NRS pain score and the group will be considered the dependent variable, the imbalanced baseline characteristic will be considered the covariate, and the centre will be considered a random effect.

The secondary outcomes will be analysed with Pearson chi-square tests and expressed with 95% CIs. Each *P*-value reported in this trial will be two-sided.

Harms and Adverse Events

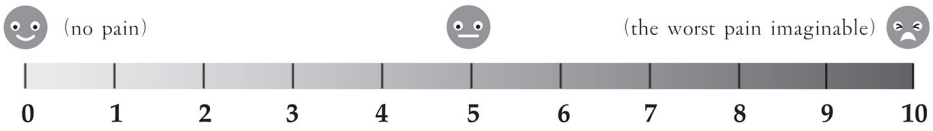
There are few reports of severe adverse events (SAEs) regarding transperineal prostate biopsies and local anaesthesia for biopsies. The main expected adverse events or side effects are listed at

APROPOS

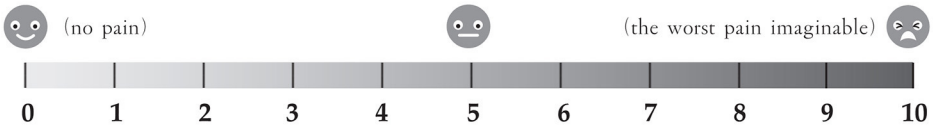
Anesthesia in PROstate biopsy
Pain Obstruction Study

Participant's number:..... Hospital number: .....

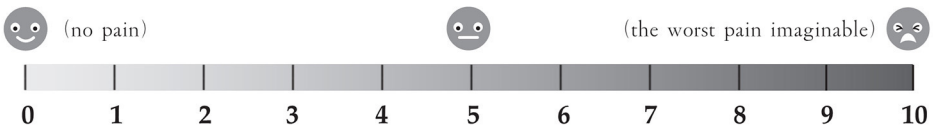
1. Worst pain during the procedure of the transperineal prostate biopsy:



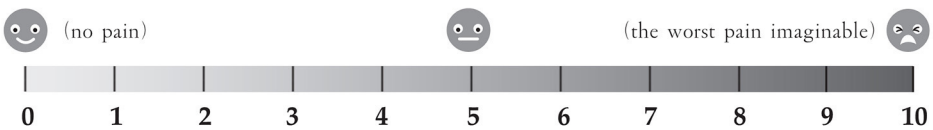
2. The pain of phlebotomizing:



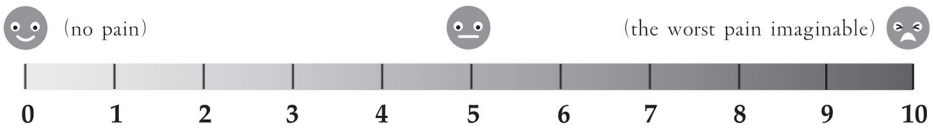
3. The pain when the first needle touches the skin while anaesthesia begins:



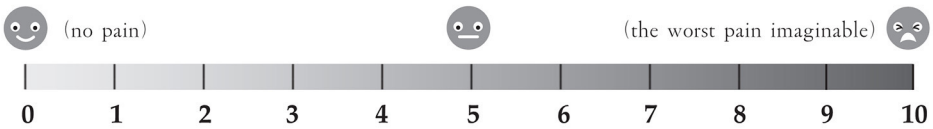
4. The pain you are feeling rightnow: (1h)



5. The pain you are feeling rightnow: (6h)



6. The pain you are feeling rightnow: (24h)



participant: ..... signature: ..... date: .....

FIGURE 4 | Form 1.

Table 2, and the participants will be informed of the risk for these adverse events or side effects before registration. The expected incidence of the adverse events is based on both our previous data and the literature (18). All complications and adverse events that occur from the date of registration to 1 week after the biopsy will be recorded by a research nurse. SAEs are defined as any of the following: (1) death; (2) life-threatening; (3) hospitalisation; and (4) disability or permanent damage. SAEs will be recorded immediately and then sent to the ethics committee and the APROPOS monitoring board within 24 h.

Blinding

All participants and research nurses measuring or recording the results will be unaware of the intervention group (perineal nerve block or periprostatic block). The researcher who collects or enters the data will also be blinded to the allocation. The

APROPOS
Anesthesia in PROstate biopsy
Pain Obstruction Study

Participant's number:..... Hospital number: .....

	0	1	2	score
Facial expression	No particular expression or smile	An occasional grimace or frown, a withdrawn expression, or a disinterested expression	Frequent to constant quivering chin or a clenched jaw	
Activity	Lying quietly or being in a normal position	Slight contractions of the hip muscles or slight movements of hip	Severe contractions of the hip or lifting the hip out of the bed	
Voice expression	Quiet or normal communication	An occasional moan or weeping sound	Constant moaning or sobbing and screaming	
Pacification	Being peaceful and not requiring pacification	Being able to be comforted easily	Being difficult to comfort	
Cooperation	Being calm and cooperative	Language resistance	Body resistance	
Total score	——	——	——	

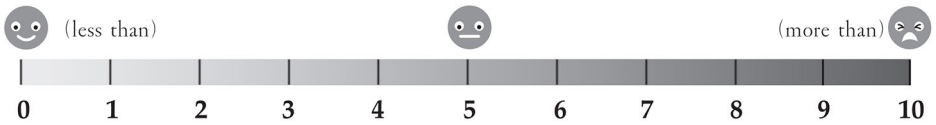
signature: ..... date: .....

FIGURE 5 | Form 2.

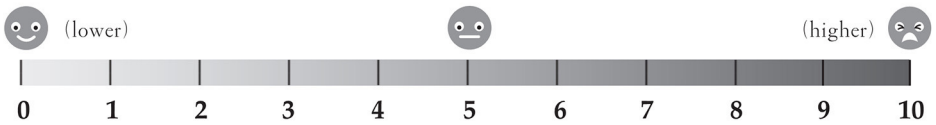
APROPOS
Anesthesia in PROstate biopsy
Pain Obstruction Study

Participant's number:..... Hospital number: .....

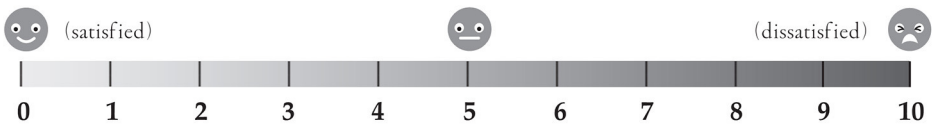
1. Do you think the pain during the biopsy is less than expected?



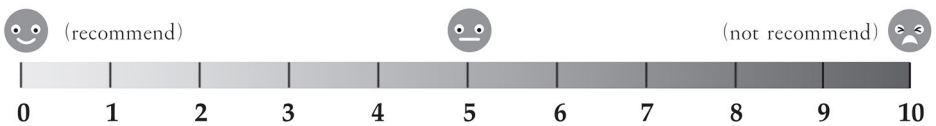
2. Do you think the pain after anaesthesia is lower than the pain during anaesthesia?



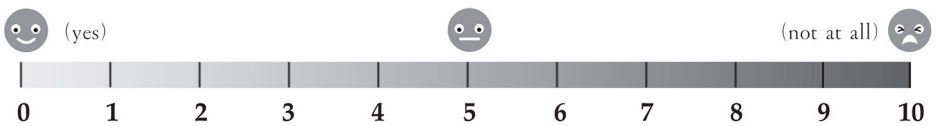
3. Are you satisfied with the overall feelings of the biopsy?



4. Would you recommend this of biopsy for other patients?



5. Will you choose this way of biopsy if you should have undergone another?



participant: ..... signature: ..... date: .....

FIGURE 6 | Form 3.

urologist who conducts the anaesthesia will be blinded to all other data, including the name and trial number of the participant, and will not aid in assessing the outcomes or processing the data. The other urologist who will perform the prostate biopsy will be unaware of the allocation, and the pathologist who will report the pathologic outcomes will be unaware of all patients' clinical information.

Data Collection and Monitoring

After informed consent is obtained from the patients, the data will be collected by a research nurse who is blinded to the allocation to ensure the integrity of evaluation and prevent bias. Demographic information, including age, body mass index (BMI), PSA level, DRE results, prostate volume and American Society of Anesthesiologists (ASA) classification will be collected before anaesthesia. The pain score will be measured and recorded *via* form 1 (**Figure 4**) at 10 min, 1, 6, and 24 h after the biopsy. Additionally, the pain of phlebotomizing and the pain at the first moment the needle touches the skin during anaesthesia will be used as the reference and baseline for the pain assessment (form 1). During the biopsy, the external manifestations of pain will be measured *via* form 2 (**Figure 5**), and the blood pressure, heart rate and breathing rate will be recorded by a multi-parameter monitor. The site of needle core will be reported, because the targeted cores of the anterior zone might be associated with more pain in comparison with those of the peripheric zone (19). Before the participant is dismissed, the anaesthesia satisfaction assessment will be collected *via* form 3 (**Figure 6**). The pathologic data will be collected within 2 weeks after the biopsy. All of these data will be entered into a particular database. An independent monitor from the APROPOS operation group will check the quality of the data at least twice a week. The monitor may pose queries to the data, and the validity of the data will not be confirmed unless the questions have been resolved.

DISCUSSION

We initially developed the perineal nerve block based on an anatomical study and then conducted a pilot trial to verify its efficacy and safety preliminarily.

To confirm the findings and ensure the results more generalizable, we plan to conduct this multicentre randomised controlled trial, used rigorous randomised design and blinding method.

Apart from the subjective NRS pain scores reported by the patients, the external manifestations of pain during the biopsy, and the indicator changes displayed on the monitor will be considered to make the pain control assessment more comprehensive and multidimensional.

In conclusion, this trial will determine the efficacy of the perineal nerve block in controlling pain in patients undergoing prostate biopsy *via* the transperineal approach.

TRIAL STATUS

This RCT was first registered online at ClinicalTrials.gov on August 2, 2020. The trial is start recruiting on August 13, 2020. Recruitment is anticipated to continue until September 15, 2021, with the 1-month follow-up expected to be completed on October 15, 2021.

ETHICS STATEMENT

Ethical approval was obtained from the Ethics Committee of all centres (**Supplementary Material**). All participants will sign a consent form prior to randomisation. The results of this trial will be disseminated to an international peer-reviewed journal and presentations at international or national academic conferences.

PATIENT AND PUBLIC INVOLVEMENT

The patients and public were not involved in the contribution of the design, recruitment or conduction of the trial. Each participant will be informed of the latest results at follow-up and received a summary of the main finding at the end of the trial.

AUTHOR CONTRIBUTIONS

Study protocol was conceived and designed by B-MH and H-FW and revised critically by R-BL. The original draft was completed by B-MH. All authors participated in the editing of the protocol.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fsurg.2021.649822/full#supplementary-material

REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin.* (2018) 68:394–424. doi: 10.3322/caac.21492
2. Shen PF, Zhu YC, Wei WR, Li YZ, Yang J, Li YT, et al. The results of transperineal versus transrectal prostate biopsy: a systematic review and meta-analysis. *Asian J Androl.* (2012) 14:310–5. doi: 10.1038/aja.2011.130
3. Xue J, Qin Z, Cai H, Zhang C, Li X, Xu W, et al. Comparison between transrectal and transperineal prostate biopsy for detection of prostate cancer

a meta-analysis and trial sequential analysis. *Oncotarget.* (2017) 8:23322–36. doi: 10.18632/oncotarget.15056
4. Marra G, Ploussard G, Futterer J, Valerio M, Party E-YPCW. Controversies in MR targeted biopsy: alone or combined, cognitive versus software-based fusion, transrectal versus transperineal approach? *World J Urol.* (2019) 37:277–87. doi: 10.1007/s00345-018-02622-5
5. Xiang J, Yan H, Li J, Wang X, Chen H, Zheng X. Transperineal versus transrectal prostate biopsy in the diagnosis of prostate cancer: a systematic review and meta-analysis. *World J Surg Oncol.* (2019) 17:31. doi: 10.1186/s12957-019-1573-0
6. Grummet JP, Weerakoon M, Huang S, Lawrentschuk N, Frydenberg M, Moon DA, et al. Sepsis and 'superbugs': should we favour the transperineal over the transrectal approach for prostate biopsy? *BJU Int.* (2014) 114:384–8. doi: 10.1111/bju.12536
7. Iremashvili VV, Chepurov AK, Kobaladze KM, Gamidov SI. Periprostatic local anesthesia with pudendal block for transperineal ultrasound-guided prostate biopsy: a randomized trial. *Urology.* (2010) 75:1023–7. doi: 10.1016/j.urology.2009.09.083
8. Knobloch Rv, Weber J, Varga Z, Feiber H, Heidenreich A, Hofmann R. Bilateral fine-needle administered local anaesthetic nerve block for pain. *Eur Urol.* (2002) 41:508–14. doi: 10.1016/S0302-2838(02)00072-6
9. Kubo Y, Kawakami S, Numao N, Takazawa R, Fujii Y, Masuda H, et al. Simple and effective local anesthesia for transperineal extended prostate biopsy: application to three-dimensional 26-core biopsy. *Int J Urol.* (2009) 16:420–3. doi: 10.1111/j.1442-2042.2009.02269.x
10. Kum F, Elhage O, Maliyil J, Wong K, Faure Walker N, Kulkarni M, et al. Initial outcomes of local anaesthetic freehand transperineal prostate biopsies in the outpatient setting. *BJU Int.* (2020) 125:244–52. doi: 10.1111/bju.14620
11. Mottet N, Cornford P, Bergh RCNvd, Briers E, Santis MD, Fanti S, et al. *EAU Guidelines-2020*. Amsterdam: Elsevier (2020).
12. Nash PA, Bruce JE, Indudhara R, Shinohara K. Transrectal ultrasound guided prostatic nerve blockade eases systematic needle biopsy of the prostate. *J Urol.* (1996) 155:607–9. doi: 10.1016/S0022-5347(01)66464-4
13. Wang H, Lin H, He B, Guo X, Zhou Y, Xi P, et al. A novel perineal nerve block approach for transperineal prostate biopsy: an anatomical analysis-based randomized single-blind controlled trial. *Urology.* (2020) 146:25–31. doi: 10.1016/j.urology.2020.01.058
14. He BM, Chen R, Shi ZK, Xiao GA, Li HS, Lin HZ, et al. Trans-perineal template-guided mapping biopsy vs. freehand trans-perineal biopsy in Chinese patients with PSA < 20 ng/ml: similar cancer detection rate but different lesion detection rate. *Front Oncol.* (2019) 9:758. doi: 10.3389/fonc.2019.00758
15. Wang HF, Chen R, He BM, Qu M, Wang Y, Lin HZ, et al. Initial experience with a novel method for cognitive transperineal magnetic resonance imaging-targeted prostate biopsy. *Asian J Androl.* (2020) 22:432–6. doi: 10.4103/aja.aja_83_19
16. Turkbey B, Rosenkrantz AB, Haider MA, Padhani AR, Villeirs G, Macura KJ, et al. Prostate imaging reporting and data system version 2.1: 2019 update of prostate imaging reporting and data system version 2. *Eur Urol.* (2019) 76:340–51. doi: 10.1016/j.eururo.2019.02.033
17. Epstein JI, Egevad L, Amin MB, Delahunt B, Srigley JR, Humphrey PA, et al. The 2014 international society of urological pathology (ISUP) consensus conference on Gleason grading of prostatic carcinoma. *Am J Surg Pathol.* (2016) 40:244–52. doi: 10.1097/PAS.0000000000000530
18. Pepe P, Aragona F. Morbidity after transperineal prostate biopsy in 3000 patients undergoing 12 vs. 18 vs. more than 24 needle cores. *Urology.* (2013) 81:1142–6. doi: 10.1016/j.urology.2013.02.019
19. Pepe P, Garufi A, Priolo GD, Galia A, Fraggetta F, Pennisi M. Is it time to perform only magnetic resonance imaging targeted cores? Our experience with 1,032 men who underwent prostate biopsy. *J Urol.* (2018) 200:774–8. doi: 10.1016/j.juro.2018.04.061

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REVIEW
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Tissue Engineering and Its Potential to Reduce Prostate Cancer Treatment Sequelae—Narrative Review

Jan Adamowicz[1†], Luis Alex Kluth[2†], Marta Pokrywczynska[1] and Tomasz Drewa[1] for the Trauma and Reconstructive Urology Working Party of the European Association of Urology Young Academic Urologists*

[1] Chair of Urology, Department of Regenerative Medicine, Collegium Medicum, Nicolaus Copernicus University, Bydgoszcz, Poland, [2] Department of Urology, University Hospital Frankfurt, Frankfurt am Main, Germany

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Edited by:
Maria Carmen Mir, Instituto Valenciano de Oncologia, Spain

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Zhongcheng Xin, Second Hospital of Tianjin Medical University, China

***Correspondence:**
Jan Adamowicz
adamowicz.jz@gmail.com

†Senior members of the Trauma and Reconstructive Urology Working Party of the European Association of Urology Young Academic Urologists

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Tissue engineering offers the possibility to overcome limitations of current management for postprostatectomy incontinence and ED. Developed in recent years biotechnological feasibility of mesenchymal stem cell isolation, *in vitro* cultivation and implantation became the basis for new cell-based therapies oriented to induce regeneration of adult tissue. The perspective to offer patients suffering from post-prostatectomy incontinence or erectile dysfunction minimal invasive one-time procedure utilizing autologous stem cell transplantation is desired management.

Keywords: prostate cancer, stem cell, tissue engineering, urology, incontenence

INTRODUCTION

Prostatectomy is recommended choice of treatment for localized disease while in advanced cases the indications for surgery are gradually extending (1). The leading disadvantage of prostatectomy are side effects such as incontinence and erectile dysfunction (ED), still occurring despite continued progress in surgery technic (2). High number of patients recover from incontinence after rehabilitation but 10–20% suffer from persistent incontinence and 20–70% from erectile dysfunction (3). GLOBOCAN 2018 estimated, 1,276,106 new cases of prostate cancer were reported worldwide in 2018, with the highest prevalence in the developed[1]. In consequence, the correspondingly large number of patients suffering from prostatectomy side effects is generated each year. Approximately 50 and 30% of patients seek some form of treatment for incontinence and ED following prostatectomy, respectively (4). Modern Urology offers obviously management options for these patients. Nevertheless, a conservative approach has limited efficiency, and invasive forms of treatment including implantation of male slings, artificial urinary sphincters, or penile prosthesis need to be performed in most cases (5).

Tissue engineering offers the possibility to overcome limitations of current management for postprostatectomy incontinence and ED. Developed in recent years biotechnological feasibility of mesenchymal stem cell isolation, *in vitro* cultivation and implantation became the basis for new cell-based therapies oriented to induce regeneration of adult tissue (6). The perspective to offer patients suffering from postprostatectomy incontinence of ED minimal invasive one-time procedure utilizing autologous stem cell transplantation is a tempting idea. In this concept stem

[1] https://gco.iarc.fr (accessed February 9, 2020).

cells are intended to induce partial regeneration of sphincter complex and neuronal network damaged during surgery what would mediate functional recovery. In this short narrative review, we are presenting current research data focused on tissue engineering strategies addressing incontinence and ED after prostatectomy.

CONSEQUENCES OF IATROGENIC INJURY AFTER PROSTATECTOMY

Despite spectacular technical advances including magnification, 3D viewing, instrument miniaturization, and computer control of movement provided by the DaVinci system, prostatectomy is still an invasive procedure. This surgery has a damaging effect on crucial continence mechanism function in a significant percentage of patients regardless of the used method (7). Reported incontinence rates after prostatectomy can be as high as 80%. First of all, the proximal sphincteric unit is completely removed and in addition, the proximal urethral sphincter is damaged during prostate apex resection. Ultimately, this destructive cascade of events results in that postoperative continence depends largely on the rhabdosphincter (8). In contrast, intact male continence mechanism relies on the coordinated interplay of the inner lissosphincter of smooth muscle and an outer rhabdosphincter of skeletal muscle (9). Notwithstanding this ambiguous morphological characteristic of the male sphincter complex, the continence primarily depends on the proper lissosphincter activity (10). The internal sphincter controls passive continence and holds urine at the level of the vesical orifice. The synchronized contraction of its circular muscle fibers closes the vesical orifice and triggers concentric narrowing of the posterior urethra. Most importantly, the proper function of the lissosphincter is enough to guarantee passive continence (11). In this scenario, rhabdosphincter acts as a supporting component responsible for voluntary continence control. The nerve supply of the vesicourethral smooth muscle descends from the hypogastric and pelvic nerves for sympathetic and parasympathetic supply, respectively (12). In contrast, the rhabdosphincter receives somatomotor innervation from the pudendal nerve. Although the gross anatomy of sphincter complex innervation is well determined the localization of the intramural branched neuronal network within lower urinary tracts is still a matter of discussion. The cavernous nerve runs as a distinct bundle structure only in 30% of patients, whereas 70% have been shown to have plate architecture (13). Eichelberg et al. demonstrated that the most periprostatic nerves contributing to cavernous nerve were found posterolaterally but a significant portion of the nerves (22–29%) was located on the anterior surface of the prostate (14). Cavernous nerve terminations originating from the pelvic plexus release nitric oxide during sexual stimulation that leads to the relaxation of the smooth muscle fibers of the arteries and arterioles of the erectile tissue. The dogmatic location of prostate neurovascular bundles (NVBs) within the posterolateral aspect was confirmed using male cadavers only in approximately half the cases (15). In fact, NVBs exposed proximally dispersed fan-shape running course widely embracing anterior prostate plate (16). Independent of the applied surgical technique, prostate mobilization causes multifocal neuropraxia of the neural plexus mainly in the dorsal prostatic capsule. Additionally, some of the collaterals running from the pudendal nerve might have been unintentionally intersected. The development of the posterior plane between the prostate and rectum results in an unintentional mechanical disruption of the thin neuronal network mainly within Denonvilliers fascia (17). Applied traction during surgical maneuvers in multilayer environments generates shear force responsible for neuronal injury (18). It might be one of the explanations of failures in the nerve sparing approach. As a result of prostatectomy, the heterogenic injury occurs involving unpredictable denervation and structural damage of sphincter complex mainly of lissosphincter running from bladder neck through surrounding prostatic and membranous urethra (19). In addition, vesicourethral anastomosis creates a new anatomical spatial configuration of urine outflow and in fact continence mechanism now on the bladder neck and remaining membranous urethra (20). Therefore, well-supported vesicourethral anastomosis remains crucial for anastomotic healing after radical prostatectomy.

The lesion after prostatectomy encompasses reaming sphincter and neuronal plexus. Developing inflammation includes the release of transforming growth factor β1 (TGF-β1), platelet-derived growth factor (PDGF), tumor necrosis factor-α (TNF-α), and interleukin-1 (IL-1) (21). In the case of the urinary tract wall, activated urothelial cells become cell population that regulates the early phase of the inflammatory response. Their important role is to stimulate muscle precursors to responsive proliferation and maturing (22). Additionally, on the tissue level the inflammatory response triggers edema, acidosis, and apoptosis, which extend the injury site beyond vesicourethral anastomosis (23). The postoperative local hypoxia upregulates TGF-β/Smad signaling being a major profibrotic pathway (24). As a result, the gradual increasing accumulation of type I and III collagens within the sphincter muscles takes place leading to disruption of its architecture impairing bladder neck closure (25). A contractile, scar may in time overgrew sphincter muscle component causing its impartment even if the neuronal supply is functional. First 3 months after prostatectomy is defined as the acute phase of the injury and thereafter the most efficient improvement in terms of continence and erectile function occurs (26). This time period corresponds to the early remodeling phase ending with developed initial scar tissue and ended neuronal regeneration (Wallerian degeneration) (27). From the physiological perspective improvement after this time is rather related to rehabilitation or adaptive mechanism rather than active regeneration *per se*.

An important deterioration factor of regeneration is the environment of urinary tracts making them vulnerable to prolonging inflammation sustained by urine and microbiological contamination (28). Dovi et al. (29) demonstrated that a deletion of polymorphonuclear leukocyte (PMN) results in acceleration of wound closure. Chronic or excessive inflammation promotes scar formation and hamper tissue mechanisms to repair. Furthermore, the persistence of urine within the healing anastomosis is an often underestimated factor that may have a negative effect on final anastomosis remodeling. It was

demonstrated that urine has a cytotoxic effect on muscles precursor cells participating in urinary tract wall regeneration (30). The primary approach of tissue engineering should aim to transform heeling pattern within the vesicourethral anastomosis and adjacent tissues.

TISSUE ENGINEERING APPROACH

Healing is a highly evolved defense mechanism against infection and further injury. Adult human healing in lower urinary tracts is mediated mainly by a fibroproliferative response leading to scar formation (31). In contrast, urothelium as typical for epithelium characterizes with spontaneous regeneration capacity. Tissue engineering utilizes biomaterials and stem cells to induce intrinsic regeneration mechanisms that were silenced during ontogenesis. Healing of the urinary tract wall is initially led by activated urothelial cells that trigger the formation of the active subpopulation of mesenchymal precursors cells within the muscle layer (32). The signaling pathways including (Shh, Wnt, and Bmp) are upregulated during this process analogously to organogenesis stages (33). Building upon recent progress in understanding the molecular background of the healing process, tissue engineering focuses on controlled modulation of the healing milieu, thus resulting in a more favorable regeneration.

Most stem cells used in induced urinary tract regeneration are bone marrow-derived mesenchymal stem cells (BMSCs) containing significant proliferative capacity, long-term self-renewal potential, and having the ability to differentiate into other lineages. These stem cell populations exhibited high plasticity potential and were able to differentiate into urothelium and muscle layer *in vitro* under defined culture conditions (34). Therefore, delivered mesenchymal stem cells act as a source of paracrine signaling molecules acting on nearby cells. BMSCs are involved in all three phases during the wound-healing process. They also may enhance wound healing by immune modulation, production of growth factors that boost neovascularization, and reepithelialization (35). Nevertheless, the harvesting procedure of BMSCs is invasive for the patients and expensive. For this reason, although BMSCs are considered as a gold standard for adult stem cells, adipose-derived stem cells (ADSCs) gained considerable attention as a suitable candidate to be used in future therapies for patients after prostatectomy (36). ADSCs are characterized by less expensive cost of harvesting, greater yield, and confirmed multilineage differentiation ability that is the same as BMSCs. Zuk et al. (37) demonstrated the efficient capacity for myocyte differentiation *in vitro* when cultured next to myoblasts. Myocyte obtained from ADSCs could repair myotubes of ischemic muscular injury. Fakhrieh et al. (38) demonstrated that ADSCs could be a source of urinary bladder smooth muscle cells.

At the beginning of tissue engineering research, the dominant belief was that implanted stem cells locally replace injured tissue by direct differentiation and forming incorporated neotissue. At present, however, we are of the opinion that the regeneration effect is a result of realizing bioactive molecules (6). In particular, paracrine stimulation of angiogenesis is of utmost importance as it is a major profibrotic factor. ADSCs were documented to mediate angiogenesis by releasing growth factors including VEGF, HGF, and basic fibroblast growth factor (bFGF) (39). Chen et al. demonstrated that ADSCs are involved in cross-talk between endothelial cells, muscle precursors, and ECM during angiogenesis (40). ADSCs promoted endothelial colony-forming cell proliferation and differentiation. Interestingly, they could also differentiate into pericytes to stabilize the newly formed vessel structure.

At present, experimental attempts to modify the healing response by targeting individual pathways were not effective due to still insufficient knowledge about intricate signaling networks. Accordingly, ADSCs play the role of natural carriers of bioactive substances realized in an efficient way including timing, dosage, and interaction profile. Pokrywczyńska et al. (41) demonstrated, that ADSCs initiated regeneration of bladder wall mainly by the upregulation of the Hedgehog signaling pathway. Molecular analysis proved that implanted ADSCs activated cardinal pathways including GF-β, Jak-STAT, PI3-Akt, and Hippo governing early stages of urinary tract organogenesis.

The significant limitation of stem cell therapies utilizing *in vivo* cell implantation is a very low survival rate (<5%) (42). Although MSCs are considered as immune-privileged due to the absence of MHC-II expression, *in vivo* testing showed that MSCs upregulate MHC-II expression at the inflammation site and can be recognized by the host immune system (43). Uncontrolled stem activity characterizes with rather a low efficiency as these cells cannot *per se* rebuild damaged structures. Hence, all types of stem cells demand guiding signals to achieve the therapeutic effect (44). In these circumstances, tissue engineering may offer solutions and needed technology. Constructing cell implantable seeded grafts with a 3D biomaterial scaffold may offer the ability to precisely deliver cells into the injury site. This approach would also allow the creation of a temporary stable and supportive environment to gain time for the stem cells to impact the local paracrine milieu.

NEUROREGENERATION

Stimulation of neuronal network regeneration mediating continence and erectile function after prostatectomy is the most challenging task awaiting to be addressed in future studies. Tissue engineering attempts to apply stem cells transplantation to reconstitute damaged intramural neuronal network (45). Conducted research showed that MSCs modulated neuroregeneration events including the Wallerian degeneration stage, accelerating remyelination, increasing neurofilament number, and enhancing fiber organization (46). Nevertheless, these results were observed using isolated peripheral nerve gap models that are not adequate to draw conclusions for potential regeneration of intramural convolutional neural network within the urogenital tract (47, 48). The targeted regeneration of neuronal network resected during prostatectomy is at present out of range of current biotechnology (28). Based on available research data MSCs contributed to neuronal regeneration by supplying the healing environment with

neuroprotective bioactive factors including nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), and neurotrophin (49). This effect was achieved by direct MSCs paracrine activity and indirectly by acting on the Schwann cells (50). There are only several studies evaluating the ability of MSCs to induce neuromuscular regeneration by delivering cells in the neighborhood of damaged nerves (51). MSCs proved feasibility to stimulate neuronal ingrowth, elongation, and restoring neuronal network (52). We need to keep in mind that the injury site after prostatectomy is a particularly adverse environment with disrupted anatomical and histological structure. Hypothetically, it would be more rational to apply hybrid cellular-biomaterial systems rather than untargeted stem cell implantation. Combing stem cells with biomaterial corresponding to tissue-engineered bypass planned to bridge transected neuronal bundles during prostatectomy may be an interesting pathway to explore. Taking into account individually variable innervation within the prostate, we could design personalized bypass graft based on mapping of periprostatic neurons using, for instance diffusion tensor magnetic resonance (53). An unorthodox solution could be also using the autologous Schwann cells intended to exert local neuroprotective effect and stimulate neuroregeneration (54).

VASCULAR REGENERATION

During prostatectomy, it is necessary to transect or ligate branches of the pudendal artery, prostatic vesical bundles, and Santorini's plexus. These steps alter the blood supply to the vesicourethral anastomosis region and the penile structures, mainly corpus cavernosa (55). A major clinical manifestation of these circulation disturbances is susceptibility to vesicourethral stenosis and regressive morphological changes in the corpus cavernosa. Although the mechanism of vesicourethral stenosis is poorly understood, it involves two main parallel events, namely, uncontrolled expansion of the muscle layer and a fibrosing reaction promoted by hypoxic environment (23). Underlying inflammation and hypoxic environment only intensify this chronic process. Analogously, progressive fibrosis takes place in the corpora cavernosa after prostatectomy as denervation and chronic ischemia (56).

Mesenchymal stem cells may be utilized in cell-based therapy to support angiogenesis of healing thereby providing potentially therapeutic benefits after prostatectomy. The lesson learned from the field of cardiology exposed the ability of MSCs to actively migrate to ischemic areas after myocardial infarction. Mesenchymal cells improved remodeling of the infraction zone by inducing transmyocardial revascularization (57). Stem cell-based therapies aimed to improve functional results after prostatectomy need to promote regional postoperative angiogenesis both within the remaining of the sphincter and corpus cavernosa. The secretome of the MSCs includes proangiogenic factors extracellular vesicles (EV) carrying miRNAs (58). Regardless of the tissue of origin, enrichment of miRNAs in MSC-EVs has been shown to promote angiogenesis *in vitro* and *in vivo*. miRNAs originated from MSCs targeted the expression of regulatory angiogenic genes encoding for cytokines, MMPs, VEGF, PDGF, fibroblast growth factor (FGF), and epidermal growth factor (EGF) (59). Several miRNAs with angiogenic potential such as miRNA-494, miR-125a, or miR-210 were described in MSC-derived EVs (60).

STEM CELL SAFETY

The safety of stem cells therapies is one of the major concerns of clinicians, especially in oncological patients. The major risk is related to the use of pluripotent embryonic cells that exposed the highest self-renewal potential and differentiation capacity. There are reports describing tumor formation after autologous multipotent stems cell transplantation (61). Particular attention should be also paid to the fact that current models of cell therapy can require hundreds of millions of cells per patient, which need to be expanded *in vitro*. Adaptation of self-renewing cells to their culture conditions poses the risk of latent cancerogenesis (62). Regardless of applied argumentation it must be underlined that the real risk of iatrogenic tumor formation after stem cell implantation within solid organs is not clearly determined. The situation becomes even more controversial if we plan to deliver stem cells in the neighborhood of the malignant tumor resection zone. In addition to the tumorigenic potential inherent to differentiation capacity, the direct influence of the remaining cancer cells is another possible hazard. It was shown that MSC-derived exosomes can promote tumor growth through a variety of mechanisms (63). The wide profile of stem cells secretome might act as a two-edged sword in this scenario. Therefore, the same bioactive molecules can simultaneously and advantageously modify the healing environment and promote cancer recurrence. However, MSC-derived exosomes were found to exhibit an inhibitory effect on prostate cancer, so this cell population seems to be particularly suitable for urological application (64). From the other hand, the in-depth interplay between MSCs and prostate cancer cells has not been established. In light of the postulated MSC involvement in the development of androgen-independent prostate cancer, the utilization of this cell population should be only limited to patients who do not pose a risk of recurrence (65).

POSTPROSTATECTOMY INCONTINENCE

To date, five clinical trials aimed to evaluate cell therapy for postprostatectomy stress incontinence were completed (**Table 1**). The first study evaluating cell-based therapy for urinary incontinence after prostatectomy was published by Mitterberger et al. (66). In this study, 63 patients with stress urinary incontinence after radical prostatectomy were treated with transurethral ultrasound-guided injections of autologous fibroblasts and myoblasts obtained from skeletal muscle biopsies. The applied combination of cellular populations was intended to act bilaterally. Accordingly, fibroblasts were aimed to counteract atrophy of submucosa within the urethra to improve the passive selling mechanism of the remaining supra-membranous urethra. Whereas, implanted myoblast was planned to contribute actively

TABLE 1 | Cell therapy clinical trials for stress urinary incontinence after prostatectomy.

Study	Number of patients	Time after prostatectomy	Type of cells	Evaluation tools	Administration method	Administrated cells	Patients with reported improvement (%)
Mitterberger et al. (66)	63	Min. 12 mths Avg. 43 mths	Fibroblasts Myoblasts	Incontinence score I-QOL Transurethral US Urodynamics	US guided endoscopic transurethral injection	Avg. 3.8×10^7 fibroblasts Avg. 2.8×10^7 myoblasts	58 (92%)
Gerullis et al. (67)	222	Min. 12 mths	MDC	"In-house" continence questionnaire	Endoscopic transurethral injection	Avg. 5.2×10^6	90 (41%)
Gotoh et al. (68)	11	12 mths	ADRC	24h pad test Urodynamics ICIQ-SF MRI	Endoscopic periurethral injection	Avg. 1.8×10^7	8 (70%)
Choi et al. (69)	6	12 mths	ADRC	24h pad test Urodynamics ICIQ-SF MRI	Endoscopic periurethral injection	(no data)	6 (100%)
Garcia-Arranz et al. (70)	9	Avg. 60.5 mths	ADSC	24h pad test Urodynamics ICIQ-SF SF-36	Endoscopic periurethral injection	2×10^6 (2 patients) 6×10^6 (8 patients)	8 (88%)

MDC, Muscle-derived cells; ADRCs, Adipose-derived regenerative cells; ADSCs, adipose-derived stem cells; I-QOL, urinary incontinence quality of life scale; US, ultrasound; ICIQ-SF, international consultation on incontinence questionnaire—Short Form; SF-36, 36 item short form survey..

to rhabdosphincter remodeling by increasing the number of contractile fibers. After 12 months of follow-up, 58 patients showed relevant improvement. Although the authors provided multicriteria analysis to evaluate therapy success using subjective and objective tools, the main limitation of the study is the low number of patients and the lack of a control group. In consequence, there is no possibility to discriminate between the effects of spontaneous regeneration and the results of guided remodeling of the cells. On the other hand, the study was distinguished by a large number of implanted cells that were precisely administered with invented ultrasound guided system. Gerullis et al. presented data from a one arm study, in which male patients with stress urinary incontinence (including 197 after prostatectomy) were treated with a transurethral injection of autologous muscle-derived cells (67). Transurethral implanted cells were at least 50% of myogenic origin and predominantly represented early stages of muscle cell differentiation. The authors demonstrated an improvement in 42% of patients. Only patients with endoscopically proven sphincter damage were included. However, the limitation of the study is the non-standardized inclusion criteria, resulting in a heterogeneous cohort. Moreover, endoscopically visible sphincter dysfunction is an indirect sign of rather a severe sphincter injury that is unlikely to be repaired with the most basic form of cell therapy. Accordingly, a medium form of stress incontinence seems to be the most adequate for a cell-based approach, which should not be categorized as an ultima ratio or alternative for artificial sphincter.

Following early studies utilizing mature adult cells, the concept evolved into using MSCs offering the potential to induce natural regeneration (**Figure 1**). Gotoh et al. were the first to introduce the concept of using adipose-derived regenerative cells (ADRCs) from abdominal adipose tissue obtained by liposuction (68). ADRCs are a heterogeneous population of cells including multipotent adipose-derived stems cells, other progenitor cells, fibroblasts, T-regulatory cells, and macrophages. In this setting, ADRCs obtained by the Celuton system were suspended in untreated lipoaspirate and transurethrally injected into the rhabdosphincter and submucosal space in 11 patients. Stress urinary incontinence improved in eight patients during 1 year of follow-up. The authors evaluated therapy success by urethral closing pressure and functional profile length, which were both significantly elevated. Although adipose-derived stem cells have the capacity to differentiate into contractile cells, no evidence demonstrating potential incorporation of implanted cells with host sphincter structure was provided. Moreover, the major concerns arose after analyzing the volume of injected material. In total each patient received apart from direct injection of 1 ml ADRCs, 20 ml of relatively a thick suspension of lipoaspirate with the narrow region of the external urethral sphincter. In this situation, it is highly probable that the observed impairment was the result of persisting bulking effect. Indeed, the authors discussed this potential problem but did not rule out this possibility by creating a control group. Based on acquired data the same group registered in the 2015 ADRESU study claimed to be the first clinical trial of regenerative treatment for stress urinary incontinence by ADRCs (71). The primary endpoint of the ADRESU study is to be urine leakage volume reduction from baseline >50% by the 24-h pad test at 52 weeks. In 2016, Choi et al. inspired by Gotoh conducted a clinical trial using the same protocol in six patients (69). Although the study was not bringing any new insight authors showed feasibility to replicate efficacy and safety of stem cell therapy for incontinence. Application of the commercially available cell-processing Celution system allowed to obtain standardized ready-to-use cell suspension. This is a role model of how modern stem cell-based therapy in the field of urology should look like. Recently, Garcia-Arranz et al. (70) demonstrated results of the first nonrandomized phase I–IIa clinical trial involving nine men after prostatectomy. The tested feasibility of using ADSCs injected in the region of the bladder neck and along the external sphincter under visual guidance using compact cystoscope guidance. Overall, 38% of patients showed an objective clinical improvement of more than 50% which is in line with the FDA definition of optimal continence improvement after therapeutic intervention. In two of the eight patients, continence improvement was noticed after initial administration of 20×10^6 cells. In the rest of the patients, the second dose, according to the study protocol, was necessary. Administration protocol of the cells including multiple cell injections into the injured sphincter is likely to be more effective in supplying regeneration environment with bioactive molecules. The studies aimed to induce regeneration of ischemic

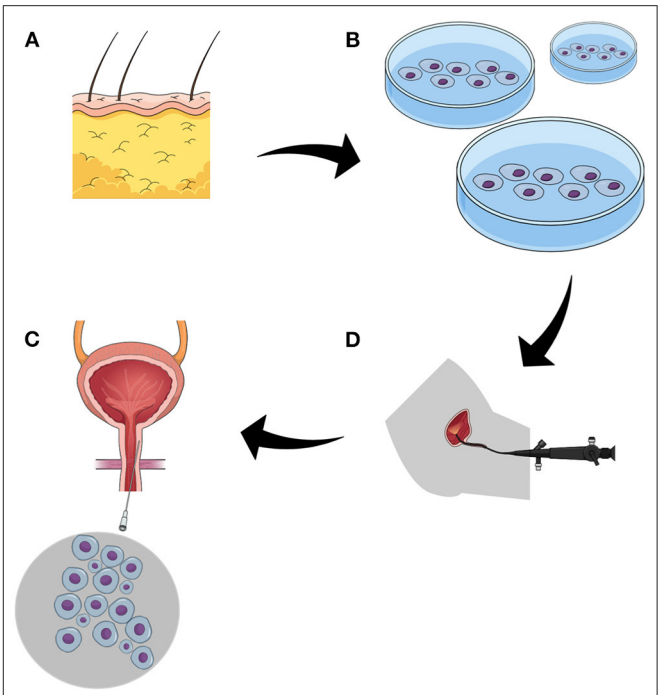

FIGURE 1 | The figure demonstrates the strategy of cell-based approach to postprostatectomy stress urinary incontinence. **(A)** adipose tissue, the source of mesenchymal stem cells. **(B)** isolated stem cells underwent purification and propagation *in vitro*. **(C)** the function of the sphincter is evaluated endoscopically, the most common approach utilizes flexible urethroscopy. **(D)** administration of stem cells to sphincter complex by targeted multiple injections.

heart exposed a very low MSC survival rate after transplantation. Similarly, the harsh microenvironment of injured sphincter with ischemia, inflammation, oxidative stress, and mechanical stress contributes to great cell loss shortly after administration. It is the rationale for developing administration protocols with several injection time schedules. Despite the low number of patients, the study of the Madrid group is so far the most advanced and complex report from the field of experimental cell-based therapy for urinary incontinence after prostatectomy. The analysis of the clinical trials database also provides information on the newly launched trial in Belarus (NCT04446884). As stated in brief, the recruitment for treatment of urinary incontinence in men after with autologous ADSCs was launched in June 2020. The summary of the achievements to date in the treatment of urinary incontinence with autologous cell implantation indicates that the field is in early clinical research phase I.

All studies are characterized by low patient numbers and the omission of control group. The inclusion of the control group should be of utmost importance in future trials as postprostatectomy incontinence improves spontaneously in an individual and difficult to predict manner. Another unknown parameter is the number of cells mandatory to obtain a therapeutic effect. Administrated cell numbers varied between studies, and more importantly, this issue was not comprehensively discussed. The choice of the number of cells in a given therapy is rather empirical and mostly depended on the efficiency of the isolation method. Indeed, we do not know what the best stem cell number is to improve continence or erectile function. In all studies, sphincter regeneration or remodeling guided by implanted cells remained within speculation. Alleged revascularization and neuronal or mesodermal regeneration were not objectively demonstrated, especially on the histological level. In this situation, it may be reasonable to focus on cell behavior after implantation using *in vitro* models or cell tracing techniques. Basic research with a purely cognitive focus is needed in this field to optimize trial protocols in terms of clinical and cost-efficiency. From a safety point of view, the demonstrated cell therapies did not have adverse effects reducing their usefulness. Importantly, liposuction needed for both cell harvesting and transurethral cell administration was well-tolerated procedures. Implantation of cells with high proliferation capacity and differentiation potential outside their normal niche may be a matter of concern in terms of local tumorogenesis. Gotoh et al. (68) conducted extensive follow-up with magnetic resonance imaging conducted every 3 months and could not observe any tumorogenesis within the injection site. The major question, however, remains in regard to the timing of the cell therapy initiation. In all clinical attempts, cells were delivered at least 1 year after prostatectomy, which clearly contradicts our understanding of the induced regeneration mechanism. Namely, at this time point, the scar tissue within the sphincter complex was already developed with silenced remodeling phase making the environment of vesicourethral anastomosis rather non-susceptible to induction of regeneration. It is also the lesson learned from clinical trials from the field of spinal cord injury where the results improved by reducing the time to administration of cells. There is a need to plan

TABLE 2 | Cell therapy clinical trials for erectile dysfunction after prostatectomy.

Study	Number of patients	Time after prostatectomy	Type of cells	Evaluation tools	Administration method	Administered cells	Patients with reported improvement (%)
Yiou et al. (78)	12	6 mths to 3 yr	BM-MNC	IIEF-15 EHS Doppler US	Intracavernous injection	2×10^7; 2×10^8 1×10^9; 2×10^9	12 (100%)
Yiou et al. (79)	12	6 mths to 3 yr	BM-MNC	IIEF-15 EHS Doppler US	Intracavernous injection	1×10^9	12 (100%)
Haahr et al. (80)	17	5–18 mths	ADRC	IIEF-5 EHS	Intracavernous injection	9×10^6	8 (47%)

BM-MNC, Bone-marrow derived mononuclear cell; ADRCs, Adipose-derived regenerative cells; IIEF-15, International Index of Erectile Function-15; EHS, Erectile Hardness Score; IIEF-15, International Index of Erectile Function-5.

a trail where cells would be delivered shortly after the first PSA testing. The concerns related to boosting of resection area with bioactive molecules must be, however, taking into account. Raj et al. (72) explained the possible link between mesenchymal stem cells and prostate cancer progression risk. On the other hand, the in-depth understanding of prostate cancer biology allows us to choose patients with local diseases with extremely low chances for recurrence after prostatectomy. Adequately, these patients with low and medium incontinence, ideally after nerve-sparing prostatectomy, should be the target population. Alternative strategies to stem cells implantation developed to ameliorate prostatectomy functional outcomes include grafts from the dehydrated human amniotic membrane (AM). Patel et al. were the first to present this method in 2015 (73). In the introduced technic AM was wrapped around the neurovascular bundle to improve healing. Reported results indicated that thanks to AM the recovery time for continence was significantly accelerated. AM is a naturally derived biomaterial containing over 226 different growth factors, cytokines, chemokines, protease inhibitors, and other bioactive molecules capable of modulating tissue healing (74). For this reason, AM is widely used in the field of ophthalmology to obtain scarless corneal healing. A significant reduction in the progression and severity of fibrosis was observed after using AM on demanding animal and clinical models. AM is gradually gaining popularity among Urologists, Barski et al. (75) described recently the design of a randomized, single-blind, placebo-controlled, phase 2 study of the efficacy and safety of AM during radical prostatectomy. An important advantage of AM is its natural high elasticity and eligibility during surgical procedures. It acts as a natural carrier of bioactive substances that could be placed in the neighborhood of neural bundles and pelvic plexus. AM was successfully evaluated for nerve bridge repair of peripheral nerve defects in animal models. These inexpensive and easy to obtain biomaterials is rich in cytokines and neurotrophic factors creating a suitable micro-environment for axonal regeneration (76).

ERECTILE DYSFUNCTION

Various degrees of cavernous nerve damage always occur during prostatectomy and even nerve-sparing surgery is no exception. Apart from mechanical injury of the pelvic plexus and its branches postprostatectomy, ED is a result of developing fibrosis due to prolonging penile flaccidity (77). The desired effects of potential stem cell-based therapy are expected to reverse the structural changes leading to ED and to mitigate patient dependence on the transitory effect of PDE5 inhibitors. Three clinical trials addressing the feasibility of using stem cell therapy in patients with ED have been completed so far (**Table 2**) (78–80). Applied subpopulations of mesenchymal stem cells were derived from multiple sources including bone marrow and adipose tissues. In all the cases, straightforward intracavernous stem cell administration was a well-tolerated procedure without relevant side effects and impact on prostate cancer follow-up. The available reports showed improvement in penile hemodynamics and cumulative erectile function scores. It is important to notice that Haahr et al. divided patients in terms of continence coexisting with ED and suggested that applied stem treatment might have a positive effect on incontinence *per se*. Nevertheless, major limitations included a low number of patients and a lack of standardized protocols, making the outcomes of the study difficult to compare and objectively judging the effectiveness of the therapy. The mechanism of stem cell action after extracavernous administration was also hypothetically formulated. The postulated regenerative effect was achieved by either secreting growth factors locally boosting cavernous tissue or by ascending migration to the pelvis plexus and supporting neuronal regeneration on ganglion level. There is a lack of evidence that implanted stem cells generate replacement structures of erectile incorporated with the native one. Despite current limitations and still unanswered questions, stem cell-based therapy for patients after prostatectomy is offered in the private medical sector (81). However, it must be underlined that its clinical suitability is still unknown and must be assessed by clinical trials.

CONCLUSIONS

Tissue engineering has an unquestionable potential to improve the current management of postprostatectomy stress incontinence and erectile dysfunction. Conducted studies provided clues that remodeling of the injured sphincter complex could be induced by stem cells. Similarly, erectile tissue was regenerated by implanted stem cells. These methods are so far the most advanced therapeutical options for patients that do not compensate action of impaired structures but try to restore proper function. Nevertheless, none of the conducted studies has enough translational potential to reliably introduce these types of therapies into clinical practice. The still unanswered questions regarding the most optimal time schedule of therapy, regenerating cell population, administration method, and advantage over the available pharmacological treatment need to be addressed in future trials.

AUTHOR CONTRIBUTIONS

JA: concept and writing. LK: concept and corrections. MP and TD: supervision. All authors contributed to the article and approved the submitted version.

REFERENCES

1. Coughlin GD, Yaxley JW, Chambers SK, Occhipinti S, Samaratunga H, Zajdlewicz L, et al. Robot-assisted laparoscopic prostatectomy versus open radical retropubic prostatectomy: 24-month outcomes from a randomised controlled study. *Lancet Oncol.* (2018) 19:1051–60. doi: 10.1016/S1470-2045(18)30357-7

2. Yaxley JW, Coughlin GD, Chambers SK, Occhipinti S, Samaratunga H, Zajdlewicz L, et al. Robot-assisted laparoscopic prostatectomy versus open radical retropubic prostatectomy: early outcomes from a randomised controlled phase 3 study. *Lancet.* (2016) 388:1057–66 doi: 10.1016/S0140-6736(16)30592-X
3. Yiou R, Binhas M. Combined implantation of a penile prosthesis and adjustable continence therapy proact in patients with erectile dysfunction and urinary incontinence after radical prostatectomy: results of a prospective pilot study. *J Sex Med.* (2015) 12:2481–4. doi: 10.1111/jsm.13059
4. Singla N, Singla AK. Post-prostatectomy incontinence: etiology, evaluation, and management. *Turk Urol Derg.* (2014) 40:1–8. doi: 10.5152/tud.2014.222014
5. Ostrowski I, Sledz E, Ciechan J, Golabek T, Bukowczan J, Przydacz M, et al. Current interventional management of male stress urinary incontinence following urological procedures. *Cent Eur J Urol.* (2015) 68:340–7. doi: 10.5173/ceju.2015.616
6. Adamowicz J, Kuffel B, Van Breda SV, Pokrwczynska M, Drewa T. Reconstructive urology and tissue engineering: converging developmental paths. *J Tissue Eng Regen Med.* (2019) 13: 522–33. doi: 10.1002/term.2812
7. Basiri A, de la Rosette JJ, Tabatabaei S, Woo HH, Laguna MP, Shemshaki H. Comparison of retropubic, laparoscopic and robotic radical prostatectomy: who is the winner? *World J Urol.* (2018) 36:609–21. doi: 10.1007/s00345-018-2174-1
8. Hoyland K, Vasdev N, Abrof A, Boustead G. Post-radical prostatectomy incontinence: etiology and prevention. *Rev Urol.* (2014) 16:181–8.
9. Hinata N, Murakami G. The urethral rhabdosphincter, levator ani muscle, and perineal membrane: a review. *Biomed Res Int.* (2014) 2014:906921. doi: 10.1155/2014/906921
10. Koraitim MM. The male urethral sphincter complex revisited: an anatomical concept and its physiological correlate. *J Urol.* (2008) 179:1683–9. doi: 10.1016/j.juro.2008.01.010
11. Comiter C V., Dobberfuhl AD. The artificial urinary sphincter and male sling for postprostatectomy incontinence: which patient should get which procedure? *Korean J Urol.* (2016) 57:3–13. doi: 10.4111/icu.2016.57.1.3
12. Hollabaugh RS, Dmochowski RR, Steiner MS. Neuroanatomy of the male rhabdosphincter. *Urology.* (1997) 49:426–34. doi: 10.1016/S0090-4295(96)00497-9
13. Ali M, Johnson IP, Hobson J, Mohammadi B. Anatomy of the Pelvic Plexus and Innervation of the Prostate Gland. *Clin Anat.* (2004). 17:123-129. doi: 10.1002/ca.10187
14. Eichelberg C, Erbersdobler A, Michl U, et al. Nerve distribution along the prostatic capsule. *Eur Urol.* (2007) 51:105–10; discussion 110-1. doi: 10.1016/j.eururo.2006.05.038
15. Walsh PC. anatomical studies of the neurovascular bundle and cavernosal nerves. *J Urol.* (2005) 174:566. doi: 10.1097/01.ju.0000168033.81966.aa
16. Alsaid B, Bessede T, Diallo D, Moszkowicz D, Karam I, Benoit G, et al. Division of autonomic nerves within the neurovascular bundles distally into corpora cavernosa and corpus spongiosum components: immunohistochemical confirmation with three-dimensional reconstruction. *Eur Urol.* (2011) 59:902–9. doi: 10.1016/j.eururo.2011.02.031
17. Chabert CC, Merrilees DA, Neill MG, Eden CG. Curtain dissection of the lateral prostatic fascia and potency after laparoscopic radical prostatectomy: A veil of mystery. *BJU Int.* (2008) 101:1285–8. doi: 10.1111/j.1464-410X.2008.07595.x
18. Boubaker MB, Ganghoffer JF. Bladder/prostate/rectum: biomechanical models of the mobility of pelvic organs in the context of prostate radiotherapy. In: *Biomechanics of Living Organs: Hyperelastic Constitutive Laws for Finite Element Modeling*. New York, NY: Springer (2017).
19. Singla AK. Male incontinence: pathophysiology and management.: *Indian J Urol.* (2007) 23:174–9. doi: 10.4103/0970-1591.32070
20. Juszczak K, Ostrowski A, Bryczkowski M, Adamczyk P, Drewa T. A hypothesis for the mechanism of urine incontinence in patients after radical prostatectomy due to urinary bladder hypertrophy. *Adv Clin Exp Med.* (2019) 28:391–5. doi: 10.17219/acem/79935
21. Gonzalez EJ, Arms L, Vizzard MA. The role(s) of cytokines/chemokines in urinary bladder inflammation and dysfunction. *Biomed Res Int.* (2014) 2014:120525. doi: 10.1155/2014/120525
22. Pokrywczynska M, Jundzill A, Rasmus M, Adamowicz J, Balcerczyk D, Buhl M, et al. Understanding the role of mesenchymal stem cells in urinary bladder regeneration - a preclinical study on a porcine model. *Stem Cell Res Ther.* (2018) 9:328. doi: 10.1186/s13287-018-1070-3
23. Golabek T, Wiatr T, Przydacz M, Bukowczan J, Dudek P, Sobczynski R, et al. Optimizing the formation of vesicourethral anastomosis and reduction of procedure time. A two-year experience with a modified technique for endoscopic running vesicourethral anastomosis. *Cent Eur J Urol.* (2015) 68:296–301. doi: 10.5173/ceju.2015.617
24. Basu RK, Hubchak S, Hayashida T, Runyan CE, Schumacker PT, Schnaper HW. Interdependence of HIF-1α and TGF-β3/Smad3 signaling in normoxic and hypoxic renal epithelial cell collagen expression. *Am J Physiol - Ren Physiol.* (2011) 300:F898–905. doi: 10.1152/ajprenal.00335.2010
25. Baskin LS, Constantinescu SC, Howard PS, McAninch JW, Ewalt DH, Duckett JW, et al. Biochemical characterization and quantitation of the collagenous components of urethral stricture tissue. *J Urol.* (1993) 150(2 Pt 2):642–7. doi: 10.1016/S0022-5347(17)35572-6
26. Kessler TM, Burkhard FC, Studer UE. Nerve-sparing open radical retropubic prostatectomy. *Eur Urol.* (2007) 51:90–97. doi: 10.1016/j.eururo.2006.10.013
27. Gaudet AD, Popovich PG, Ramer MS. Wallerian degeneration: gaining perspective on inflammatory events after peripheral nerve injury. *J Neuroinflammation.* (2011) 8:110. doi: 10.1186/1742-2094-8-110
28. Adamowicz J, Pokrywczynska M, Van Breda SV, Kloskowski T, Drewa T. Concise review: tissue engineering of urinary bladder; we still have a long way to go? *Stem Cells Transl Med.* (2017) 6:2033–43. doi: 10.1002/sctm.17-0101
29. Hermann DM, Kleinschnitz C, Gunzer M. Role of polymorphonuclear neutrophils in the reperfused ischemic brain: insights from cell-type-specific immunodepletion and fluorescence microscopy studies. *Ther Adv Neurol Disord.* (2018) 11:1756286418798607. doi: 10.1177/1756286418798607
30. Pokrywczyńska M, Kloskowski T, Balcerczyk D, Buhl M, Jundziłł A, Nowacki M, et al. Stem cells and differentiated cells differ in their sensitivity to urine *in vitro*. *J Cell Biochem.* (2018) 119:2307–19. doi: 10.1002/jcb.26393
31. Trans P, Lond RS, Ferguson MWJ, Kane SO. Scar – free healing : from embryonic mechanisms to adult therapeutic intervention email alerting service Scar-free healing : from embryonic mechanisms to adult therapeutic intervention. (2004) 359:839–50. doi: 10.1098/rstb.2004.1475
32. Drewa T, Adamowicz J, Sharma A. Tissue engineering for the oncologic urinary bladder. *Nat Rev Urol.* (2012) 9:561–72. doi: 10.1038/nrurol.2012.158
33. Adamowicz J, Kowalczyk T, Drewa T. Tissue engineering of urinary bladder-current state of art and future perspectives. *Cent Eur J Urol.* (2013) 66:202–6. doi: 10.5173/ceju.2013.02.art23
34. Adamowicz J, Juszczak K, Bajek A, Tworkiewicz J, Nowacki M, Marszalek A, et al. Morphological and urodynamic evaluation of urinary bladder wall regeneration: muscles guarantee contraction but not proper function-a rat model research study. *Transplant Proc.* (2012) 44:1429–34. doi: 10.1016/j.transproceed.2012.01.144
35. Pokrywczynska M, Adamowicz J, Sharma AK, Drewa T. Human urinary bladder regeneration through tissue engineering - an analysis of 131 clinical cases. *Exp Biol Med.* (2014) 239:264–71. doi: 10.1177/1535370213517615
36. Schäffler A, Büchler C. Concise review: adipose tissue-derived stromal cells-basic and clinical implications for novel cell-based therapies. *Stem Cells.* (2007) 25:818–27. doi: 10.1634/stemcells.2006-0589
37. Zuk PA, Zhu M, Ashjian P, De Ugarte DA, Huang JI, Mizuno H, et al. Human adipose tissue is a source of multipotent stem cells. *Mol Biol Cell.* (2002) 13:4279–95. doi: 10.1091/mbc.e02-02-0105
38. Fakhrieh M, Darvish M, Ardeshirylajimi A, Taheri M, Omrani MD. Improved bladder smooth muscle cell differentiation of the mesenchymal stem cells when grown on electrospun polyacrylonitrile/polyethylene oxide nanofibrous scaffold. *J Cell Biochem.* (2019) 120:15814–22. doi: 10.1002/jcb.28852
39. Jundziłł A, Pokrywczyńska M, Adamowicz J, Kowalczyk T, Nowacki M, Bodnar M, et al. Vascularization potential of electrospun poly(L-lactide-co-caprolactone) scaffold: the impact for tissue engineering. *Med Sci Monit.* (2017) 23:1540–51. doi: 10.12659/MSM.899659
40. Chen G, Shi X, Sun C, Li M, Zhou Q, Zhang C, et al. VEGF-mediated proliferation of human adipose tissue-derived stem cells. *PLoS ONE.* (2013) 8:e73673.doi: 10.1371/journal.pone.0073673
41. Pokrywczynska M, Rasmus M, Jundzill A, Balcerczyk D, Adamowicz J, Warda K, et al. Mesenchymal stromal cells modulate the molecular pattern of healing

process in tissue-engineered urinary bladder: the microarray data. *Stem Cell Res Ther.* (2019) 10:176. doi: 10.1186/s13287-019-1266-1
42. Baldari S, Di Rocco G, Piccoli M, Pozzobon M, Muraca M, Toietta G. Challenges and strategies for improving the regenerative effects of mesenchymal stromal cell-based therapies. *Int J Mol Sci.* (2017) 18:2087. doi: 10.3390/ijms18102087
43. Berglund AK, Fortier LA, Antczak DF, Schnabel L V. Immunoprivileged no more: measuring the immunogenicity of allogeneic adult mesenchymal stem cells. *Stem Cell Res Ther.* (2017) 8:288. doi: 10.1186/s13287-017-0742-8
44. Kshitiz, Park J, Kim P, Engler AJ, Levchenko A, Kim D-H. Control of stem cell fate and function by engineering physical microenvironments. *Integr Biol (Camb).* (2012) 4:1008–1018. doi: 10.1039/c2ib20080e
45. Adamowicz J, Pasternak I, Kloskowski T, Gniadek M, Van Breda SV, Buhl M, et al. Development of a conductive biocomposite combining graphene and amniotic membrane for replacement of the neuronal network of tissue-engineered urinary bladder. *Sci Rep.* (2020) 10:5824. doi: 10.1038/s41598-020-62197-3
46. Hussain G, Wang J, Rasul A, Anwar H, Qasim M, Zafar S, et al. Current status of therapeutic approaches against peripheral nerve injuries: a detailed story from injury to recovery. *Int J Biol Sci.* (2020) 16:116–134. doi: 10.7150/ijbs.35653
47. Jiang L, Jones S, Jia X. Stem cell transplantation for peripheral nerve regeneration: current options and opportunities. *Int J Mol Sci.* (2017) 18:94. doi: 10.3390/ijms18010094
48. Carvalho CR, Oliveira JM, Reis RL. modern trends for peripheral nerve repair and regeneration: beyond the hollow nerve guidance conduit. *Front Bioeng Biotechnol.* (2019) 7:337. doi: 10.3389/fbioe.2019.00337
49. Kamelska-Sadowska AM, Wojtkiewicz J, Kowalski IM. Review of the current knowledge on the role of stem cell transplantation in neurorehabilitation. *Biomed Res Int.* (2019) 2019:3290894. doi: 10.1155/2019/3290894
50. Cooney DS, Wimmers EG, Ibrahim Z, Grahammer J, Christensen JM, Brat GA, et al. Mesenchymal stem cells enhance nerve regeneration in a rat sciatic nerve repair and hindlimb transplant model. *Sci Rep.* (2016) 6:31306. doi: 10.1038/srep31306
51. Caseiro AR, Pereira T, Ivanova G, Luís AL, Maurício AC. Neuromuscular regeneration: perspective on the application of mesenchymal stem cells and their secretion products. *Stem Cells Int.* (2016) 2016:9756973. doi: 10.1155/2016/9756973
52. Kruminis-Kaszkiel E, Osowski A, Bejer-Oleńska E, Dziekoński M, Wojtkiewicz J. Differentiation of human mesenchymal stem cells from wharton's jelly towards neural stem cells using a feasible and repeatable protocol. *Cells.* (2020) 9:739. doi: 10.3390/cells9030739
53. Finley DS, Ellingson BM, Natarajan S, Zaw TM, Raman SS, Schulam P, et al. Diffusion tensor magnetic resonance tractography of the prostate: feasibility for mapping periprostatic fibers. *Urology.* (2012) 80:219–23. doi: 10.1016/j.urology.2012.03.027
54. Adamowicz J, Drewa T, Tworkiewicz J, Kloskowski T, Nowacki M, Pokrywczyńska M. Schwann cells - a new hope in tissue engineered urinary bladder innervation. A method of cell isolation. *Cent Eur J Urol.* (2011) 64:87. doi: 10.5173/ceju.2011.02.art8
55. Gomez RG, Scarberry K. Anatomy and techniques in posterior urethroplasty. *Transl Androl Urol.* (2018) 7:567–79. doi: 10.21037/tau.2018.03.05
56. Albersen M, Joniau S, Claes H, Van Poppel H. Preclinical evidence for the benefits of penile rehabilitation therapy following nerve-sparing radical prostatectomy. *Adv Urol.* (2008) 2008:594868. doi: 10.1155/2008/594868
57. Guo Y, Yu Y, Hu S, Chen Y, Shen Z. The therapeutic potential of mesenchymal stem cells for cardiovascular diseases. *Cell Death Dis.* (2020) 11:349. doi: 10.1038/s41419-020-2542-9
58. Simitzi C, Hendow E, Li Z, Day RM. Promotion of proangiogenic secretome from mesenchymal stromal cells via hierarchically structured biodegradable microcarriers. *Adv Biosyst.* (2020) 4:e2000062. doi: 10.1002/adbi.202000062
59. Ferguson SW, Wang J, Lee CJ, Liu M, Neelamegham S, Canty JM, et al. The microRNA regulatory landscape of MSC-derived exosomes: a systems view. *Sci Rep.* (2018) 8:1419. doi: 10.1038/s41598-018-19581-x
60. Merino-González C, Zuñiga FA, Escudero C, Ormazabal V, Reyes C, Nova-Lamperti E,et al. Mesenchymal stem cell-derived extracellular vesicles promote angiogenesis: potencial clinical application. *Front Physiol.* (2016) 7:24. doi: 10.3389/fphys.2016.00024
61. Sato Y, Bando H, Di Piazza M, Gowing G, Herberts C, Jackman S, et al. Tumorigenicity assessment of cell therapy products: the need for global consensus and points to consider. *Cytotherapy.* (2019) 21:1095–1111. doi: 10.1016/j.jcyt.2019.10.001
62. Vazin T, Freed WJ. Human embryonic stem cells: derivation, culture, and differentiation: a review. *Restor Neurol Neurosci.* (2010) 28:589–603. doi: 10.3233/RNN-2010-0543
63. Zhou J, Tan X, Tan Y, Li Q, Ma J, Wang G. Mesenchymal stem cell derived exosomes in cancer progression, metastasis and drug delivery: a comprehensive review. *J Cancer.* (2018) 9:3129–37. doi: 10.7150/jca.25376
64. Zhao R, Chen X, Song H, Bie Q, Zhang B. Dual role of msc-derived exosomes in tumor development. *Stem Cells Int.* (2020) 2020:8844730. doi: 10.1155/2020/8844730
65. Cheng J, Yang K, Zhang Q, Yu Y, Meng Q, Mo N, et al. The role of mesenchymal stem cells in promoting the transformation of androgen-dependent human prostate cancer cells into androgen-independent manner. *Sci Rep.* (2016) 6:16993. doi: 10.1038/srep16993
66. Mitterberger M, Marksteiner R, Margreiter E, Pinggera GM, Frauscher F, Ulmer H, et al. Myoblast and fibroblast therapy for post-prostatectomy urinary incontinence: 1-year followup of 63 patients. *J Urol.* (2008) 179:226–31. doi: 10.1016/j.juro.2007.08.154
67. Gerullis H, Eimer C, Georgas E, Homburger M, El-Baz AG, Wishahi M, et al. Muscle-derived cells for treatment of iatrogenic sphincter damage and urinary incontinence in men. *Sci World J.* (2012) 2012:898535. doi: 10.1100/2012/898535
68. Gotoh M, Yamamoto T, Kato M, Majima T, Toriyama K, Kamei Y, et al. Regenerative treatment of male stress urinary incontinence by periurethral injection of autologous adipose-derived regenerative cells: 1-year outcomes in 11 patients. *Int J Urol.* (2014) 21:294–300. doi: 10.1111/iju.12266
69. Choi JY, Kim TH, Yang JD, Suh JS, Kwon TG. Adipose-Derived regenerative cell injection therapy for postprostatectomy incontinence: a phase i clinical study. *Yonsei Med J.* (2016) 57:1152–8. doi: 10.3349/ymj.2016.57.5.1152
70. Garcia-Arranz M, Alonso-Gregorio S, Fontana-Portella P, Bravo E, Sebastian JD, Fernandez-Santos ME, et al. Two phase I/II clinical trials for the treatment of urinary incontinence with autologous mesenchymal stem cells. *Stem Cells Transl Med.* 9:1500–8. doi: 10.1002/sctm.19-0431
71. Shimizu S, Yamamoto T, Nakayama S, Hirakawa A, Kuwatsuka Y, Funahashi Y, et al. Design of a single-arm clinical trial of regenerative therapy by periurethral injection of adipose-derived regenerative cells for male stress urinary incontinence in Japan: The ADRESU study protocol. *BMC Urol.* (2017) 17:89. doi: 10.1186/s12894-017-0282-7
72. Raj AT, Kheur S, Bhonde R, Gupta AA, Patil VR, Kharat A. Use of bone marrow-derived mesenchymal stem cells in prostate cancer could increase the risk of cancer progression. *Stem Cells Transl Med.* (2019) 8:737–8. doi: 10.1002/sctm.19-0050
73. Patel VR, Samavedi S, Bates AS, Kumar A, Coelho R, Rocco B, et al. Dehydrated human amnion/chorion membrane allograft nerve wrap around the prostatic neurovascular bundle accelerates early return to continence and potency following robot-assisted radical prostatectomy: propensity score-matched analysis. *Eur Urol.* (2015) 67:977–80. doi: 10.1016/j.eururo.2015.01.012
74. Adamowicz J, Van Breda S, Tyloch D, Pokrywczynska M, Drewa T. Application of amniotic membrane in reconstructive urology; the promising biomaterial worth further investigation. *Expert Opin Biol Ther.* (2019) 19:9–24. doi: 10.1080/14712598.2019.1556255
75. Barski D, Gerullis H, Ecke T, Boros M, Brune J, Beutner U, et al. Application of dried human amnion graft to improve post-prostatectomy incontinence and potency: a randomized exploration study protocol. *Adv Ther.* (2020) 37:592–602. doi: 10.1007/s12325-019-01158-3
76. Bourgeois M, Loisel F, Obert L, Pluvy I, Gindraux F. Can the amniotic membrane be used to treat peripheral nerve defects? A review of literature. *Hand Surg Rehabil.* (2019) 38, 223–32. doi: 10.1016/j.hansur.2019.05.006
77. Saleh A, Abboudi H, Ghazal-Aswad MB, Mayer EK, Vale JA. Management of erectile dysfunction post-radical prostatectomy. *Res Reports Urol.* (2015) 7:19–33. doi: 10.2147/RRU.S58974
78. Yiou R, Hamidou L, Birebent B, Bitari D, Lecorvoisier P, Contremoulins I, et al. Safety of intracavernous bone marrow-mononuclear cells for postradical prostatectomy erectile dysfunction: an open dose-escalation pilot study. *Eur Urol.* (2016) 69:988–91. doi: 10.1016/j.eururo.2015.09.026
79. Yiou R, Hamidou L, Birebent B, Bitari D, Corvoisier PL, Contremoulins I, et al. Intracavernous injections of bone marrow mononucleated cells for postradical prostatectomy erectile dysfunction: final results of the

INSTIN clinical trial. *Eur Urol Focus.* (2017) 3:643–5. doi: 10.1016/j.euf.2017.06.009
80. Haahr MK, Jensen CH, Toyserkani NM, Andersen DC, Damkier P, Sørensen JA, et al. Safety and potential effect of a single intracavernous injection of autologous adipose-derived regenerative cells in patients with erectile dysfunction following radical prostatectomy: an open-label phase i clinical trial. *EBioMedicine.* (2016) 5:204–10. doi: 10.1016/j.ebiom.2016.01.024
81. Stemedix. Available online at: https://stemedix.com (accessed September, 2021).

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