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Reconstructive surgery in Peyronie's disease: What's new?

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(buccal mucosa, vein, dermis, *etc.*) and heterologous grafts (bovine pericardium, swine intestinal submucosa, porcine dermis, *etc.*) none currently represents the real "gold standard" because the data are extremely variable and frequently not representative. Several factors seem to favor buccal mucosa grafts over inert biocompatible materials: as vital tissue, buccal mucosa tends to heal rapidly, immediately integrating with the surrounding albuginea tissue. This translates into a more rapid resumption of spontaneous erections (after 3/4 d) and sexual activity and into a reduced risk of curvature relapse and erectile dysfunction after surgery. Another advantage of the buccal mucosa graft is its low cost. In conclusion, despite the recent development of some exciting new surgical techniques we are still unable to deliver a definitive take-home message about reconstructive surgery in PD because the majority of the studies reported insufficient data. However, since it is clear that major outcomes, besides the cosmetic result, are the patient's and partner's satisfaction and the economic impact of each technique, we recommend they be included among the outcome assessment parameters in further studies

Key words: Reconstructive urology; Peyronie's disease; Corporoplasty

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Abstract

Surgical treatment of Peyronie's disease (PD) is still a challenge and a gold standard approach does not exist; however the main goal is to straight penile shaft, and to restore penetrative and coital capacity. The less invasive approach aims to correct curvature without intervening directly on the fibrous plaque while the more complex "corporoplasty" applies specific geometric criteria and uses different autologous and heterologous grafts. Each approach has its pros and cons and decision-making should be tailored to the individual patient's expectations. Other surgical options include different use of patches to cover the tunica albuginea defect, with the choice depending on the surgeon's personal experience. Despite the wide range of autologous

Core tip: Surgical treatment of Peyronie's disease is still a challenge and a "gold standard" approach does not exist. This paper tries to review the main surgical techniques making an assessment of functional and aesthetical results, underling costs and benefits.

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INTRODUCTION

Even though Peyronie's disease (PD) may affect 1% to 23% of men between 40 and 70 years of age its real incidence could be under-estimated because of men's embarrassment and health care providers' limited reporting^[1]. Treatment of PD is still a challenge and a gold standard approach does not exist. Basically, when conservative therapies fail, the only option is surgery, which is usually reserved for patients with stabilized chronic disease. Surgical treatment avails of two main approaches to achieve its principal objectives of straightening the penile shaft, and restoring penetrative and coital capacity^[2,3]. The less invasive approach aims at correcting curvature without intervening directly on the fibrous plaque while the more complex corporoplasty applies specific geometric criteria and uses different autologous and heterologous grafts^[4]. Each approach has its pros and cons and decision-making should be tailored to the individual patient's expectations.

Many surgeons avoid plaque surgery by performing techniques like the Nesbit^[5] or Yachia^[6] in elderly patients with their associated risk factors and in patients with a sufficiently long penis and no more than 30°/40° curvature. These approaches act prevalently on the convex side of the curvature to counterbalance the lines of force caused by plaque fibrosis. Cosmetic results are good but not completely satisfactory because penile shaft shortening, the extent of which depends on the pre-existing degree of curvature, often creates notable psychological problems for patients.

An alternative option is fibrous plaque incision which aims at reducing traction but cannot restore length and girth to the penis^[7-9]. Consequently, to achieve the best cosmetic and functional results, simple incision has evolved to include application of "geometric" principles (Austoni *et al.*^[7] and Egydio *et al.*^[8,9] and Zucchi *et al.*^[10]).

The complex Egydio technique requires a series of measurements that enable the surgeon to perform a single, relaxing incision and prepare the graft, which is a collagenous matrix of bovine pericardium, precisely. It restores penile length and girth with good functional results and sexual satisfaction^[8,9,11].

The simpler Austoni technique is reserved for PD patients with curvature and a slight erectile dysfunction (ED). A special silicone axial support (Virilis I®) is implanted to help extend the shaft and identify with extreme precision the point of maximum penile curvature, thus facilitating corporoplasty and preventing scarring and graft retraction^[7,10].

Rolle *et al.*^[12] recently described a new lengthening procedure to resolve severe shortening of the penis due to PD in 3 cases. It is based on a ventro-dorsal incision of the tunica albuginea, penile prosthesis implantation, and double dorsal-ventral patch grafting with porcine small intestinal submucosa. The average increase in length was 3.2 cm and all patients resumed sexual intercourse with satisfaction, no significant loss

of sensitivity or any sign of vascular distress in the glans. Since the technique was carried out in such a limited number of cases, the results need to be confirmed by larger prospective studies^[12].

Another innovative approach links the geometrical principles of the Egydio technique with a circular tunica albuginea incision at the point of maximum curvature in order to achieve maximum restoration of the original penile girth and length. Inflatable two- or three-piece or malleable penile prostheses are implanted and pericardium grafts are used to cover the defects. In cases of severe penile shortening and narrowing this extensive penile shaft reconstruction is highly effective, as it achieves maximum penile length gain and girth restoration, regardless of plaque characteristics^[13].

Other surgical options include corporoplasty and the use of a patch to cover the tunica albuginea defect, with the choice depending on the surgeon's personal experience. Autologous grafts include buccal mucosa, saphenous vein and derma while the most commonly used materials for the heterologous patch are the pericardium, the Swine Intestinal Submucosa (SIS) and the porcine dermis. Since these materials tend to mimic the tunica albuginea scarring, which could cause graft retraction and surgical failure, is prevented as much as possible^[14-16]. Despite the wide range of autologous and heterologous grafts, none currently represents the real "gold standard"^[14,15] because the data are extremely variable and frequently not representative.

A recent review by Levine *et al.*^[14] assessed 37 of the major case studies reported in the literature. It included corporoplasty with plaque incision and grafting, and demonstrated that biocompatible materials do not provide better outcomes in terms of satisfaction or postoperative ED than autologous grafts or buccal mucosa. Many studies did not include complete information. In 4 studies which used SIS (227 patients), only one reported a 79% satisfaction rate and globally ED ranged from 9% to 45%^[17-20]. In 7 studies which implanted a pericardial graft (136 patients), only 3 reported the satisfaction rate (74% to 92%) with ED varying from 0%-30%^[21-27]. Outcomes are comparable in the buccal mucosa graft series with ED in 0-3% of the cases and a 85%-100% satisfaction rate^[16,28].

Since corporoplasty with buccal mucosa provides such promising results it is worth focusing on how it is performed^[16]. The mouth is prepared using 0.4% chlorhexidine solution and the largest possible free buccal mucosa graft is harvested from the cheek; the wound is sutured using a continuous 2-0 Vicryl rapid suture. Under general anesthesia penile degloving is followed by an hydraulic erection. Buck's fascia is bilaterally incised, close to the urethra to isolate the neuro-vascular bundles or the urethra, according to plaque location. After a double Y-shaped plaque incision at the site of maximal curvature the penis is manually stretched to carefully dissect the underlying cavernous tissue by the tunica and to measure the size

of the gap that the buccal mucosa graft has to cover. Because of buccal mucosa's intrinsic property of great elasticity, the graft does not require oversizing. It is stretched over a table for "defatting", placed with its submucosal surface on cavernous tissue and sutured to the tunica margins with reabsorbable sutures (Vicryl 3/0). Penile straightening and length are tested in a hydraulic erection. If correction of the primary curvature is incomplete a contralateral albuginea plication may be needed.

Several factors seem to favor buccal mucosa grafts over inert biocompatible materials. The latter need an integration time of 4 to 6 wk to reconstitute scar tissue which is surely more "abundant" and "reactive" than after implants made of a living tissue, such as buccal mucosa which, thanks to its elevated binding capacity and revascularization, is immediately supplied with blood from the cavernous tissue. As vital tissue, buccal mucosa tends to heal rapidly, immediately integrating with the surrounding albuginea tissue. This translates into a more rapid resumption of spontaneous erections and sexual activity and into a reduced risk of curvature relapse and ED after surgery^[28]. Another advantage of the buccal mucosa graft is its low cost. The average cost of most bio-compatible materials that are usually implanted in Europe ranges 500-1000 euros, to which the cost of buying or hiring a vacuum device must be added as patients require rehabilitation to prevent scarring-related retraction. Consequently, the total costs rise to about 1500/2000 euro per patient. When the buccal mucosa graft is used, the patients do not need a vacuum device, as spontaneous erections return 2/3 d after surgery.

In conclusion, despite the recent development of some exciting new surgical techniques we are still unable to deliver a definitive take-home message about reconstructive surgery in Peyronie's Disease because the majority of the studies reported insufficient data. However, since it is clear that major outcomes, besides the cosmetic result, are the patient's and partner's satisfaction, we recommend they be included among the outcome assessment parameters in further studies. Last but not least a look at the economic impact of each technique would not go amiss in the era of spending reviews on health care.

REFERENCES

- 1 Peyronie's disease. Urology Care Foundation website. Available from: URL: <http://www.urologyhealth.org/urology/index.cfm?article=115>
- 2 Vardi Y, Levine LA, Chen J, Hatzimouratidis K, Sohn M. Is there a place for conservative treatment in Peyronie's disease? *J Sex Med* 2009; **6**: 903-909 [PMID: 19338644]
- 3 Taylor FL, Levine LA. Non-surgical therapy of Peyronie's disease. *Asian J Androl* 2008; **10**: 79-87 [PMID: 18087647]
- 4 Ralph D, Gonzalez-Cadavid N, Mirone V, Perovic S, Sohn M, Usta M, Levine L. The management of Peyronie's disease: evidence-based 2010 guidelines. *J Sex Med* 2010; **7**: 2359-2374 [PMID: 20497306 DOI: 10.1111/j.1743-6109.2010.01850.x]
- 5 Pryor JP. Correction of penile curvature and Peyronie's disease: why I prefer the Nesbit technique. *Int J Impot Res* 1998; **10**: 129-131 [PMID: 9647952]
- 6 Yachia D. Modified corporoplasty for the treatment of penile curvature. *J Urol* 1990; **143**: 80-82 [PMID: 2294269]
- 7 Austoni E, Colombo F, Romanò AL, Guarneri A, Kartalas Goumas I, Cazzaniga A. Soft prosthesis implant and relaxing albuginea incision with saphenous grafting for surgical therapy of Peyronie's disease: a 5-year experience and long-term follow-up on 145 operated patients. *Eur Urol* 2005; **47**: 223-229; discussion 229 [PMID: 15661418]
- 8 Egydio PH, Lucon AM, Arap S. A single relaxing incision to correct different types of penile curvature: surgical technique based on geometrical principles. *BJU Int* 2004; **94**: 1147-1157 [PMID: 15541152]
- 9 Egydio PH, Sansalone S. Peyronie's reconstruction for maximum length and girth gain: geometrical principles. *Adv Urol* 2008; 205739 [PMID: 19081785 DOI: 10.1155/2008/205739]
- 10 Zucchi A, Silvani M, Pecoraro S. Corporoplasty with small soft axial prostheses (VIRILIS I®) and bovine pericardial graft (HYDRIX®) in Peyronie's disease. *Asian J Androl* 2013; **15**: 275-279 [PMID: 23353721 DOI: 10.1038/aja.2012.156]
- 11 Sansalone S, Garaffa G, Djinic R, Pecoraro S, Silvani M, Barbagli G, Zucchi A, Vespasiani G, Loreto C. Long-term results of the surgical treatment of Peyronie's disease with Egydio's technique: a European multicentre study. *Asian J Androl* 2011; **13**: 842-845 [PMID: 21743482 DOI: 10.1038/aja.2011.42]
- 12 Rolle L, Ceruti C, Timpano M, Sedigh O, Destefanis P, Galletto E, Falcone M, Fontana D. A new, innovative, lengthening surgical procedure for Peyronie's disease by penile prosthesis implantation with double dorsal-ventral patch graft: the "sliding technique". *J Sex Med* 2012; **9**: 2389-2395 [PMID: 22429331 DOI: 10.1111/j.1743-6109.2012.02675.x]
- 13 Egydio PH, Kuehhas FE, Sansalone S. Penile length and girth restoration in severe Peyronie's disease using circular and longitudinal grafting. *BJU Int* 2013; **111**: E213-E219 [PMID: 23107452 DOI: 10.1111/j.1464-410X.2012.11582.x]
- 14 Levine LA, Larsen SM. Surgery for Peyronie's disease. *Asian J Androl* 2013; **15**: 27-34 [PMID: 23178395 DOI: 10.1038/aja.2012.92]
- 15 Levine LA, Burnett AL. Standard operating procedures for Peyronie's disease. *J Sex Med* 2013; **10**: 230-244 [PMID: 23211057 DOI: 10.1111/j.1743-6109.2012.03003.x]
- 16 Cormio L, Zucchi A, Lorusso F, Selvaggio O, Fioretti F, Porena M, Carrieri G. Surgical treatment of Peyronie's disease by plaque incision and grafting with buccal mucosa. *Eur Urol* 2009; **55**: 1469-1475 [PMID: 19084325 DOI: 10.1016/j.eururo.2008.11.041]
- 17 Breyer BN, Brant WO, Garcia MM, Bella AJ, Lue TF. Complications of porcine small intestine submucosa graft for Peyronie's disease. *J Urol* 2007; **177**: 589-591 [PMID: 17222639]
- 18 Knoll LD. Use of small intestinal submucosa graft for the surgical management of Peyronie's disease. *J Urol* 2007; **178**: 2474-2478; discussion 2478 [PMID: 17976656]
- 19 Staerman F, Pierrelvein J, Ripert T, Menard J. Medium-term follow-up of plaque incision and porcine small intestinal submucosal grafting for Peyronie's disease. *Int J Impot Res* 2010; **22**: 343-348 [PMID: 21124338 DOI: 10.1038/ijir.2010.28]
- 20 Lee EW, Shindel AW, Brandes SB. Small intestinal submucosa for patch grafting after plaque incision in the treatment of Peyronie's disease. *Int Braz J Urol* 2008; **34**: 191-196; discussion 197 [PMID: 18462517]
- 21 Egydio PH, Lucon AM, Arap S. Treatment of Peyronie's disease by incomplete circumferential incision of the tunica albuginea and plaque with bovine pericardium graft. *Urology* 2002; **59**: 570-574 [PMID: 11927316]
- 22 Chun JL, McGregor A, Krishnan R, Carson CC. A comparison of dermal and cadaveric pericardial grafts in the modified Horton-Devine procedure for Peyronie's disease. *J Urol* 2001; **166**: 185-188 [PMID: 11435853]
- 23 Usta MF, Bivalacqua TJ, Sanabria J, Koksai IT, Moparty K, Hellstrom WJ. Patient and partner satisfaction and long-term results after surgical treatment for Peyronie's disease. *Urology* 2003; **62**:

- 105-109 [PMID: 12837432]
- 24 **Hellstrom WJ**, Reddy S. Application of pericardial graft in the surgical management of Peyronie's disease. *J Urol* 2000; **163**: 1445-1447 [PMID: 10751854]
- 25 **Kovac JR**, Brock GB. Surgical outcomes and patient satisfaction after dermal, pericardial, and small intestinal submucosal grafting for Peyronie's disease. *J Sex Med* 2007; **4**: 1500-1508 [PMID: 17433088]
- 26 **Leungwattanakij S**, Bivalacqua TJ, Reddy S, Hellstrom WJ. Long-term follow-up on use of pericardial graft in the surgical management of Peyronie's disease. *Int J Impot Res* 2001; **13**: 183-186 [PMID: 11525318]
- 27 **Levine LA**, Estrada CR. Human cadaveric pericardial graft for the surgical correction of Peyronie's disease. *J Urol* 2003; **170**: 2359-2362 [PMID: 14634416]
- 28 **Zucchi A**, Silvani M, Pastore AL, Fioretti F, Fabiani A, Villirillo T, Costantini E Corporoplasty Using Buccal Mucosa Graft in Peyronie Disease: Is It a First Choice? *Urology* 2014; In press [PMID: 25582815 DOI: 10.1016/j.urology.2014.10.026]

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Urological manifestations and treatment of the primary systemic vasculitides

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Purpura (HSP), anti-neutrophil cytoplasm antibody associated Vasculitides (AAV), Giant Cell Arteritis (GCA) and Kawasaki disease. Prostatic vasculitis has been reported in association with GCA and AAV. Ureteric involvement has been noted in PAN, HSP and AAV. Other urogenital manifestations of PSV include genital ulceration and bladder dysfunction in Behçets Disease and haematuria which is commonly seen in many of the PSV. Finally, therapies used to treat the PSV, especially cyclophosphamide, are associated with urological side-effects including haemorrhagic cystitis and urothelial malignancy. The aim of this review is to examine how the urological system is involved in the PSV. Each PSV is examined in turn, with a brief clinical description of the disease followed by a description of the urological manifestations and management. Identification of urological manifestations of PSV is important as in many cases symptoms may improve with immunosuppressive therapy, avoiding the need for invasive surgery. Additionally, patients who present with isolated urogenital PSV are at higher risk of developing subsequent systemic vasculitis and will need to be followed up closely.

Key words: Urology; Vasculitis; Takayasu arteritis; Giant cell arteritis; Polyarteritis Nodosa; Kawasaki disease; Henoch-Schönlein Purpura; Anti-neutrophil cytoplasm antibody associated vasculitides; Granulomatosis with polyangiitis; Microscopic polyangiitis; Behçets disease; Eosinophilic granulomatosis with polyangiitis; Epididymo-orchitis; Prostatitis; Ureteric stenosis

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Abstract

The primary systemic vasculitides (PSV) are a group of rare inflammatory disorders affecting blood vessels of varying size and multiple organs. Urological manifestations of PSV are uncommon. Testicular vasculitis is the most commonly reported finding and is associated with Polyarteritis Nodosa (PAN), Henoch-Schönlein

Core tip: Urogenital manifestations of primary systemic vasculitides are rare. Patients will usually have other systemic signs and symptoms to suggest an underlying vasculitic process. Inflammatory markers including erythrocyte sedimentation rate and C-reactive protein are often raised and specific auto-antibody testing may be useful in identifying the underlying diagnosis.

If an underlying vasculitic process is suspected, early involvement of a specialist is essential. Symptoms usually improve with immunosuppressive therapy and may avoid the need for invasive surgery. Patients who present with isolated single-organ vasculitis of the urogenital tract will need to be followed up closely in case they subsequently develop systemic disease.

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INTRODUCTION

The primary systemic vasculitides (PSV) are a group of rare inflammatory disorders affecting blood vessels of varying sizes and multiple organs. The PSV are classified according to the size of vessel they predominantly affect. Nomenclature and detailed definitions for each of the PSV were set out by the Chapel Hill Consensus Conference (CHCC) in 1994 and reviewed again in 2012^[1]. In this review each PSV is examined in turn, with a brief clinical description of the disease followed by a description of the urological manifestations and management (Table 1). It should however be borne in mind that the treatments for these diseases change and improve over time and management of these rare diseases should be undertaken in collaboration with a specialist with appropriate expertise.

LARGE VESSEL VASCULITIDES

Takayasu arteritis

Takayasu arteritis (TA) is a rare, systemic, large-vessel vasculitis of unknown aetiology. It is defined by the CHCC as "granulomatous inflammation of the aorta and its major branches". TA occurs most commonly in Mexico, Japan and parts of Asia, predominantly in women of childbearing age. It is classified depending on the specific part of the aorta that is affected. Complications of disease include stroke, seizures, hypertension and retinopathy. Treatment is usually with immunosuppression to control inflammation but if vessels become fibrosed and stenotic, angioplasty + stenting and bypass grafting may be necessary^[2,3].

No specific urological manifestations of TA have been reported in the literature. There are a few isolated case reports of retroperitoneal fibrosis causing obstructive uropathy in association with TA. In the acute setting this was managed with ureteric stents and long-term improvement in symptoms was noted with immunosuppressive therapy^[4-6].

Giant cell arteritis

Giant cell arteritis (GCA) is a large vessel vasculitis

characterized by granulomatous inflammation predominantly affecting the thoracic aorta and its branches.

Epidemiology and clinical features: It is predominantly a disease of older people with the highest incidence in patients 70-80 years of age. The incidence of disease is also highest in patients of Northern European, North American or Scandinavian descent^[7].

Constitutional symptoms such as fever, fatigue and weight loss are common in GCA as are specific manifestations of the disease include headache, scalp tenderness, jaw claudication and visual disturbance. Approximately 20% of patients will manifest clinical signs of large vessel involvement, including aneurysmal and stenotic lesions of the abdominal aorta^[8].

Treatment and prognosis: The mainstay of treatment in GCA is with high dose corticosteroids to induce disease remission. Methotrexate may be used as adjunctive therapy, whilst TNF inhibitors and the IL-6 inhibitor, tocilizumab, may have a role in the treatment of relapsing and refractory disease^[9,10].

The most serious complication in patients with GCA is blindness secondary to ischaemic optic neuropathy, which develops in approximately 7%-14% of all patients. As a result, patients often receive prolonged courses of steroids, with an average duration of therapy of two years. Side effects from long-term steroid therapy, include hypertension, diabetes and osteoporosis^[11].

Urological manifestations: Urological manifestations of GCA are seldom reported. Epididymal involvement has been reported in a 66-year-old male with a 3 mo history of generalised fatigue, right sided epididymal tenderness, raised inflammatory markers and a normochromic normocytic anaemia. Epididymal biopsy demonstrated chronic inflammatory cell infiltration and the presence of "giant cells". The patient subsequently underwent a temporal artery biopsy, which confirmed the diagnosis of giant cell arteritis. This patient responded well to high dose corticosteroids^[12].

Testicular involvement has also been reported in a 76-year-old male with weight loss, malaise and right testicular swelling. His ultrasound scan was suggestive of testicular malignancy and he underwent radical orchidectomy. The excised specimen showed a shrunken testis surrounded by dense, focally calcified tissue, up to 7 mm thick with patchy intimal thickening of the spermatic cord and a chronic inflammatory cell infiltrate in the vessel walls. One arteriole showed a focus of destructive arteritis with the presence of giant cells^[13].

MEDIUM VESSEL VASCULITIDES

Polyarteritis Nodosa

Polyarteritis Nodosa (PAN) is a rare necrotising systemic

Table 1 Summary of the urogenital manifestations of the primary systemic vasculitides, defined according to the Chapel Hill Consensus Criteria

Primary systemic vasculitides		Urogenital manifestations
Large vessel	Takayasu arteritis	Obstructive uropathy secondary to retroperitoneal fibrosis
	Giant cell arteritis	Epididymo-orchitis
Medium vessel	Polyarteritis Nodosa	Orchitis, ureteric stricture, haematuria, glomerulonephritis, spontaneous peri-renal haemorrhage
	Kawasaki's disease	Orchitis, ureteric stricture
Small vessel	Antineutrophil cytoplasmic antibody associated vasculitis	Glomerulonephritis, prostatitis
	Microscopic polyangiitis	Glomerulonephritis, prostatitis, orchitis, ureteric stenosis, penile ulceration, necrotizing urethritis, large renal and bladder granulomas ("pseudotumours")
	Granulomatosis with polyangiitis (Wegener's)	Prostatitis, ureteric stricture, urethral ulceration
	Eosinophilic granulomatosis with polyangiitis (Churg-Strauss)	
	Immune complex small vessel vasculitis	Glomerulonephritis, haematuria
	Anti-glomerular basement membrane disease	Glomerulonephritis, haematuria
	IgA vasculitis (Henoch-Schonlein)	Glomerulonephritis, haematuria, epididymo-orchitis, ureteric strictures, bladder wall hematoma, haemorrhagic cystitis, penile and scrotal pain and swelling, priapism, spermatic vein thrombosis
	Cryoglobulinaemic vasculitis	Glomerulonephritis, haematuria
	Hypocomplementaemic urticarial Vasculitis (anti-C1q vasculitis)	
Variable vessel	Behçets disease	Genital ulceration, epididymitis, sterile urethritis, bladder wall ulceration, cystitis, vesico-vaginal fistula, neuropathic bladder
	Cogan's syndrome	Nil

vasculitis typically affecting medium and small sized arteries. Inflammation usually targets muscular arteries at bifurcations or branch points. The inflammatory lesions start at the vessel intima and may progress to involve the entire arterial wall, destroying the internal and external elastic lamina and resulting in fibrinoid necrosis. The weakened vessel walls are prone to aneurysm formation and subsequent rupture, haemorrhage and thrombosis. During the healing process medial and intimal proliferation may result in occlusion of vessels, leading to tissue ischaemia or infarction^[14].

Glomerulonephritis and pulmonary involvement are not usually a feature of PAN, as there is characteristic sparing of smaller blood vessels including arterioles, capillaries and venules^[1].

PAN may be idiopathic or secondary to specific viral triggers, the most common of these being Hepatitis B viral (HBV) infection but rare associations with hepatitis C virus and HIV have been reported^[15,16]. Patients may display a wide variety of clinical presentations from limited single organ disease to widespread fulminant multi-organ failure.

Epidemiology: PAN is a rare disease. Accurate estimation of incidence and prevalence rates are difficult and largely dependent on the disease classification method used. Reported annual incidence of PAN in most developed countries is estimated between 2-9 cases/million population/year^[17-19], with overall prevalence of the disease estimated at approximately 30 cases/million population in France^[20]. PAN can affect patients of any age, ethnicity or gender but a peak in incidence has been consistently noted in the 5th and 6th decades

of life. Males are also more commonly affected than females^[21].

Over the past 20 years PAN has become less common. This may be due to a reduction in the number of PAN cases secondary to HBV infection, falling from approximately one third of all cases to 7%-10% in more recent estimates^[22] which may be secondary to widespread HBV vaccination of high risk groups and screening of blood products^[23]. The reduction in PAN cases may also be due to re-classification of a number of other necrotising systemic vasculitides, which were previously grouped together as PAN, including Microscopic polyangiitis (MPA) and cryoglobulinaemic vasculitis.

Clinical features: Patients typically present with systemic symptoms including malaise, weight loss and fever. The kidneys, skin, joints, muscles, nerves, and gastrointestinal tract are commonly involved (Table 2)^[21].

Classification and diagnosis: There is no specific serological test for PAN and a combined assessment of clinical, angiographic and biopsy findings are usually required for diagnosis. Angiographic evaluation is key to this process with conventional arteriography remaining a "gold standard" despite MRI and CT being increasingly used for this purpose. Typical findings are multiple small aneurysms (< 1 cm) which are most commonly seen in the distribution of the renal and mesenteric arteries, although these are not pathognomic for PAN^[24]. Biopsy findings include the presence of transmural non-granulomatous necrotising inflammation in medium sized arteries^[25]. Areas most likely to be biopsied are those easily accessible

Table 2 Main clinical manifestations of patients with polyarteritis nodosa^[7,14]

Manifestation	Specific problems	Frequency
Systemic symptoms	Fever, malaise, weight loss, myalgias arthralgias	80%
Neuropathy	Mononeuritis multiplex, polyneuropathy	75%
Arthralgias and/or myalgias	Articular and/or diffuse extremity pain	60%
Cutaneous	Livedo reticularis, purpura, ulcers	50%
Renal disease	Elevated creatinine, haematuria, proteinuria	50%
Gastrointestinal symptoms	Abdominal pain, nausea/vomiting, diarrhoea rectal bleeding, ulceration, peritonitis	40%
Hypertension	New onset	35%
Central nervous system disease	Stroke, confusion	20%
Orchitis	Testicular pain, swelling	20%
Cardiac involvement	Cardiomyopathy, pericarditis, palpitations, myocardial infarction	10%
Peripheral vascular disease	Claudication, ischaemia, necrosis	10%
Ophthalmological	Exudates, vasculitis	10%

including, sural nerve, muscles and testes^[26,27].

Classification of PAN was published by the American College of rheumatology (ACR) in 1990^[28]. This classification lists the following typical signs and symptoms of PAN: (1) Livedo reticularis; (2) Testicular pain or tenderness; (3) Myalgia (excluding that of the shoulder hip and girdle) or weakness; (4) Mononeuropathy or polyneuropathy; (5) New onset rise in diastolic blood pressure > 90 mmHg; (6) Elevated levels of serum blood urea nitrogen (> 40 mg/dL or > 14.3 mmol/L) or creatinine (> 1.5 mg/dL or > 132 mmol/L); (7) Evidence of hepatitis B virus infection *via* serum antibody or antigen serology; (8) Characteristic arteriographic abnormalities not resulting from non-inflammatory disease processes; and (9) A biopsy of medium or small sized artery containing polymorphonuclear cells.

According to the ACR criteria, the presence of at least 3 of these features is required for classification of disease as PAN with 82% sensitivity and 87% specificity rate.

Treatment and prognosis: Previously, untreated PAN was fatal in weeks to months in approximately 50% of patients. The five year survival rate was as low as 13%. In 1996 the French Vasculitis Study Group (FVSG) analysed data from a prospective study of 346 patients with PAN and eosinophilic granulomatosis with polyangiitis (EGPA) and identified five factors that were associated with poor prognosis. These factors are: (1) Renal Involvement-Proteinuria > 1 g/24 h; (2) Renal Impairment-Serum creatinine > 1.5 mg/dL; (3) Gastrointestinal Involvement-Presence of bleeding, perforation, infarction or pancreatitis; (4) Neurological Involvement; and (5) Cardiac involvement-Presence of cardiomyopathy.

These factors were adapted into a prognostic "Five Factor Score" (FFS) system. The presence of any one of these five factors is associated with poor prognosis and increased mortality^[29]. When the FFS is zero, the predicted mortality rate at 5 years is 11.9%. When the FFS is 1, the mortality rate is 25.9%, and when the FFS is 2 or more, the mortality rate is as high as

45.9%.

Trials conducted by the FVSG suggest that corticosteroids alone are adequate first line therapy for patients with PAN with a FFS of zero although 40% may require additional immunosuppression^[30]. Patients with a FFS ≥ 1 should receive intermittent intravenous cyclophosphamide in addition to corticosteroids^[31]. For cases of HBV associated PAN, antiviral therapy, including vidarabine, lamivudine and interferon alpha 2-b, may be added to corticosteroid therapy, with or without plasma exchange^[32,33].

Urological manifestations: Urogenital manifestations are reported more commonly in patients with PAN secondary to HBV infection than in patients with primary PAN^[34]. Autopsy data from patients with PAN confirms testicular involvement in 38%-86% of cases. Of these patients only 18% will manifest any clinical signs and symptoms^[35]. Testicular involvement may be part of a spectrum of systemic involvement or in rare cases it may be an isolated presentation of the disease. It is not unusual to see unilateral testicular involvement as part of a spectrum of systemic disease. Symptoms of testicular involvement are hugely variable, ranging from completely asymptomatic to severe pain, swelling, erythema and/or a local mass, with one isolated case report of asynchronous bilateral complete testicular necrosis in association with PAN^[36]. This clinical picture often leads to a misdiagnosis of acute orchitis, torsion or neoplasm. As laboratory data and radiological findings are often non-specific in these cases, histological analysis of biopsy specimens remains the mainstay of diagnosis. Testicular biopsies in PAN commonly reveal transmural necrotising arteritis with focal infarcts and haemorrhagic lesions, vasculitis of testicular and epididymal arteries is commonly noted^[36-45].

Corticosteroid therapy, with or without cyclophosphamide in refractory cases, has good outcomes for testicular symptoms in PAN. Length of therapy and dosage will vary in each individual case^[37,38,46]. Current consensus is that orchidectomy is the treatment of choice in cases of isolated single-organ testicular

PAN. In many of these cases exclusion of a testicular neoplasm is difficult on the basis of clinical findings and the safest option is to remove the testicle. Close follow up and monitoring of these patients is also essential to rule out subsequent development of systemic PAN, although analysis of case reports show that this has rarely been reported^[39].

There are a number of case reports describing ureteral strictures in polyarteritis nodosa^[47-55]. The finding of imprints on the ureteral wall or a nodular appearance of the ureter, simulating a string of pearls, on an excretory urogram, are suggested to be pathognomonic for this disorder^[51]. In the majority of these cases resolution of the stricture was achieved with systemic therapy for PAN but in isolated cases, resection of the stenosed ureteric segment became necessary^[49].

There is a single case report of a patient with hepatitis B-associated PAN presenting with bilateral hydronephrosis in the absence of an obstructive lesion. It was presumed that vasculitis-related myopathy or neuropathy of the ureter was the most likely cause of this finding. The patient was treated with high-dose steroids, cyclophosphamide, and plasmapheresis with successful resolution of the hydronephrosis and resolution of acute kidney injury^[56].

Kidneys are commonly affected in PAN. Luminal narrowing of inflamed renal arteries leads to glomerular ischemia but not inflammation or necrosis. Urinalysis in PAN, when abnormal, tends to show sub-nephrotic range proteinuria and microscopic hematuria. Red blood cell casts (indicative of a glomerular focus of inflammation) are usually absent. In patients with red blood cell casts, alternative diagnoses should be considered, including anti-neutrophil cytoplasm antibody (ANCA)-associated vasculitis or systemic lupus erythematosus.

Aneurysm formation of renal arteries in PAN may lead to life-threatening spontaneous peri-renal haemorrhage (SPH). In a meta-analysis of 165 cases of SPH, PAN was the reported cause in 12% of patients and is the most likely cause in patients with bilateral SPH^[57]. The typical clinical presentation is of a patient with loin pain and a peri-renal mass, in combination with hypotension and a significant fall in haemoglobin. Rapid recognition of this condition and emergency resuscitation is essential. CT angiogram is the imaging modality of choice and endovascular management, such as percutaneous transcatheter embolisation is used with increased frequency to deal with ruptured visceral artery aneurysms associated with PAN^[58]. In some cases the haemorrhage resolved with conservative therapy and observation but in other cases surgical evacuation of the haematoma or partial/complete nephrectomy was necessary^[57].

syndrome of early childhood.

Epidemiology and clinical features: KD is one of the commonest vasculitides in early childhood, with the majority of cases occurring in patients less than 5 years of age and a peak in incidence occurring at approximately 30 mo of age. There is significant geographical variation in the incidence of KD with the majority of cases occurring in East Asia^[59].

Diagnosis of KD is confirmed by the presence of fever for > 5 d and four of the following American Heart Association diagnostic criteria, listed below^[60]: (1) Bilateral conjunctival injection; (2) Changes of the mucous membranes of the upper respiratory tract: injected pharynx; injected, fissured lips; strawberry tongue; (3) Polymorphous rash; (4) Changes of the extremities: peripheral oedema, peripheral erythema, periungual desquamation; and (5) Cervical adenopathy.

KD is a self-limiting disease, lasting for an average of 10-12 d without treatment. However coronary artery aneurysms develop in 20%-25% of cases with significant morbidity and mortality if untreated^[59].

Urological manifestations: Urogenital involvement in KD is extremely rare, described in two isolated case reports. A six year old boy presented with typical symptoms of KD and it was incidentally noted that he had pain and swelling of his left testicle, in keeping with epididymo-orchitis. The inflammation settled over the next few weeks with symptomatic treatment only and at six weeks follow up there were no persisting abnormalities. A second case report describes a seven year old boy with a one week history of cough, neck pain and swelling, fever and vague abdominal pain. He was diagnosed with KD and subsequently developed left sided pelvi-ureteric junction obstruction. Initially he was treated conservatively but due to worsening hydronephrosis, a nephrostomy was inserted and immunoglobulin therapy initiated. Subsequent scans confirmed an inflammatory stricture at the level of the left pelvi-ureteric junction. The stricture was surgically excised and a left sided dismembered pyeloplasty was performed. The patient subsequently recovered normal function of the left kidney and pelvi-calyceal system. The excised section of ureter showed findings in keeping with vasculitis^[61,62].

Management: As KD is a self-limiting illness, the aim of therapy is to limit cardiovascular morbidity and mortality. Patients are treated with aspirin and intravenous immunoglobulin, as the addition of intravenous immunoglobulin has been shown to reduce the incidence of coronary artery complications compared with aspirin alone^[63].

KAWASAKI DISEASE

Kawasaki disease (KD) or "Mucocutaneous Lymph Node Syndrome" is an acute medium-vessel vasculitis

SMALL VESSEL VASCULITIS

ANCA associated vasculitis

AAV are multisystem necrotising small vessel vasculitides

of unknown cause. Included in this group are: (1) Granulomatosis with polyangiitis (GPA) (formerly Wegener's granulomatosis); (2) MPA; and (3) Eosinophilic granulomatosis with polyangiitis (EGPA) (formerly Churg-Strauss syndrome).

The AAV are a group of rare disorders, with varying estimates of incidence and prevalence worldwide. In the United Kingdom reported incidence is estimated at 10.3/million population/year (GPA), 8.9/million (MPA) and 3.7/million (EGPA)^[17]. There is a peak in incidence in the 7th and 8th decades of life^[64].

Clinical features and diagnosis: Constitutional symptoms such as fever, malaise, anorexia, myalgia and weight loss are common in AAV.

Granulomatosis with polyangiitis

In GPA, necrotising granulomatous inflammation most commonly affects the upper and lower respiratory tract and kidneys. Upper respiratory tract symptoms include rhinorrhoea, epistaxis, sinusitis, otitis media, collapse of the nasal bridge, and tracheal stenosis. Lung involvement in GPA usually presents with cough, haemoptysis, and dyspnoea and can progress to life-threatening pulmonary haemorrhage. Rapidly progressive crescentic glomerulonephritis is also common. GPA may also affect the eyes; the bowel, causing ischemia and haemorrhage; the heart, causing myocardial ischemia, and the peripheral nervous system, causing mononeuritis multiplex^[65,66].

MPA

MPA is clinically very similar to GPA, except there is no granuloma formation and upper respiratory tract involvement is rare. Renal involvement is very common, and pulmonary haemorrhage can also occur^[66].

EGPA

EGPA, is characterized by eosinophilia, asthma, and necrotizing vasculitis. Vasculitis can affect the skin, peripheral nerves, muscles, and the intestine. Renal involvement is usually mild, and severe renal failure is uncommon^[67].

Diagnostic tests

The diagnosis of ANCA-associated vasculitis is made using a combination of clinical findings, biopsies from relevant involved organs (typically kidney, nasal mucosa, or occasionally lung) and the presence of ANCA autoantibodies. ANCA autoantibodies may be directed against the neutrophil enzymes proteinase-3 (PR3) and/or myeloperoxidase (MPO). These specific ANCAs can be detected by enzyme-linked-immunosorbent assays (ELISA). Initial screening for detection of ANCA antibodies is by indirect immunofluorescence (IIF), prior to antigen specific ELISAs. ANCA detected by IIF are described as having a cytoplasmic (cANCA) or perinuclear (pANCA) pattern. cANCA found by IIF

usually corresponds to anti-PR3 on ELISA and pANCA to anti-MPO. cANCA is seen in 81% of GPA patients and less commonly in MPA and EGPA. pANCA are detected in 65% of patients with MPA and less commonly in GPA and EGPA. In patients with clinical symptoms suggestive of these diseases, a combination of cANCA and positive PR3 ELISA has a positive predictive value (PPV) for GPA of nearly 100% but a sensitivity of only 69%. pANCA and MPO positive ELISA has a PPV of 47.5% for MPA and a specificity of 99.5%^[68].

Treatment and prognosis: Although previously almost universally fatal the current five-year survival is approximately 80%. Early morbidity and mortality are mainly due to side effects of immunosuppressive therapy^[69].

Treatment consists of two phases. Remission induction (3-6 mo) followed by maintenance of remission (at least 18 mo) to prevent disease relapse. Corticosteroids and cyclophosphamide are most commonly used to induce remission although there may be a role for methotrexate in more limited disease and rituximab in refractory cases and patients with a contraindication to cyclophosphamide. In order to minimise cyclophosphamide toxicity, patients are usually changed to azathioprine or a suitable alternative for maintenance therapy^[70-72].

Urological manifestations: Renal involvement is common in GPA and MPA. In studies from the National Institute of Health in the United States, glomerulonephritis (GN) was present in 18% of patients at the time of presentation and subsequently developed in 77% to 85% of patients, usually within the first two years of disease onset. Patients with active GN and AKI will have haematuria and glomerular red cell casts. Cases of intermittent asymptomatic haematuria in association with normal renal function have also been reported.

Lower urogenital tract involvement in AAV is not commonly reported. Of the reported cases, the majority are in association with GPA.

Approximately 2.3%-7.4% of GPA patients will suffer from urogenital manifestations of the disease. The prostate is the most commonly involved organ but the ureters, testes, epididymis, seminal vesicles and penis may also be affected.

Prostatitis secondary to GPA may present with dysuria, haematuria or bladder outflow tract obstruction and urinary retention. A combination of histopathological and serological tests are usually necessary to confirm the diagnosis. Resolution of symptoms is successfully achieved in most patients with medical therapy alone^[65,73-87].

In a study of 72 male patients with testicular vasculitis, GPA was the second most common diagnosis, after PAN. Approximately 17% of all cases of isolated testicular vasculitis were due to GPA. As with other

forms of testicular vasculitis, patients may present with testicular pain, erythema, swelling or a localised mass. Ultrasound imaging may demonstrate multiple hypo-echoic areas and impaired blood flow. Diagnosis is usually confirmed with serological testing for ANCA autoantibodies and testicular biopsy, demonstrating granulomatous necrotising inflammation. Therapy with corticosteroids and immunosuppressants is reported to result in rapid resolution of symptoms^[88-94].

Ureteric stenosis has also been reported in patients with GPA. Ureteric stents may be required in the short-term to relieve acute obstructive uropathy. Systemic therapy with immunosuppressants is usually successful in treating the inflammatory ureteric lesions but surgical intervention may become necessary^[78,95-98].

There are a few case reports describing aggressive penile ulceration, which may become necrotic, in association with GPA. It is a rare, but important differential diagnosis, for penile lesions in the elderly population^[78,99-104]. There are also a few case reports describing aggressive necrotising urethritis in both male and female elderly patients. This form of destructive urethritis may mimic invasive urethral carcinoma, but may respond well to immunosuppression^[102,105,106].

Rarely patients with GPA present with large granulomas of the kidney and bladder or "pseudotumours". Radiologically these lesions mimic malignant tumours but immunosuppressive therapy usually results in a rapid reduction in the size of these masses^[78,93,107,108].

There are two isolated case reports of prostatic involvement with MPA. In both cases 79-year-old males who presented with fever, malaise, weight loss and a cough. One had interstitial pneumonitis and the other a small mass in the left lower lobe of the lung. In both urinalysis revealed non-visible haematuria and serum prostate specific antigen (PSA) was elevated. In the first case prostate biopsy demonstrated fibrinoid degeneration with vasculitic changes involving the arterioles. In the second, prostate biopsy revealed changes consistent with vasculitis. Both had detectable serum MPO-ANCA. Both patients responded well to corticosteroids and cyclophosphamide^[109,110].

Prostatic involvement is also reported in EGPA. In one a 74-year-old male, who had previously been treated for asthma, underwent transurethral resection of the prostate. Post-operatively he developed pyrexia and eosinophilia. The biopsy specimens showed eosinophilic prostatitis in keeping with EGPA. The patient's symptoms responded to oral prednisolone^[111].

Ureteric obstruction secondary to calcification and stenosis has been reported in a 19-year-old male with multiple bowel perforations due to EGPA. Initially nephrostomies were inserted and subsequent ureteroscopy revealed multiple ureteral stones and dystrophic calcification within the ureteric walls. The obstruction was managed with repeated ureteroscopy and ureteric stent insertion with preservation of renal function^[112].

A 33-year-old male with known EGPA presented

ulceration of the mid-penile urethra. Biopsy showed chronic inflammation with infiltration of eosinophils as well as granulomas, giant cells and histiocytes and a thick walled blood vessel. This was occluded and infiltrated with inflammatory cells indicating active vasculitis. The patient responded well to intermittent intravenous cyclophosphamide with corticosteroids^[113].

HENOCH-SCHÖNLEIN PURPURA

Henoch-Schönlein purpura (HSP), also known as IgA vasculitis, anaphylactoid purpura and purpura rheumatica, is a systemic inflammatory disorder of small vessels characterised by IgA immune complex deposition and leukocytoclastic vasculitis. Skin, joints, bowel and kidneys are the most commonly affected organs.

Epidemiology

HSP is the commonest form of systemic vasculitis in childhood. Seventy five percent of all HSP cases involve children aged 2-11 years. The incidence of HSP in children < 17 years has been variously reported between 10-20 per 100000 population per year, with a peak in incidence between 5-7 years of age^[114-116]. Exact incidence of adult HSP is not known but it is relatively rare and known to follow a more severe course, with a higher incidence of renal impairment and end-stage renal disease^[117,118].

Clinical features and classification

Clinical Features of HSP typically include prodromal symptoms including headache, fever and anorexia. The hallmark of disease is the presence of a palpable purpuric rash in the absence of thrombocytopaenia or coagulopathy. This rash is typically found on the lower limbs and buttocks and less commonly on the upper limbs. This rash is present in almost all cases of HSP and is the presenting feature in over half of all patients^[119]. The rash may be accompanied by arthralgia, especially of the knees and ankles, in up to 80% of cases^[119,120].

Gastrointestinal manifestations of the disease are common, including colicky abdominal pain and vomiting, diarrhoea, GI bleeding, intussusception, infarction, strictures, perforation, fistula formation, gall bladder hydrops and acute appendicitis^[121].

Renal disease occurs in approximately half of all patients. Haematuria and significant proteinuria are common and renal biopsy may demonstrate a diffuse or focal segmental mesangioproliferative pattern of glomerulonephritis. HSP nephritis may lead to progressive chronic kidney disease. Approximately 1%-5% of patients will develop end stage renal failure^[120,122].

Urological manifestations of HSP

A wide variety of urogenital manifestations of HSP have been reported in the literature. This includes: (1)

Haematuria (visible and non-visible); (2) Unilateral or bilateral ureteritis with associated stenosis and hydronephrosis^[123]; (3) Bladder wall hematoma^[124]; (4) Haemorrhagic Cystitis^[125]; (5) Painful swelling of the scrotum and penis^[126,127]; (6) Epididymo-orchitis or orchitis^[128-133]; (7) Priapism^[134]; and (8) Thrombosis of the spermatic veins^[135].

Many of the above complications are rare and have only been described in isolated case reports.

Haematuria is a common feature of the disease. A prospective study of 250 patients noted that 85% of patients had non-visible haematuria at the time of presentation and a further 10% had visible haematuria^[118].

Scrotal and testicular involvement are the commonest lower urogenital tract manifestations of HSP and are reported in approximately 13% of cases. Clinical findings include pain, tenderness, and swelling of the involved testicle and/or scrotum. Occasionally, testicular symptoms may precede the development of a rash and may be the first presentation of disease^[136]. There is only one confirmed case of testicular torsion in HSP^[137].

Diagnosis

Diagnosis of HSP in childhood is primarily clinical. In adults a skin or renal biopsy may be performed. Serum IgA is raised in 50% of cases and autoantibodies that are present in other forms of vasculitis are usually absent^[122]. Radiology, especially ultrasound evaluation, may be useful for identifying GI complications of disease including bowel wall thickening, intussusception and haematomas^[138]. Similarly ultrasound examination of the scrotum and testicle is useful to assess for suspected epididymo-orchitis. Additionally Doppler flow studies and technetium Tc99m radionuclide scanning can aid in ruling out testicular torsion. In cases of torsion, these studies demonstrate decreased blood flow to the testicle, in contrast to the normal or increased flow seen in HSP^[136].

Treatment and outcomes

HSP is typically an acute and self-limiting illness, usually lasting less than four weeks. Short-term morbidity is dependent on the presence and severity of gastrointestinal involvement and long-term prognosis is dependent on the extent and chronicity of renal involvement^[121]. There is no form of therapy that has been found to shorten the duration of HSP and the focus of therapy therefore remains supportive, ensuring adequate hydration and analgesia. There is no convincing evidence at present to suggest that corticosteroid therapy will reduce the risk of developing serious renal or gastrointestinal complications of the disease or that it will significantly shorten the duration of illness. Use of corticosteroids may however be considered in cases of persistent nephritic syndrome, with significant crescent formation or alternatively in patients with severe

abdominal pain, GI haemorrhage, significant soft tissue or scrotal oedema or neurological involvement^[139-142]. In severe and resistant cases of HSP, additional immunosuppressive agents and plasmapheresis may be considered^[143-145].

Testicular and epididymal disease in HSP is usually self-limiting and resolves in a matter of days with conservative management. Corticosteroid therapy may be indicated in patients with severe testicular pain and swelling which is slow to improve or in cases accompanied by severe systemic symptoms^[146]. In the isolated case report of a patient with spermatic vein thrombosis, treatment with low molecular weight heparin was required^[135]. Anecdotal evidence in those patients presenting with ureteritis and associated stenotic lesions suggest that some cases are self-limiting and in other cases complete resolution was noted with a course of corticosteroids. In a few cases though, residual stenotic lesions and subsequent urinary tract obstruction necessitated surgical intervention^[136].

ANTI-GLOMERULAR BASEMENT MEMBRANE ANTIBODY DISEASE

Anti-glomerular basement membrane antibody (Anti-GBM) disease (Goodpasture's Syndrome) is a rare condition with an incidence of 1-2/million population/year. In this condition antibodies are generated against the alpha-3 chain of type IV collagen, found in the glomerular basement membrane. Haematuria in association with rapidly progressive glomerulonephritis and pulmonary haemorrhage are common features of this condition. No other urological manifestations of anti-GBM disease have been reported in the literature^[147].

Cryoglobulinaemic vasculitis

Cryoglobulins are immunoglobulins that precipitate in the cold and dissolve on rewarming. There are three main types of cryoglobulins: (1) Type I - a monoclonal antibody that is most commonly associated with lymphoma, Waldenström's macroglobulinemia, and multiple myeloma. Because type I cryoglobulins do not easily activate complement, patients with type I are usually asymptomatic until the level of cryoglobulinemia is sufficiently high to cause hyperviscosity syndrome; (2) Type II - A mixture of both monoclonal and polyclonal cryoglobulins commonly associated with hepatitis C virus (HCV); and (3) Type III - Rheumatoid factor is polyclonal in type III and is usually associated with rheumatic disease and chronic infections especially HCV.

Type II and III cryoglobulinemia frequently presents as vasculitis, most commonly with recurrent lower extremity purpura, glomerulonephritis, and peripheral neuropathy. Glomerulonephritis with non-visible haematuria appears to be the only reported urological manifestation of Cryoglobulinaemic vasculitis^[148,149].

Hypocomplementaemic urticarial Vasculitis (anti-C1q vasculitis)

Hypocomplementaemic urticarial Vasculitis (HUV) is a rare form of vasculitis characterised by urticarial lesions, biopsy evidence of small vessel vasculitis and hypocomplementaemia. There may also be other systemic findings including arthralgia or arthritis, mild glomerulonephritis, uveitis or episcleritis and recurrent abdominal pain. It is estimated that approximately 50% of all HUV patients will have renal involvement. Although this is usually mild, haematuria and proteinuria are commonly noted^[150].

VARIABLE VESSEL VASCULITIS**Behçets disease**

Behçets disease (BD) is a variable vessel vasculitis of unknown aetiology. BD is a multi-system chronic relapsing and remitting condition characterised by a triad of^[151]: (1) Recurrent oral aphthous ulcers; (2) Genital ulcers; and (3) Uveitis.

Epidemiology: There is a peak incidence in the 3-5th decades of life. The exact aetiology and pathogenesis of BD remains unknown, although carriers of HLA B5/HLA B51 are at increased risk of developing BD^[152].

Clinical features and classification: Clinical manifestations of BD include recurrent aphthous ulcers of the oral mucosa, skin lesions, genital ulceration, ocular inflammatory lesions, arthritis, epididymitis, intestinal ulcers, vascular lesions, neuropsychiatric symptoms and a positive pathergy test (the forearm is pricked with a small, sterile needle-occurrence of a small red bump or pustule at the site of needle insertion constitutes a positive test). There is no one diagnostic test for BD and therefore diagnosis is usually clinical. A number of classifications have been published to aid in diagnosis including the "International Study Group Criteria", published in 1990, which is one of the most widely used and accepted (Table 3)^[153].

Urological manifestations: A number of Urological manifestations of BD have been reported in the literature. The most common of these is genital ulceration. Genital ulceration in males is most commonly noted in the scrotal area but lesions may also be found on the shaft of the penis or in the peri-anal region. In women the labia are commonly affected, although vaginal and cervical ulcers can also occur^[154]. Genital lesions are usually deeper and last longer than oral ulcers, they are also much more likely to cause significant scarring after they heal. A prospective study of 100 BD patients in Turkey (70 males and 30 females) reported genital ulceration in 89% of those enrolled^[155]. In a separate survey of 2031 patients in Japan, genital lesions were present in 76% of the males and 83.8% of the females^[156].

In a prospective study from Turkey of 100 BD

patients, 6% of males had experienced episodes of epididymitis and a further 3% of males were found to have had episodes of sterile urethritis with discharge^[155].

Bladder involvement is uncommon in BD and is mainly limited to vasculitis of the bladder wall and neuropathic bladder symptoms^[157]. Direct involvement of blood vessels in the bladder wall may result in localised ischemia, which can progress, to mucosal necrosis and bladder ulceration, nodules or recurrent cystitis. This process is likely to be responsible for the haematuria, storage symptoms and urge incontinence that patients with bladder involvement in BD report^[157]. There is also an isolated report of vesico-vaginal fistula as a result of posterior extension of the necrotic process in BD^[158].

Approximately 5%-10% of BD patients have neurological disease involvement and of these patients approximately 5% report voiding symptoms^[159]. Bladder symptoms secondary to neurological involvement in BD may vary considerably depending on the level of brain and spinal cord involvement. Detrusor areflexia, hyperreflexia and detrusor sphincter dysynergia have all been reported^[160]. In severe cases there may be complete urinary retention, incontinence and hydronephrosis, necessitating surgical intervention. Augmentation ileocystoplasty in these patients has been shown to have good clinical outcomes^[157]. Despite pathergy being a well-known phenomena in BD patients, cystoscopy, bladder biopsy, and even ileocystoplasty or radical cystoprostatectomy have been performed in this group without complication^[157].

Management and prognosis: Management of patients with BD will depend largely on the specific organs affected by disease and the severity of organ involvement. In 2008 the European League Against Rheumatism (EULAR) published consensus guidelines on management of BD.

For mild oral and genital ulcerations, the current recommendation is for localised application of topical steroids or sucralfate solution, as a first-line therapy. Colchicine has been widely used in more severe cases of BD but the evidence suggests that additional benefit may only be gained in females with genital ulcers and patients with erythema nodosum^[161,162]. For severe mucocutaneous lesions, systemic corticosteroids, azathioprine, interferon-alfa and TNF-alpha antagonists may be considered^[163].

The management of bladder involvement in BD needs to be tailored to each individual bearing in mind their specific symptoms and findings on cystoscopy and urodynamic testing. This may include intermittent self-catheterisation for patients suffering from urinary retention and anti-cholinergics for patients suffering from urge incontinence or surgical intervention in more severe cases^[164].

Cogan's syndrome

Cogan's syndrome (CS) is a rare variable vessel

Table 3 International Study Group Criteria for Behçets disease^[153]

Required criteria	
Recurrent oral ulceration (obligatory)	Minor aphthous, major aphthous, or herpetiform ulceration (observed by physician or patient); recurring at least 3 times in a 12 mo period
Plus 2 of	
Recurrent genital ulceration	Aphthous ulceration or scarring (observed by physician or patient)
Eye lesions	Anterior uveitis, posterior uveitis, or cells in vitreous on slit lamp examination; or retinal vasculitis observed by ophthalmologist
Skin lesions	Erythema nodosum (observed by physician or patient), pseudofolliculitis, or papulopustular lesions; or acneiform nodules (observed by physician) in post-adolescent patients not on corticosteroid treatment
Positive Pathergy test	Read by physician at 24-48 h

vasculitis of young adults characterised by interstitial keratitis, vestibuloauditory dysfunction and other features including aortitis. There are no reported urogenital manifestations of CS^[165].

TREATMENT RELATED UROLOGICAL ADVERSE EFFECTS

An important consideration for urologists is the use of potent immunosuppressive therapies for vasculitis and potential urological complications that may arise as a result of this.

The most well-known urological complication of immunosuppressive therapy is the association of cyclophosphamide with haemorrhagic cystitis and bladder cancer. The active metabolite of cyclophosphamide, acrolein, is excreted in urine and is toxic to urothelium. In a study of 145 GPA patients treated with daily oral cyclophosphamide in the United States, 73 patients (50%) experienced episodes of non-glomerular haematuria +/- dysuria. Sixty of these patients went on to have cystoscopic examination and cyclophosphamide-induced bladder injury was confirmed in 42 cases^[166].

In the same study seven patients treated with oral cyclophosphamide for GPA subsequently developed transitional cell carcinoma of the bladder. All seven of these patients had previous episodes of non-glomerular haematuria and six of the patients had received a total cumulative cyclophosphamide dose exceeding 100 g, with the cumulative duration of cyclophosphamide therapy exceeding 2.7 years. On the basis of these findings the incidence of bladder cancer after the first exposure to cyclophosphamide was estimated at 5% at 10 years and 16% at 15 years. A series of 12 case reports of bladder cancer in association with cyclophosphamide, found that the disease phenotype in these patients was very aggressive, with all tumours grade 3 or 4 at the time of presentation^[167].

Risk of developing bladder cancer appears to be related to cumulative dose and/or length of therapy received^[168] Risk of cyclophosphamide associated bladder toxicity can be reduced *via* a number of measures: (1) Co-administration of sodium 2-mercaptoethanesulfonate (Mesna) inactivates acrolein in urine,

protecting the bladder from its toxic effects. Some controversy exists with regards to the effectiveness of mesna therapy and at present "The American Society of Clinical Oncology" does not recommend the use of mesna in patients receiving cyclophosphamide except when high doses are used (*e.g.*, 50 mg/kg or 2 g/m²). The EULAR however continue to recommend its use^[169,170]; (2) Good hydration; (3) Treatment in the early morning to avoid overnight bladder accumulation of acrolein; and (4) Intermittent pulsed intravenous cyclophosphamide therapy rather than daily oral dosing. This has been shown to decrease the total cyclophosphamide dose received by up to half^[171]. Consequently intermittent pulsed intravenous cyclophosphamide use is associated with a decreased incidence of drug-induced cystitis^[172].

A bladder cancer surveillance program is also suggested for patients that have received cyclophosphamide therapy. It is recommended that urinalysis is obtained from these patients on a six monthly basis to screen for haematuria. This should be repeated within one week if haematuria is detected. Patients with confirmed non-glomerular haematuria should then undergo cystoscopy to exclude bladder cancer. For patients with cystoscopic evidence of bladder damage, the procedure should be repeated every 6 to 12 mo^[166].

Cyclophosphamide is also teratogenic and causes gonadal toxicity. In females this may lead to irregularity of the menstrual cycle and reduced ovarian function. In males, alkylating drug therapy may reduce sperm count and testicular endocrine function^[173]. A study of men with BD showed significant infertility after cyclophosphamide therapy with oligospermia or azoospermia occurring in 13 of 17 men treated with cyclophosphamide but in none of the 10 men treated with colchicine alone or in the four control patients who did not receive any treatment^[174]. A separate study looking at the effect of colchicine alone on sperm production, in 62 male patients with BD, found evidence of oligonecrospermia in 37% of patients and azoospermia in 3% of patients^[175].

Patients may have the option of cryopreservation of sperm and ova prior to commencing cyclophosphamide therapy. The induction of gonadal quiescence during

therapy with alkylating agents may minimize the risk of testicular and ovarian failure. Studies looking at the use of a gonadotropin-releasing hormone agonist such as leuprolide to achieve gonadal quiescence in women are ongoing and results remain inconclusive^[176,177]. In male patients, studies are looking into adjuvant testosterone therapy to induce gonadal quiescence. Again the results remain inconclusive^[178].

In both male and female patients where preservation of fertility is a consideration the patient's management should be discussed early on with local fertility services and consideration given to minimising or avoiding the use of alkylating agents.

CONCLUSION

The PSV are a heterogeneous group of rare disorders with many varying features and presentations, which may affect urological organs. PAN, HSP, BD and GPA are the PSV that have the most commonly reported urological manifestations. Testes, prostate and ureters are the most commonly involved urological organs. Identification of vasculitic disease in the urogenital tract is important as not only may this be the first presentation of systemic disease but also management with immunosuppressive therapy may allow rapid resolution of symptoms and avoid the need for invasive surgical management.

REFERENCES

- Jennette JC, Falk RJ, Bacon PA, Basu N, Cid MC, Ferrario F, Flores-Suarez LF, Gross WL, Guillevin L, Hagen EC, Hoffman GS, Jayne DR, Kallenberg CG, Lamprecht P, Langford CA, Luqmani RA, Mahr AD, Matteson EL, Merkel PA, Ozen S, Pusey CD, Rasmussen N, Rees AJ, Scott DG, Specks U, Stone JH, Takahashi K, Watts RA. 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. *Arthritis Rheum* 2013; **65**: 1-11 [PMID: 23045170 DOI: 10.1002/art.37715]
- Wen D, Du X, Ma CS. Takayasu arteritis: diagnosis, treatment and prognosis. *Int Rev Immunol* 2012; **31**: 462-473 [PMID: 23215768 DOI: 10.3109/08830185.2012.740105]
- Alibaz-Oner F, Aydin SZ, Direskeneli H. Advances in the diagnosis, assessment and outcome of Takayasu's arteritis. *Clin Rheumatol* 2013; **32**: 541-546 [PMID: 23271611 DOI: 10.1007/s10067-012-2149-3]
- Jghaimi F, Kabbaj A, Essaadouni L. [Takayasu's arteritis and retroperitoneal fibrosis: a case report]. *Rev Med Interne* 2010; **31**: e1-e3 [PMID: 19231040 DOI: 10.1016/j.revmed.2009.01.001]
- Houman H, Haouet S, Lamloum M, Ghorbel IB, Miled M. [Retroperitoneal fibrosis associated with Takayasu arteritis]. *Ann Med Interne (Paris)* 1998; **149**: 107-108 [PMID: 11490523]
- Fajac A, Galezowski N, Cormier JM, Duclos FM, Herreman G. [Inflammatory arteritis of Takayasu's disease type and retroperitoneal fibrosis]. *Rev Med Interne* 1988; **9**: 436-437 [PMID: 2906167]
- Salvarani C, Pipitone N, Versari A, Hunder GG. Clinical features of polymyalgia rheumatica and giant cell arteritis. *Nat Rev Rheumatol* 2012; **8**: 509-521 [PMID: 22825731 DOI: 10.1038/nrrheum.2012.97]
- Kermani TA, Warrington KJ, Crowson CS, Ytterberg SR, Hunder GG, Gabriel SE, Matteson EL. Large-vessel involvement in giant cell arteritis: a population-based cohort study of the incidence-trends and prognosis. *Ann Rheum Dis* 2013; **72**: 1989-1994 [PMID: 23253927 DOI: 10.1136/annrheumdis-2012-202408]
- Caylor TL, Perkins A. Recognition and management of polymyalgia rheumatica and giant cell arteritis. *Am Fam Physician* 2013; **88**: 676-684 [PMID: 24364483]
- Mackie SL, Pease CT. Diagnosis and management of giant cell arteritis and polymyalgia rheumatica: challenges, controversies and practical tips. *Postgrad Med J* 2013; **89**: 284-292 [PMID: 23355687 DOI: 10.1136/postgradmedj-2012-131400]
- Gonzalez-Gay MA, Garcia-Porrúa C, Llorca J, Hajeer AH, Branas F, Dababneh A, Gonzalez-Louzao C, Rodriguez-Gil E, Rodriguez-Ledo P, Ollier WE. Visual manifestations of giant cell arteritis. Trends and clinical spectrum in 161 patients. *Medicine* 2000; **79**: 283-292 [PMID 11039076]
- Arnillas E, de la Fuente J, Núñez M, Domínguez F. [Giant cell arteritis with epididymal involvement]. *Med Clin (Barc)* 2009; **132**: 485 [PMID: 19344797 DOI: 10.1016/j.medcli.2008.07.020]
- Sundaram S, Smith DH. Giant cell arteritis mimicking a testicular tumour. *Rheumatol Int* 2001; **20**: 215-216 [PMID: 11518043]
- Ronco P, Verroust P, Mignon F, Kourilsky O, Vanhille P, Meyrier A, Mery JP, Morel-Maroger L. Immunopathological studies of polyarteritis nodosa and Wegener's granulomatosis: a report of 43 patients with 51 renal biopsies. *Q J Med* 1983; **52**: 212-223 [PMID: 6193553]
- Somer T, Finegold SM. Vasculitides associated with infections, immunization, and antimicrobial drugs. *Clin Infect Dis* 1995; **20**: 1010-1036 [PMID: 7795045]
- Hughes LB, Bridges SL. Polyarteritis nodosa and microscopic polyangiitis: etiologic and diagnostic considerations. *Curr Rheumatol Rep* 2002; **4**: 75-82 [PMID: 11798986 DOI: 10.1007/s11926-002-0027-8]
- Watts RA, Lane SE, Bentham G, Scott DG. Epidemiology of systemic vasculitis: a ten-year study in the United Kingdom. *Arthritis Rheum* 2000; **43**: 414-419 [PMID: 10693883 DOI: 10.1002/21529-0131(200002)43:2<414::aid-anr23>3.0.co;2-0]
- Stone JH. Polyarteritis nodosa. *JAMA* 2002; **288**: 1632-1639 [PMID: 12350194 DOI: 10.1001/jama.288.13.1632]
- González-Gay MA, García-Porrúa C. Systemic vasculitis in adults in northwestern Spain, 1988-1997. Clinical and epidemiologic aspects. *Medicine (Baltimore)* 1999; **78**: 292-308 [PMID: 10499071]
- Mahr A, Guillevin L, Poissonnet M, Aymé S. Prevalences of polyarteritis nodosa, microscopic polyangiitis, Wegener's granulomatosis, and Churg-Strauss syndrome in a French urban multiethnic population in 2000: a capture-recapture estimate. *Arthritis Rheum* 2004; **51**: 92-99 [PMID: 14872461 DOI: 10.1093/rheumatology/kem107]
- Pagnoux C, Seror R, Henegar C, Mahr A, Cohen P, Le Guern V, Biennu B, Mouthon L, Guillevin L. Clinical features and outcomes in 348 patients with polyarteritis nodosa: a systematic retrospective study of patients diagnosed between 1963 and 2005 and entered into the French Vasculitis Study Group Database. *Arthritis Rheum* 2010; **62**: 616-626 [PMID: 20112401 DOI: 10.1002/art.27240]
- Guillevin L, Lhote F, Cohen P, Sauvaget F, Jarrousse B, Lortholary O, Noël L-H, Trépo C. Polyarteritis nodosa related to hepatitis b virus a prospective study with long-term observation of 41 patients. *Medicine* 1995; **74**: 238-253 [PMID: 7565065]
- Trepo C, Guillevin L. Polyarteritis nodosa and extrahepatic manifestations of HBV infection: the case against autoimmune intervention in pathogenesis. *J Autoimmun* 2001; **16**: 269-274 [PMID: 11334492 DOI: 10.1006/jaut.2000.0502]
- Lee KN, Ha HK, Lee JJ, Kim JK, Sung KB, Cho KS, Kim PN, Lee MG, Lim HK, Choi CS, Auh YH. Radiologic findings of abdominal polyarteritis nodosa. *AJR Am J Roentgenol* 2000; **174**: 1675-1679 [PMID: 10845504 DOI: 10.2214/ajr.174.6.1741675]
- Croker BP, Lee T, Gunnells JC. Clinical and pathologic features of polyarteritis nodosa and its renal-limited variant: primary crescentic and necrotizing glomerulonephritis. *Hum Pathol* 1987; **18**: 38-44 [PMID: 2880791 DOI: 10.1016/S0046-8177(87)80191-0]

- 26 **Wees SJ**, Sunwoo IN, Oh SJ. Sural nerve biopsy in systemic necrotizing vasculitis. *Am J Med* 1981; **71**: 525-532 [PMID: 6116431 DOI: 10.1016/0002-9343(81)90195-9]
- 27 **Albert DA**, Rimón D, Silverstein MD. The diagnosis of polyarteritis nodosa. I. A literature-based decision analysis approach. *Arthritis Rheum* 1988; **31**: 1117-1127 [PMID: 2901840 DOI: 10.1002/art.1780310906]
- 28 **Lightfoot RW**, Michel BA, Bloch DA, Hunder GG, Zvaifler NJ, McShane DJ, Arend WP, Calabrese LH, Leavitt RY, Lie JT. The American College of Rheumatology 1990 criteria for the classification of polyarteritis nodosa. *Arthritis Rheum* 1990; **33**: 1088-1093 [PMID: 1975174 DOI: 10.1002/art.1780330805]
- 29 **Guillevin L**, Lhote F, Gayraud M, Cohen P, Jarrousse B, Lortholary O, Thibault N, Casassus P. Prognostic factors in polyarteritis nodosa and Churg-Strauss syndrome. A prospective study in 342 patients. *Medicine* (Baltimore) 1996; **75**: 17-28 [PMID: 8569467]
- 30 **Ribi C**, Cohen P, Pagnoux C, Mahr A, Arène JP, Puéchal X, Carli P, Kyndt X, Le Hello C, Letellier P, Cordier JF, Guillevin L. Treatment of polyarteritis nodosa and microscopic polyangiitis without poor-prognosis factors: A prospective randomized study of one hundred twenty-four patients. *Arthritis Rheum* 2010; **62**: 1186-1197 [PMID: 20131268 DOI: 10.1002/art.27340]
- 31 **Guillevin L**, Cohen P, Mahr A, Arène JP, Mouthon L, Puéchal X, Pertuiset E, Gilson B, Hamidou M, Lanoux P, Bruet A, Ruivard M, Vanhille P, Cordier JF. Treatment of polyarteritis nodosa and microscopic polyangiitis with poor prognosis factors: a prospective trial comparing glucocorticoids and six or twelve cyclophosphamide pulses in sixty-five patients. *Arthritis Rheum* 2003; **49**: 93-100 [PMID: 12579599 DOI: 10.1002/art.10922]
- 32 **Guillevin L**, Lhote F, Sauvaget F, Deblois P, Rossi F, Levallois D, Pourrat J, Christoforov B, Trépo C. Treatment of polyarteritis nodosa related to hepatitis B virus with interferon-alpha and plasma exchanges. *Ann Rheum Dis* 1994; **53**: 334-337 [PMID: 7912504 DOI: 10.1136/ard.53.5.334]
- 33 **Guillevin L**, Mahr A, Cohen P, Larroche C, Queyrel V, Loustaud-Ratti V, Imbert B, Hausfater P, Roudier J, Bielefeld P, Petitjean P, Smadja D. Short-term corticosteroids then lamivudine and plasma exchanges to treat hepatitis B virus-related polyarteritis nodosa. *Arthritis Rheum* 2004; **51**: 482-487 [PMID: 15188337 DOI: 10.1002/art.20401]
- 34 **Azar N**, Guillevin L, Huang Du LT, Herremán G, Meyrier A, Godeau P. Symptomatic urogenital manifestations of polyarteritis nodosa and Churg-Strauss angiitis: analysis of 8 of 165 patients. *J Urol* 1989; **142**: 136-138 [PMID: 2567358]
- 35 **Teichman JM**, Mattrey RF, Demby AM, Schmidt JD. Polyarteritis nodosa presenting as acute orchitis: a case report and review of the literature. *J Urol* 1993; **149**: 1139-1140 [PMID: 8097793]
- 36 **Toepfer NJ**, Lountzis NI, Ugoe JC, Ferringer TC. Polyarteritis nodosa with bilateral asynchronous testicular necrosis: a case report. *Case Rep Urol* 2011; **2011**: 465353 [PMID: 22606613 DOI: 10.1155/2011/465353]
- 37 **Pannek J**, Haupt G. Orchitis due to vasculitis in autoimmune diseases. *Scand J Rheumatol* 1997; **26**: 151-154 [PMID: 9225868]
- 38 **Warfield AT**, Lee SJ, Phillips SM, Pall AA. Isolated testicular vasculitis mimicking a testicular neoplasm. *J Clin Pathol* 1994; **47**: 1121-1123 [PMID: 7876390]
- 39 **Atis G**, Memis OF, Güngör HS, Arıkan O, Saglıcan Y, Caskurlu T. Testicular polyarteritis nodosa mimicking testicular neoplasm. *ScientificWorldJournal* 2010; **10**: 1915-1918 [PMID: 20890580 DOI: 10.1100/tsw.2010.194]
- 40 **Dotan ZA**, Laufer M, Heldenberg E, Langevitz P, Fridman E, Duvdevani M, Ramon J. Isolated testicular polyarteritis nodosa mimicking testicular neoplasm-long-term follow-up. *Urology* 2003; **62**: 352 [PMID: 12893362]
- 41 **Fraenkel-Rubin M**, Ergas D, Sthoeger ZM. Limited polyarteritis nodosa of the male and female reproductive systems: diagnostic and therapeutic approach. *Ann Rheum Dis* 2002; **61**: 362-364 [PMID: 11874844 DOI: 10.1136/ard.61.4.362]
- 42 **Kolar P**, Schneider U, Filimonow S, Burmester GR, Buttgerit F. Polyarteritis nodosa and testicular pain: ultrasonography reveals vasculitis of the testicular artery. *Rheumatology* (Oxford) 2007; **46**: 1377-1378 [PMID: 17586861 DOI: 10.1093/rheumatology/kem165]
- 43 **Meeuwissen J**, Maertens J, Verbeken E, Blockmans D. Case reports: testicular pain as a manifestation of polyarteritis nodosa. *Clin Rheumatol* 2008; **27**: 1463-1466 [PMID: 18651100 DOI: 10.1007/s10067-008-0970-5]
- 44 **Susanto CR**, Fedder G, Looijen-Salamon MG. Acute, painful, and swollen testicle as the presenting feature in polyarteritis nodosa. *Eur J Intern Med* 2003; **14**: 441-443 [PMID: 14614979]
- 45 **Tanuma Y**, Oda T, Yokoo A, Ito S, Takeuchi K. Recurrent polyarteritis nodosa limited to the testis. *J Urol* 2003; **170**: 1953 [PMID: 14532825 DOI: 10.1097/01.ju.0000089740.11360.e0]
- 46 **Brimo F**, Lachapelle J, Epstein JI. Testicular vasculitis: a series of 19 cases. *Urology* 2011; **77**: 1043-1048 [PMID: 21419476 DOI: 10.1016/j.urology.2011.01.021]
- 47 **Abós Fanlo P**, Vilardell Tarrés M, Pastor Mouron J, Solé-Balcels F, Tornos Solano J. Secondary hydronephrosis to polyarteritis nodosa. *Eur Urol* 1979; **5**: 211-213 [PMID: 36277]
- 48 **Bulbuloglu E**, Kantarceken B, Yuksel M, Ciralik H, Sahinkanat T, Kale IT. An unusual presentation of polyarteritis nodosa: A case report. *West Indian Med J* 2006; **55**: 56-59 [PMID: 16755822]
- 49 **Duclos JM**, Bensadoun H, Herremán G, Baviera E. [Pseudotumor of the ureter manifesting periarteritis nodosa]. *Ann Urol (Paris)* 1984; **18**: 418-419 [PMID: 6152385]
- 50 **Ekeland A**, Sander S. Stenosis of the ureter caused by periarteritis. *J Oslo City Hosp* 1974; **24**: 78-82 [PMID: 4153076]
- 51 **Glanz I**, Grünebaum M. Ureteral changes in polyarteritis nodosa as seen during excretory urography. *J Urol* 1976; **116**: 731-733 [PMID: 12376]
- 52 **Hefty TR**, Bonafede P, Stenzel P. Bilateral ureteral stricture from polyarteritis nodosa. *J Urol* 1989; **141**: 600-601 [PMID: 2563780]
- 53 **Kaskarelis IS**, Zarifi M, Dantis P, Vrachliotis G. Bilateral ureteral involvement in polyarteritis nodosa. *Scand J Urol Nephrol* 1995; **29**: 323-326 [PMID: 8578276]
- 54 **Melin JP**, Lemaire P, Birembaut P, Aubert L, Cohen J, Lardennois B, Chanard J. Polyarteritis nodosa with bilateral ureteric involvement. *Nephron* 1982; **32**: 87-89 [PMID: 6129579]
- 55 **Samellas W**, Bellonias E, Papacharalampous N. Polyarteritis nodosa: ureteral involvement. *J Urol* 1971; **105**: 186-187 [PMID: 4397427]
- 56 **Casserly LF**, Reddy SM, Rennke HG, Carpinito GA, Levine JS. Reversible bilateral hydronephrosis without obstruction in hepatitis B-associated polyarteritis nodosa. *Am J Kidney Dis* 1999; **34**: e11 [PMID: 10471757]
- 57 **Zhang JQ**, Fielding JR, Zou KH. Etiology of spontaneous perirenal hemorrhage: a meta-analysis. *J Urol* 2002; **167**: 1593-1596 [PMID: 11912370 DOI: 10.1016/S0022-5347(05)65160-9]
- 58 **Koc O**, Ozbek O, Gumus S, Demir A. Endovascular management of massive gastrointestinal bleeding associated with polyarteritis nodosa. *J Vasc Interv Radiol* 2009; **20**: 277-279 [PMID: 19054689 DOI: 10.1016/j.jvir.2008.10.023]
- 59 **Burns JC**, Glodé MP. Kawasaki syndrome. *Lancet* 2004; **364**: 533-544 [PMID: 15302199 DOI: 10.1016/s0140-6736(04)16814-1]
- 60 **Freeman AF**, Shulman ST. Kawasaki disease: summary of the American Heart Association guidelines. *Am Fam Physician* 2006; **74**: 1141-1148 [PMID: 17039750]
- 61 **Subramaniam R**, Lama T, Chong CY. Pelviureteric junction obstruction as sequelae of Kawasaki disease. *Pediatr Surg Int* 2004; **20**: 553-555 [PMID: 15248077 DOI: 10.1007/s00383-004-1218-3]
- 62 **Connolly KD**, Timmons D. Mucocutaneous lymph node syndrome with testicular involvement. *Ir J Med Sci* 1980; **149**: 26-27 [PMID: 7380632]
- 63 **Newburger JW**, Takahashi M, Beiser AS, Burns JC, Bastian J, Chung KJ, Colan SD, Duffy CE, Fulton DR, Glodé MP. A single intravenous infusion of gamma globulin as compared with four infusions in the treatment of acute Kawasaki syndrome. *N Engl J Med* 1991; **324**: 1633-1639 [PMID: 1709446 DOI: 10.1056/nejm199106063242305]
- 64 **Harper L**, Savage CO. ANCA-associated renal vasculitis at the end

- of the twentieth century--a disease of older patients. *Rheumatology* (Oxford) 2005; **44**: 495-501 [PMID: 15613403 DOI: 10.1093/rheumatology/keh522]
- 65 **Hoffman GS**, Kerr GS, Leavitt RY, Hallahan CW, Lebovics RS, Travis WD, Rottm M, Fauci AS. Wegener granulomatosis: an analysis of 158 patients. *Ann Intern Med* 1992; **116**: 488-498 [PMID: 1739240]
 - 66 **Guillevin L**, Durand-Gasselin B, Cevallos R, Gayraud M, Lhote F, Callard P, Amouroux J, Casassus P, Jarrousse B. Microscopic polyangiitis: clinical and laboratory findings in eighty-five patients. *Arthritis Rheum* 1999; **42**: 421-430 [PMID: 10088763 DOI: 10.1002/1529-0131(199904)42: 3<421::AID-ANR5>3.0.CO; 2-6]
 - 67 **Guillevin L**, Le Thi Huong Du, Godeau P, Jais P, Wechsler B. Clinical findings and prognosis of polyarteritis nodosa and Churg-Strauss angitis: a study in 165 patients. *Br J Rheumatol* 1988; **27**: 258-264 [PMID: 2900659]
 - 68 **Schönermarck U**, Lamprecht P, Csernok E, Gross WL. Prevalence and spectrum of rheumatic diseases associated with proteinase 3-antineutrophil cytoplasmic antibodies (ANCA) and myeloperoxidase-ANCA. *Rheumatology* (Oxford) 2001; **40**: 178-184 [PMID: 11257154]
 - 69 **Bhamra K**, Luqmani R. Damage assessment in ANCA-associated vasculitis. *Curr Rheumatol Rep* 2012; **14**: 494-500 [PMID: 22983618 DOI: 10.1007/s11926-012-0291-1]
 - 70 **Li X**, Chen N. Management of crescentic glomerulonephritis: what are the recent advances? *Contrib Nephrol* 2013; **181**: 229-239 [PMID: 23689584 DOI: 10.1159/000348479]
 - 71 **Talarico R**, Baldini C, Della Rossa A, Carli L, Tani C, Bombardieri S. Systemic vasculitis: a critical digest of the recent literature. *Clin Exp Rheumatol* 2013; **31**: S84-S88 [PMID: 23663686]
 - 72 **Rich EN**, Brown KK. Treatment of antineutrophil cytoplasmic antibody-associated vasculitis. *Curr Opin Pulm Med* 2012; **18**: 447-454 [PMID: 22854508 DOI: 10.1097/MCP.0b013e32835701d6]
 - 73 **Heldmann F**, Brandt J, Schoppe H, Braun J. [A 46-year-old-patient with granulomatous prostatitis, arthralgia and haemorrhagic rhinitis]. *Dtsch Med Wochenschr* 2006; **131**: 22-25 [PMID: 16374738 DOI: 10.1055/s-2006-924915]
 - 74 **Menown IB**, McKane WR, Kennedy JA, Kelly IM, MacLennan BA, Best BG, Walsh MY. Detection and follow-up of Wegener's prostatitis by transrectal ultrasound. *Br J Rheumatol* 1998; **37**: 805-806 [PMID: 9714370]
 - 75 **Mundinger A**, Pumpe K, Grosser G, Herbst EW, Grotz W, Kröpelin T. [Primary manifestation of Wegener's granulomatosis of the prostate]. *Urologe A* 1989; **28**: 234-236 [PMID: 2474881]
 - 76 **Stillwell TJ**, DeRemee RA, McDonald TJ, Weiland LH, Engen DE. Prostatic involvement in Wegener's granulomatosis. *J Urol* 1987; **138**: 1251-1253 [PMID: 2444721]
 - 77 **Pumpe K**, Mundinger A, Herbst EW, Peter P. [An unusual course of Wegener's granulomatosis: initial manifestation in the prostate and development of arterial microaneurysms in the kidney]. *Pathologe* 1989; **10**: 318-321 [PMID: 2798359]
 - 78 **Huong DL**, Papo T, Piette JC, Wechsler B, Bletty O, Richard F, Valcke JC, Godeau P. Urogenital manifestations of Wegener granulomatosis. *Medicine* (Baltimore) 1995; **74**: 152-161 [PMID: 7760722]
 - 79 **Vaught WW**, Wilson TM, Raife MJ, Horne DW. Wegener granulomatosis: prostatic involvement and bladder outlet obstruction. *Urology* 1989; **34**: 43-45 [PMID: 2749956]
 - 80 **Gaber KA**, Ryley NG, Macdermott JP, Goldman JM. Wegener's granulomatosis involving prostate. *Urology* 2005; **66**: 195 [PMID: 16014287 DOI: 10.1016/j.urology.2005.01.045]
 - 81 **Gunnarsson R**, Omdal R, Kjelleveid KH, Ellingsen CL. Wegener's granulomatosis of the prostate gland. *Rheumatol Int* 2004; **24**: 120-122 [PMID: 12879271 DOI: 10.1007/s00296-003-0343-y]
 - 82 **Middleton G**, Karp D, Lee E, Cush J. Wegener's granulomatosis presenting as lower back pain with prostatitis and ureteral obstruction. *J Rheumatol* 1994; **21**: 566-569 [PMID: 8006905]
 - 83 **Davies CW**, Wathen CG. Wegener's granulomatosis presenting as prostate and submandibular gland disease. *Sarcoidosis Vasc Diffuse Lung Dis* 1997; **14**: 190-191 [PMID: 9306514]
 - 84 **Murty GE**, Powell PH. Wegener's granulomatosis presenting as prostatitis. *Br J Urol* 1991; **67**: 107-108 [PMID: 1993268]
 - 85 **Brunner A**, Tzankov A, Akkad T, Lhotka K, Bartsch G, Mikuz G. Wegener's granulomatosis presenting with gross hematuria due to prostatitis. *Virchows Arch* 2004; **444**: 92-94 [PMID: 14576940 DOI: 10.1007/s00428-003-0916-x]
 - 86 **Sözer IT**. Wegener's granulomatosis with infiltration of the prostate. *Br J Urol* 1986; **58**: 335 [PMID: 3719257]
 - 87 **Yalowitz PA**, Greene LF, Sheps SG, Carlin MR. Wegener's granulomatosis involving the prostate gland: report of a case. *J Urol* 1966; **96**: 801-804 [PMID: 5923308]
 - 88 **Minnee RC**, van den Berk GE, Groeneveld JO, van Dijk J, Turkcan K, Visser MJ, Vahl AC. Aortic aneurysm and orchitis due to Wegener's granulomatosis. *Ann Vasc Surg* 2009; **23**: 786.e15-786.e19 [PMID: 19748223 DOI: 10.1016/j.avsg.2009.06.011]
 - 89 **Paik ML**, MacLennan GT, Seftel AD. Embolic testicular infarction secondary to nonbacterial thrombotic endocarditis in Wegener's granulomatosis. *J Urol* 1999; **161**: 919-920 [PMID: 10022717]
 - 90 **Lee SS**, Tang SH, Sun GH, Yu CP, Jin JS, Chang SY. Limited Wegener's granulomatosis of the epididymis and testis. *Asian J Androl* 2006; **8**: 737-739 [PMID: 16855769 DOI: 10.1111/j.1745-7262.2006.00207.x]
 - 91 **Barber TD**, Al-Omar O, Poulik J, McLorie GA. Testicular infarction in a 12-year-old boy with Wegener's granulomatosis. *Urology* 2006; **67**: 846.e9-846.10 [PMID: 16566986 DOI: 10.1016/j.urology.2005.10.036]
 - 92 **Hernández-Rodríguez J**, Tan CD, Koenig CL, Khasnis A, Rodríguez ER, Hoffman GS. Testicular vasculitis: findings differentiating isolated disease from systemic disease in 72 patients. *Medicine* (Baltimore) 2012; **91**: 75-85 [PMID: 22391469 DOI: 10.1097/MD.0b013e31824156a7]
 - 93 **Davenport A**, Downey SE, Goel S, Maciver AG. Wegener's granulomatosis involving the urogenital tract. *Br J Urol* 1996; **78**: 354-357 [PMID: 8881941]
 - 94 **Di Comite G**, Bonavida G, Bozzolo E, Bianchi S, Ciboddo G, Tresoldi M, Praderio L, Sabbadini MG. [Wegener's granulomatosis: an analysis of 50 patients]. *Reumatismo* 2005; **57**: 187-192 [PMID: 16258603]
 - 95 **Guillevin L**, Brauner M. Magnetic resonance imaging of ureter stenosis in Wegener's granulomatosis. *Ann Med Interne* (Paris) 1998; **149**: 287 [PMID: 9791562]
 - 96 **Rich LM**, Piering WF. Ureteral stenosis due to recurrent Wegener's granulomatosis after kidney transplantation. *J Am Soc Nephrol* 1994; **4**: 1516-1521 [PMID: 8025224]
 - 97 **Sataa S**, Ben Rhouma S, Tanguour M, Rebai S, Cherif K, Kchir N, Noura Y, Benrais N, Horchani A. Ureteral stenosis due to Wegener's granulomatosis. *Tunis Med* 2011; **89**: 725-726 [PMID: 21948672]
 - 98 **Ben Ghorbel I**, Chebbi W, Zouari M, Hentati F, Miled M, Houman MH. [Ureteral stenosis in Wegener's granulomatosis. Case report]. *Presse Med* 2006; **35**: 1659-1663 [PMID: 17086121]
 - 99 **Matsuda S**, Mitsukawa S, Ishii N, Shirai M. A case of Wegener's granulomatosis with necrosis of the penis. *Tohoku J Exp Med* 1976; **118**: 145-151 [PMID: 982429]
 - 100 **Stucker F**, Masouyé I, Toutous-Trellu L. Fever and penis ulcer in an 87-year-old man. *Dermatology* 2006; **212**: 397-398 [PMID: 16707897 DOI: 10.1159/000092298]
 - 101 **Bories N**, Becuwe C, Marcilly MC, Wolf F, Balme B, Thomas L. Glans penis ulceration revealing Wegener's granulomatosis. *Dermatology* 2007; **214**: 187-189 [PMID: 17341873 DOI: 10.1159/000098583]
 - 102 **Ebo DG**, Mertens AV, De Clerck LS, Gentens P, Daelemans R. Relapse of Wegener's granulomatosis presenting as a destructive urethritis and penile ulceration. *Clin Rheumatol* 1998; **17**: 239-241 [PMID: 9694061 DOI: 10.1007/BF01451056]
 - 103 **Palacios J**, Picazo ML, Enriquez R, de Miguel JL. [Unusual clinical manifestations in a case of Wegener's disease]. *Med Clin* (Barc) 1986; **87**: 870 [PMID: 3492641]
 - 104 **Dufour JF**, Le Gallou T, Cordier JF, Aumaitre O, Pinède L, Aslangul E, Pagnoux C, Marie I, Puéchal X, Decaux O, Dubois A, Agard C, Mahr A, Comoz F, Boutemy J, Broussolle C, Guillevin L, Sève P, Bienvenu B. Urogenital manifestations in Wegener

- granulomatosis: a study of 11 cases and review of the literature. *Medicine* (Baltimore) 2012; **91**: 67-74 [PMID: 22391468 DOI: 10.1097/MD.0b013e318239add6]
- 105 **Jensen KM**, Nielsen KK, Kock K. Necrotising urethritis in Wegener's granulomatosis. *Br J Urol* 1982; **54**: 435-436 [PMID: 7116115]
- 106 **Fowler M**, Martin SA, Bowles WT, Packman R, Katzenstein AL. Wegener granulomatosis. Unusual cause of necrotizing urethritis. *Urology* 1979; **14**: 66-69 [PMID: 452226]
- 107 **Verswijvel G**, Eerens I, Messiaen T, Oyen R. Granulomatous renal pseudotumor in Wegener's granulomatosis: imaging findings in one case. *Eur Radiol* 2000; **10**: 1265-1267 [PMID: 10939487]
- 108 **Hooda D**, Parsons J, Hooda S, Nuss M, Layne R. Isolated bladder vasculitis: a rare presentation of Wegener's granulomatosis. *W V Med J* 2011; **107**: 24-25 [PMID: 21322469]
- 109 **Ashikaga E**, Iyoda M, Suzuki H, Nagai H, Shibata T, Akizawa T. [Case of microscopic polyangiitis presenting initially as prostatic vasculitis]. *Nihon Jinzo Gakkai Shi* 2009; **51**: 1075-1079 [PMID: 1999587]
- 110 **Lamarque JA**, Peguero AM, Rosario JO, Patel A, Courville C. Anti-MPO small-vessel vasculitis causing prostatitis and nephritis. *Clin Exp Nephrol* 2007; **11**: 180-183 [PMID: 17593520 DOI: 10.1007/s10157-007-0473-8]
- 111 **Kiyokawa H**, Koyama M, Kato H. Churg-Strauss syndrome presenting with eosinophilic prostatitis. *Int J Urol* 2006; **13**: 838-840 [PMID: 16834677 DOI: 10.1111/j.1442-2042.2006.01419.x]
- 112 **Symes A**, Kalsi V, Rickards D, Allen C, Choong S, Philp T. Dystrophic ureteral calcification associated with Churg-Strauss vasculitis. *Urology* 2004; **64**: 1231.e9-1231.11 [PMID: 15596209 DOI: 10.1016/j.urology.2004.06.036]
- 113 **Walsh I**, Loughridge WG, Keane PF. Eosinophilic vasculitis (Churg-Strauss syndrome) involving the urethra. *Br J Urol* 1994; **74**: 255-256 [PMID: 7921951 DOI: 10.1111/j.1464-410X.1994.tb16601.x]
- 114 **Dolezalová P**, Telekesová P, Nemcová D, Hoza J. Incidence of vasculitis in children in the Czech Republic: 2-year prospective epidemiology survey. *J Rheumatol* 2004; **31**: 2295-2299 [PMID: 15517648]
- 115 **Gardner-Medwin JM**, Dolezalova P, Cummins C, Southwood TR. Incidence of Henoch-Schönlein purpura, Kawasaki disease, and rare vasculitides in children of different ethnic origins. *Lancet* 2002; **360**: 1197-1202 [PMID: 12401245 DOI: 10.1016/S0140-6736(02)11279-7120]
- 116 **Yang YH**, Hung CF, Hsu CR, Wang LC, Chuang YH, Lin YT, Chiang BL. A nationwide survey on epidemiological characteristics of childhood Henoch-Schönlein purpura in Taiwan. *Rheumatology* (Oxford) 2005; **44**: 618-622 [PMID: 15671050 DOI: 10.1093/rheumatology/keh544]
- 117 **Blanco R**, Martínez-Taboada VM, Rodríguez-Valverde V, García-Fuentes M, González-Gay MA. Henoch-Schönlein purpura in adulthood and childhood: two different expressions of the same syndrome. *Arthritis Rheum* 1997; **40**: 859-864 [PMID: 9153547 DOI: 10.1002/art.1780400513]
- 118 **Pillebout E**, Thervet E, Hill G, Alberti C, Vanhille P, Nochy D. Henoch-Schönlein Purpura in adults: outcome and prognostic factors. *J Am Soc Nephrol* 2002; **13**: 1271-1278 [PMID: 11961015]
- 119 **Rostoker G**. Schönlein-henoch purpura in children and adults: diagnosis, pathophysiology and management. *BioDrugs* 2001; **15**: 99-138 [PMID: 11437679 DOI: 10.2165/00063030-200115020-00004]
- 120 **Saulsbury FT**. Henoch-Schönlein purpura in children. Report of 100 patients and review of the literature. *Medicine* (Baltimore) 1999; **78**: 395-409 [PMID: 10575422]
- 121 **Dillon MJ**. Henoch-Schönlein purpura (treatment and outcome). *Cleve Clin J Med* 2002; **69** Suppl 2: SII121-SII123 [PMID: 12086251 DOI: 10.3949/ccjm.69.Suppl_2.SII12]
- 122 **Trapani S**, Micheli A, Grisolia F, Resti M, Chiappini E, Falcini F, De Martino M. Henoch Schonlein purpura in childhood: epidemiological and clinical analysis of 150 cases over a 5-year period and review of literature. *Semin Arthritis Rheum* 2005; **35**: 143-153 [PMID: 16325655 DOI: 10.1016/j.semarthrit.2005.08.007]
- 123 **Pfister C**, Liard-Zmuda A, Dacher J, Dubois D, Grise P, Mitrofanoff P. Total bilateral ureteral replacement for stenosing ureteritis in Henoch-Schönlein purpura. *Eur Urol* 2000; **38**: 96-99 [PMID: 10859449]
- 124 **Macpherson RI**. The radiological manifestations of Henoch-Schönlein purpura. *J Can Assoc Radiol* 1974; **25**: 275-281 [PMID: 4443362]
- 125 **Pery M**, Alon U, Lachter JH, Kaftori JK, Gaitini D, Rosenberger A. The value of ultrasound in Schoenlein-Henoch purpura. *Eur J Pediatr* 1990; **150**: 92-94 [PMID: 2279515 DOI: 10.1007/BF02072045]
- 126 **Sandell J**, Ramanan R, Shah D. Penile involvement in Henoch-Schönlein purpura. *Indian J Pediatr* 2002; **69**: 529-530 [PMID: 12139142 DOI: 10.1007/BF02722659]
- 127 **Ferrara P**, Marrone G, Nicoletti A, Mastrangelo A, Tiberi E, Rigante D, Stabile A. Penile involvement in Henoch-Schönlein purpura with good prognosis. *Scand J Urol Nephrol* 2007; **41**: 567-569 [PMID: 17853026 DOI: 10.1080/00365590701365487]
- 128 **Clark WR**, Kramer SA. Henoch-Schönlein purpura and the acute scrotum. *J Pediatr Surg* 1986; **21**: 991-992 [PMID: 3794962 DOI: 10.1016/S0022-3468(86)80120-8]
- 129 **Katz S**, Borst M, Seekri I, Grosfeld JL. Surgical evaluation of Henoch-Schönlein purpura. Experience with 110 children. *Arch Surg* 1991; **126**: 849-853; discussion 853-854 [PMID: 1854244 DOI: 10.1001/archsurg.1991.01410310059008]
- 130 **Ben-Sira L**, Laor T. Severe scrotal pain in boys with Henoch-Schönlein purpura: incidence and sonography. *Pediatr Radiol* 2000; **30**: 125-128 [PMID: 10663526 DOI: 10.1007/s002470050029]
- 131 **Chamberlain RS**, Greenberg LW. Scrotal involvement in Henoch-Schönlein purpura: a case report and review of the literature. *Pediatr Emerg Care* 1992; **8**: 213-215 [PMID: 1513732]
- 132 **Mintzer CO**, Nussinovitch M, Danziger Y, Mimouni M, Varsano I. Scrotal involvement in Henoch-Schönlein purpura in children. *Scand J Urol Nephrol* 1998; **32**: 138-139 [PMID: 9606788 DOI: 10.1080/003655998750014530]
- 133 **Khan AU**, Williams TH, Malek RS. Acute scrotal swelling in Henoch-Schönlein syndrome. *Urology* 1977; **10**: 139-141 [PMID: 898453]
- 134 **Lind J**, Mackay A, Withers SJ. Henoch-Schönlein purpura and priapism. *J Paediatr Child Health* 2002; **38**: 526-527 [PMID: 12354274]
- 135 **Diana A**, Gaze H, Laubscher B, De Meuron G, Tschantz P. A case of pediatric Henoch-Schönlein purpura and thrombosis of spermatic veins. *J Pediatr Surg* 2000; **35**: 1843 [PMID: 11101753 DOI: 10.1053/jpsu.2000.9293]
- 136 **Søreide K**. Surgical management of nonrenal genitourinary manifestations in children with Henoch-Schönlein purpura. *J Pediatr Surg* 2005; **40**: 1243-1247 [PMID: 16080926 DOI: 10.1016/j.jpedsurg.2005.05.005]
- 137 **Loh HS**, Jalan OM. Testicular torsion in Henoch--Schonlein syndrome. *Br Med J* 1974; **2**: 96-97 [PMID: 4545143]
- 138 **Connolly B**, O'Halpin D. Sonographic evaluation of the abdomen in Henoch-Schonlein purpura. *Clin Radiol* 1994; **49**: 320-323 [PMID: 8013195 DOI: 10.1016/S0009-9260(05)81796-9]
- 139 **Ronkainen J**, Koskimies O, Ala-Houhala M, Antikainen M, Merenmies J, Rajantie J, Ormälä T, Turtinen J, Nuutinen M. Early prednisone therapy in Henoch-Schönlein purpura: a randomized, double-blind, placebo-controlled trial. *J Pediatr* 2006; **149**: 241-247 [PMID: 16887443 DOI: 10.1016/j.jpeds.2006.03.024]
- 140 **Chartapisak W**, Opastiraku S, Willis NS, Craig JC, Hodson EM. Prevention and treatment of renal disease in Henoch-Schönlein purpura: a systematic review. *Arch Dis Child* 2009; **94**: 132-137 [PMID: 18701559 DOI: 10.1136/adc.2008.141820]
- 141 **Saulsbury FT**. Clinical update: Henoch-Schönlein purpura. *Lancet* 2007; **369**: 976-978 [PMID: 17382810 DOI: 10.1016/S0140-6736(07)60474-7]
- 142 **Huber AM**, King J, McLaine P, Klassen T, Pothos M. A randomized, placebo-controlled trial of prednisone in early Henoch Schönlein Purpura [ISRCTN85109383]. *BMC Med* 2004; **2**: 7

- [PMID: 15059282 DOI: 10.1186/1741-7015-2-7]
- 143 **Donnithorne KJ**, Atkinson TP, Hinze CH, Nogueira JB, Saeed SA, Askenazi DJ, Beukelman T, Cron RQ. Rituximab therapy for severe refractory chronic Henoch-Schönlein purpura. *J Pediatr* 2009; **155**: 136-139 [PMID: 19559299 DOI: 10.1016/j.jpeds.2008.12.049]
 - 144 **Jauhola O**, Ronkainen J, Autio-Harmainen H, Koskimies O, Ala-Houhala M, Arikoski P, Hölttä T, Jahnukainen T, Rajantie J, Ormälä T, Nuutinen M. Cyclosporine A vs. methylprednisolone for Henoch-Schönlein nephritis: a randomized trial. *Pediatr Nephrol* 2011; **26**: 2159-2166 [PMID: 21626222 DOI: 10.1007/s00467-011-1919-5]
 - 145 **Flynn JT**, Smoyer WE, Bunchman TE, Kershaw DB, Sedman AB. Treatment of Henoch-Schönlein Purpura glomerulonephritis in children with high-dose corticosteroids plus oral cyclophosphamide. *Am J Nephrol* 2001; **21**: 128-133 [PMID: 11359020 DOI: 10.1159/000046235]
 - 146 **Gedalia A**. Henoch-Schönlein purpura. *Curr Rheumatol Rep* 2004; **6**: 195-202 [PMID: 15134598 DOI: 10.1007/s11926-004-0068-2]
 - 147 **Kambham N**. Crescentic Glomerulonephritis: an update on Pauci-immune and Anti-GBM diseases. *Adv Anat Pathol* 2012; **19**: 111-124 [PMID: 22313839 DOI: 10.1097/PAP.0b013e318248b7a1]
 - 148 **Schena FP**. Survey of the Italian Registry of Renal Biopsies. Frequency of the renal diseases for 7 consecutive years. The Italian Group of Renal Immunopathology. *Nephrol Dial Transplant* 1997; **12**: 418-426 [PMID: 9075118 DOI: 10.1093/ndt/12.3.418]
 - 149 **Braun GS**, Horster S, Wagner KS, Ihrler S, Schmid H. Cryoglobulinaemic vasculitis: classification and clinical and therapeutic aspects. *Postgrad Med J* 2007; **83**: 87-94 [PMID: 17308210 DOI: 10.1136/pgmj.2006.046078]
 - 150 **Buck A**, Christensen J, McCarty M. Hypocomplementemic urticarial vasculitis syndrome: a case report and literature review. *J Clin Aesthet Dermatol* 2012; **5**: 36-46 [PMID: 22328958]
 - 151 Behçet's disease. *Lancet* 1989; **1**: 761-762 [PMID: 2564568 DOI: 10.1016/S0140-6736(89)92578-6]
 - 152 **Khairallah M**, Accorinti M, Muccioli C, Kahloun R, Kempen JH. Epidemiology of Behçet disease. *Ocul Immunol Inflamm* 2012; **20**: 324-335 [PMID: 23030353 DOI: 10.3109/09273948.2012.723112]
 - 153 Criteria for diagnosis of Behçet's disease. International Study Group for Behçet's Disease. *Lancet* 1990; **335**: 1078-1080 [PMID: 1970380 DOI: 10.1016/0140-6736(90)92643-V]
 - 154 **Yazici H**, Fresko I, Hamuryudan V, Mat C, Melikoglu M, Ozyazgan Y, Tuzun Y, Yurdakul S. Behçet's syndrome. In: Mallia C, Uitto J Rheumaderm. USA: Springer, 1999: 135-140 [DOI: 10.1007/978-1-4615-4857-7_19]
 - 155 **Kirkali Z**, Yigitbasi O, Sasmaz R. Urological aspects of Behçet's disease. *Br J Urol* 1991; **67**: 638-639 [PMID: 2070210 DOI: 10.1111/j.1464-410X.1991.tb15230.x]
 - 156 **Mishima S**, Masuda K, Izawa Y, Mochizuki M, Namba K. The eighth Frederick H. Verhoeff Lecture. presented by saichi mishima, MD Behçet's disease in Japan: ophthalmologic aspects. *Trans Am Ophthalmol Soc* 1979; **77**: 225-279 [PMID: 397657]
 - 157 **Cetinel B**, Akpınar H, Tüfek I, Uygün N, Solok V, Yazici H. Bladder involvement in Behçet's syndrome. *J Urol* 1999; **161**: 52-56 [PMID: 10037367 DOI: 10.1016/S0022-5347(01)62060-3]
 - 158 **Monteiro H**, Nogueira R, de Carvalho H. Behçet's syndrome and vesicovaginal fistula: an unusual complication. *J Urol* 1995; **153**: 407-408 [PMID: 7815600 DOI: 10.1097/00005392-199502000-00036]
 - 159 **Davatchi F**, Shahram F, Chams-Davatchi C, Shams H, Nadji A, Akhlaghi M, Faezi T, Ghodsi Z, Faridar A, Ashofteh F, Sadeghi Abdollahi B. Behçet's disease: from East to West. *Clin Rheumatol* 2010; **29**: 823-833 [PMID: 20354748 DOI: 10.1007/s10067-010-1430-6]
 - 160 **Nakagawa H**, Namima T, Aizawa M, Uchi K, Orikasa S. [Three cases of neurogenic bladder due to neuro-Beçhet disease]. *Nihon Hinyokika Gakkai Zasshi* 1994; **85**: 1399-1402 [PMID: 7967304]
 - 161 **Yurdakul S**, Mat C, Tüzün Y, Ozyazgan Y, Hamuryudan V, Uysal O, Senocak M, Yazici H. A double-blind trial of colchicine in Behçet's syndrome. *Arthritis Rheum* 2001; **44**: 2686-2692 [PMID: 11710724]
 - 162 **Aktulga E**, Altaç M, Müftüoğlu A, Ozyazgan Y, Pazarlı H, Tüzün Y, Yalçın B, Yazici H, Yurdakul S. A double blind study of colchicine in Behçet's disease. *Haematologica* 1980; **65**: 399-402 [PMID: 6778795]
 - 163 **Hatemi G**, Silman A, Bang D, Bodaghi B, Chamberlain AM, Gul A, Houman MH, Kötter I, Olivieri I, Salvarani C, Sfrikakis PP, Siva A, Stanford MR, Stübiger N, Yurdakul S, Yazici H. EULAR recommendations for the management of Behçet disease. *Ann Rheum Dis* 2008; **67**: 1656-1662 [PMID: 18245110 DOI: 10.1136/ard.2007.080432]
 - 164 **Alizadeh F**, Khorrami MH, Izadpanahi MH, Nouri-Mahdavi K, Mohammadi Sichani M. Bladder involvement in Behçet's disease. *Urol J* 2012; **9**: 347-350 [PMID: 22395828]
 - 165 **Norton EW**, Cogan DG. Syndrome of nonsyphilitic interstitial keratitis and vestibuloauditory symptoms; a long-term follow-up. *AMA Arch Ophthalmol* 1959; **61**: 695-697 [PMID: 13636563 DOI: 10.1001/archoph.1945.00890140064007]
 - 166 **Talar-Williams C**, Hijazi YM, Walther MM, Linehan WM, Hallahan CW, Lubensky I, Kerr GS, Hoffman GS, Fauci AS, Sneller MC. Cyclophosphamide-induced cystitis and bladder cancer in patients with Wegener granulomatosis. *Ann Intern Med* 1996; **124**: 477-484 [PMID: 8602705]
 - 167 **Fernandes ET**, Manivel JC, Reddy PK, Ercole CJ. Cyclophosphamide associated bladder cancer—a highly aggressive disease: analysis of 12 cases. *J Urol* 1996; **156**: 1931-1933 [PMID: 8911359 DOI: 10.1016/S0022-5347(01)65395-3]
 - 168 **Knight A**, Askling J, Ekblom A. Cancer incidence in a population-based cohort of patients with Wegener's granulomatosis. *Int J Cancer* 2002; **100**: 82-85 [PMID: 12115591 DOI: 10.1002/ijc.10444]
 - 169 **Monach PA**, Arnold LM, Merkel PA. Incidence and prevention of bladder toxicity from cyclophosphamide in the treatment of rheumatic diseases: a data-driven review. *Arthritis Rheum* 2010; **62**: 9-21 [PMID: 20039416 DOI: 10.1002/art.25061]
 - 170 **Mukhtyar C**, Guillemin L, Cid MC, Dasgupta B, de Groot K, Gross W, Hauser T, Hellmich B, Jayne D, Kallenberg CG, Merkel PA, Raspe H, Salvarani C, Scott DG, Stegeman C, Watts R, Westman K, Witter J, Yazici H, Luqmani R. EULAR recommendations for the management of primary small and medium vessel vasculitis. *Ann Rheum Dis* 2009; **68**: 310-317 [PMID: 18413444 DOI: 10.1136/ard.2008.088096]
 - 171 **Harper L**, Morgan MD, Walsh M, Hoglund P, Westman K, Flossmann O, Tesar V, Vanhille P, de Groot K, Luqmani R, Flores-Suarez LF, Watts R, Pusey C, Bruchfeld A, Rasmussen N, Blockmans D, Savage CO, Jayne D. Pulse versus daily oral cyclophosphamide for induction of remission in ANCA-associated vasculitis: long-term follow-up. *Ann Rheum Dis* 2012; **71**: 955-960 [PMID: 22128076 DOI: 10.1136/annrheumdis-2011-200477]
 - 172 **Austin HA**, Klippel JH, Balow JE, le Riche NG, Steinberg AD, Plotz PH, Decker JL. Therapy of lupus nephritis. Controlled trial of prednisone and cytotoxic drugs. *N Engl J Med* 1986; **314**: 614-619 [PMID: 3511372 DOI: 10.1056/NEJM198603063141004]
 - 173 **Watson AR**, Rance CP, Bain J. Long term effects of cyclophosphamide on testicular function. *Br Med J (Clin Res Ed)* 1985; **291**: 1457-1460 [PMID: 3933709]
 - 174 **Fukutani K**, Ishida H, Shinohara M, Minowada S, Nijima T, Hijikata K, Izawa Y. Suppression of spermatogenesis in patients with Behçet's disease treated with cyclophosphamide and colchicine. *Fertil Steril* 1981; **36**: 76-80 [PMID: 6788612]
 - 175 **Sarica K**, Suzer O, Gurler A, Baltaci S, Ozdiler E, Dincel C. Urological evaluation of behcet patients and the effect of colchicine on fertility. *Eur Urol* 1995; **27**: 39-42
 - 176 **Blumenfeld Z**, Shapiro D, Shteinberg M, Avivi I, Nahir M. Preservation of fertility and ovarian function and minimizing gonadotoxicity in young women with systemic lupus erythematosus treated by chemotherapy. *Lupus* 2000; **9**: 401-405 [PMID: 10981642 DOI: 10.1191/096120300678828596]
 - 177 **Somers EC**, Marder W, Christman GM, Ognenovski V, McCune WJ. Use of a gonadotropin-releasing hormone analog for protection against premature ovarian failure during cyclophosphamide therapy in women with severe lupus. *Arthritis Rheum* 2005; **52**: 2761-2767 [PMID: 16142702 DOI: 10.1002/art.21263]
 - 178 **Masala A**, Faedda R, Alagna S, Satta A, Chiarelli G, Rovasio PP,

Ivaldi R, Taras MS, Lai E, Bartoli E. Use of testosterone to prevent cyclophosphamide-induced azoospermia. *Ann Intern Med* 1997;

126: 292-295 [PMID: 9036801 DOI: 10.7326/0003-4819-126-4-199702150-00005]

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Role of transperineal template biopsy in prostate cancer

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number of biopsies being utilised. However there is no consensus regarding the ideal number of biopsies that should be utilised with TPT. Furthermore it is felt that the increased number of biopsies utilised with TPT is associated the higher complication rates with TPT. The role of TPT biopsy is recognised in those with previous negative biopsies with transrectal ultrasound but further work is required regarding the ideal number of biopsies. Furthermore, it is felt that TPT biopsy may have a role in primary biopsy.

Key words: Transrectal prostate biopsy; Transperineal prostate biopsy; Prostate biopsy

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Core tip: Transperineal template biopsies are utilised in prostate cancer at an increasing rate instead of transrectal biopsies, yet there is no consensus on how this investigation should be utilised. Here we assess when this method of prostate biopsy is utilised, the number of biopsies that are taken and the method of transperineal template biopsy as well the likelihood of the increase in accuracy in diagnosing prostate cancer.

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Abstract

Prostate cancer is the most common neoplasm diagnosed in men. Whilst treatment modalities have progressed, diagnostic investigations in terms of biopsy methods have been assessed but there is no consensus of when the different diagnostic methods in terms of transrectal ultrasound (TRUS) or transperineal template (TPT) should be utilised. TPT biopsy has a higher diagnostic yield than TRUS in those with a primary biopsy, in those with previous negative biopsies with TRUS as well as those undergoing saturation biopsies. Despite the increased likelihood of diagnosing cancer with TPT than TRUS this maybe secondary to the increased

INTRODUCTION

Prostate cancer is now recognised as a major burden on the global health-care system. In the United States and in Europe, it is the most common neoplasm diagnosed in men and is responsible for 11% of all male cancer deaths^[1,2]. After a diagnosis of prostate cancer is made, a number of treatments may be considered depending on the information provided by

staging investigations. In patients who are thought to have organ confined prostate cancer, treatment options include radical prostatectomy, external beam radiation therapy, brachytherapy, focal treatment and active monitoring.

The main diagnostic tools utilised for a diagnosis of prostate cancer are digital rectal examination (DRE), serum concentration of Prostate Specific Antigen (PSA) and transrectal ultra sound guided (TRUS) biopsy. Prostate cancer can be detected by DRE alone in patients irrespective of the PSA reading^[3]. A suspicious DRE is associated with more aggressive prostate cancer once diagnosed following biopsy^[4] with the chance of having malignancy at biopsy higher in those with a suspicious DRE^[5].

PSA measurement is now standard practise in prostate cancer diagnosis^[6,7] since its first discovery as a serum marker for prostate cancer^[8] having been demonstrated to be an independent predictor of cancer in comparison to a suspicious DRE or TRUS^[9].

It is felt that performing biopsies under ultrasound guide where a transrectal approach is used for most biopsies is the standard. This is guided by hypoechoic areas in the peripheral zone but this is not always seen as Gray-scale TRUS does not detect areas of malignancy with adequate reliability^[10] and as a consequence performing biopsies on only those areas that are hypoechoic would lead to cancers being missed^[11] and has led to systematic biopsies being performed^[11].

Pathological studies have demonstrated that prostate cancer can be a unifocal and unilateral disease^[12] leading to a growing demand for minimally invasive treatment modalities prompting research into focal therapies which allows treatment of the cancer focus and sparing of normal tissue and therefore preserving genitourinary function^[13,14]. It is felt that transperineal template (TPT) biopsy has a higher detection rate not of only prostate cancer^[15-25] but also of clinically significant prostate cancer^[17-19,26-29], anterior cancers^[30,31] and has a higher detection rate than TRUS in those with a normal DRE^[32]. TPT has a slightly longer training time^[33] but has been demonstrated to diagnose cancer in those that have undergone previous negative biopsies *via* TRUS^[26,29,34-39]. TPT biopsies are directed longitudinally to the peripheral zone and anterior part of the prostate so they should detect more cancer than *via* TRUS^[40]. It is felt that this may be due to the inclusion of lateral cores explaining the higher diagnosis rate. It has been demonstrated that TPT biopsies detected significant cancers in those that had undergone TRUS biopsies with earlier negative findings^[26,29,34-39] whilst others have demonstrated no difference between TRUS and TPT^[41-43].

NUMBER OF BIOPSIES

It is felt that TRUS sextant biopsies are inadequate compared to TPT^[15,44] and this results in a significant difference in the detection rates of prostate cancer when

compared to twelve biopsies *via* TRUS or TPT^[45-47]. It is felt that sextant biopsies *via* TPT can be utilised but only in cases of an abnormal DRE or increased PSA otherwise twelve biopsies are required^[48]. This also increases the accuracy in Gleason grade in comparison to the final pathology following surgery^[49]. It has been suggested that performing twenty two biopsies *via* TPT may increase the diagnostic accuracy^[34] especially for larger sized prostates^[50] whilst eight peripheral cores are sufficient for prostate volumes < 30 cc^[23]. Furthermore, there is evidence that eighteen biopsies should be utilised in certain situations^[51]. It has been demonstrated that using thirty six biopsies *via* TPT has a better diagnostic yield of prostate cancer than twelve *via* TRUS in those with normal DRE^[25] whilst fourteen biopsies maybe sufficient but there is a risk of missing cancers^[52]. Others have suggested that utilising a brachytherapy template with a 5 millimetre grid to guide template biopsies allows the detection of clinically significant prostate cancer^[19] and that the volume of the prostate should be utilised as a guide to the number of biopsies with eight cores sufficient for small prostates and more extensive biopsies utilised for larger prostates^[23] whereas it is felt that twelve biopsies are sufficient utilising a fan technique^[17]. Clearly, larger prostates require higher numbers of biopsies for representative sampling.

Magnetic resonance imaging (MRI) has been demonstrated to have a high degree of accuracy in the detection of clinically significant prostate cancer when compared to radical prostatectomy specimens^[53]. This has led to reports that MRI guided TRUS biopsies increase the detection of prostate cancer^[54,55] as well as the detection of significant disease^[56] with the possibility of utilising less biopsies^[57,58]. However, MRI guided biopsy is not a modality that is utilised on a regular basis at the present time.

SATURATION BIOPSIES

In cases where saturation biopsies are utilised for investigation for previous negative biopsies with TRUS, it has been demonstrated that the detection rate can increase between 30%-40% using TRUS saturation biopsies, with the majority of these diagnoses being minimally differentiated disease^[59-61]. Furthermore, there is an increase of 38% detection rate by TPT saturation biopsies after previous negative TRUS biopsies suggesting no advantage of TPT saturation biopsies over TRUS saturation biopsies^[41,62]. Others have demonstrated that saturation biopsies do increase the detection rate of prostate cancer in those with previous negative biopsies with TRUS but have recommended that saturation biopsies should not be utilised as an initial strategy^[63].

PREPARATION

As the TPT approach does not pass through the rectum it should be considered a sterile approach and

therefore antibiotics should be recommended for those patients at a high risk of infection. There is little work looking at the role of antibiotics in the setting of TPT and yet many reports of TPT utilise antibiotics on a standard basis^[17,23] which can be of concern given the prevalence of antibiotic resistance.

Bowel preparation is common amongst many urologists prior to TPT^[64] as is felt that it reduces bacterial load^[65] but given that TPT is a sterile procedure, the role of preventing infection may not be appropriate but it is felt that removing faecal material may improve the image of the prostate^[66].

COMPLICATIONS

TPT is more invasive, has resource implications^[19,67,68] as well as being associated with more complications thought to be as a result of increased number of biopsies being utilised^[28,69,70]. There has been no difference in the complication rates following baseline TRUS or TPT^[15,23,26,29,41,71-73], even in those that are thought to be at increased risk of sepsis undergoing a biopsy *via* TPT as the primary choice^[29] whilst it has been reported that there is a higher rate of urinary retention following saturation biopsies with TPT^[62]. This may be the result that some TPT biopsy cores go through the external urethral sphincter. Where saturation biopsies are to be utilised with TRUS, then the cost implications are similar to TPT as both would require anaesthesia as well as post procedure recovery.

CONCLUSION

Prostate biopsy plays a very important role in the diagnosis of prostate cancer. As prostate cancer is multifocal, it is felt that the detection rate may differ with the number of biopsies and biopsy method.

It has been suggested that TPT biopsies may have a lower rate of sepsis than TRUS and should not be used for only those undergoing a repeat biopsy but in all those in whom a biopsy is indicated^[73]. Some authors have demonstrated no difference in detection rates, others have demonstrated a significant difference in the detection of clinically relevant disease and this is the group that it is often difficult in terms of management. Furthermore, this is the group that would benefit the most in terms of appropriate therapy. Those on active surveillance had their disease up-staged following TPT^[74] and therefore any additional information in terms of Gleason grade would prove most useful to help plan treatment in this group.

Some issues need to be addressed in terms of TPT biopsies. There is still not much information regarding the ideal number of biopsies that should be performed using this method and a consensus needs to be agreed upon this number as a significant difference in detection rates has been demonstrated when eighteen biopsies were taken in comparison to six-twelve *via* TPT^[75], suggesting that prostate size should be utilised to decide

the ideal number of biopsies^[19,23]. The complication rates have been demonstrated to correlate with increased number of biopsies^[76] and therefore it is suggested that twelve biopsies are sufficient^[17]. Furthermore, despite evidence that TPT biopsies offer a higher diagnostic yield than TRUS, this could be secondary just due to the fact that more biopsies are taken at the time of TPT than TRUS. It is agreed that TPT biopsies are useful in those where previous biopsies have been negative and therefore may aid in the diagnosis in these patients^[32,34,39].

REFERENCES

- Boyle P, Ferlay J. Cancer incidence and mortality in Europe, 2004. *Ann Oncol* 2005; **16**: 481-488 [PMID: 15718248 DOI: 10.1093/annonc/mdi098]
- Jemal A, Siegel R, Xu J, Ward E. Cancer statistics, 2010. *CA Cancer J Clin* 2010; **60**: 277-300 [PMID: 20610543 DOI: 10.3322/caac.20073]
- Richie JP, Catalona WJ, Ahmann FR, Hudson MA, Scardino PT, Flanigan RC, deKernion JB, Ratliff TL, Kavoussi LR, Dalkin BL. Effect of patient age on early detection of prostate cancer with serum prostate-specific antigen and digital rectal examination. *Urology* 1993; **42**: 365-374 [PMID: 7692657 DOI: 10.1016/0090-4295(93)90359-I]
- Okotie OT, Roehl KA, Han M, Loeb S, Gashti SN, Catalona WJ. Characteristics of prostate cancer detected by digital rectal examination only. *Urology* 2007; **70**: 1117-1120 [PMID: 18158030 DOI: 10.1016/j.urol.2007.07.019]
- Gosselaar C, Roobol MJ, Roemeling S, Schröder FH. The role of the digital rectal examination in subsequent screening visits in the European randomized study of screening for prostate cancer (ERSPC), Rotterdam. *Eur Urol* 2008; **54**: 581-588 [PMID: 18423977 DOI: 10.1016/j.eururo.2008.03.104]
- Stamey TA, Kabalin JN, McNeal JE, Johnstone IM, Freiha F, Redwine EA, Yang N. Prostate specific antigen in the diagnosis and treatment of adenocarcinoma of the prostate. II. Radical prostatectomy treated patients. *J Urol* 1989; **141**: 1076-1083 [PMID: 2468795]
- Stamey TA, Kabalin JN, Ferrari M, Yang N. Prostate specific antigen in the diagnosis and treatment of adenocarcinoma of the prostate. IV. Anti-androgen treated patients. *J Urol* 1989; **141**: 1088-1090 [PMID: 2468797]
- Stamey TA, Yang N, Hay AR, McNeal JE, Freiha FS, Redwine E. Prostate-specific antigen as a serum marker for adenocarcinoma of the prostate. *N Engl J Med* 1987; **317**: 909-916 [PMID: 2442609 DOI: 10.1056/NEJM198710083171501]
- Catalona WJ, Partin AW, Slawin KM, Brawer MK, Flanigan RC, Patel A, Richie JP, deKernion JB, Walsh PC, Scardino PT, Lange PH, Subong EN, Parson RE, Gasior GH, Loveland KG, Southwick PC. Use of the percentage of free prostate-specific antigen to enhance differentiation of prostate cancer from benign prostatic disease: a prospective multicenter clinical trial. *JAMA* 1998; **279**: 1542-1547 [PMID: 9605898 DOI: 10.1001/jama.279.19.1542]
- Lee F, Torp-Pedersen ST, Siders DB, Littrup PJ, McLeary RD. Transrectal ultrasound in the diagnosis and staging of prostatic carcinoma. *Radiology* 1989; **170**: 609-615 [PMID: 2644656 DOI: 10.1148/radiology.170.3.2644656]
- Flanigan RC, Catalona WJ, Richie JP, Ahmann FR, Hudson MA, Scardino PT, deKernion JB, Ratliff TL, Kavoussi LR, Dalkin BL. Accuracy of digital rectal examination and transrectal ultrasonography in localizing prostate cancer. *J Urol* 1994; **152**: 1506-1509 [PMID: 7523707]
- Karavitis M, Winkler M, Abel P, Livni N, Beckley I, Ahmed HU. Histological characteristics of the index lesion in whole-mount radical prostatectomy specimens: implications for focal therapy.

- Prostate Cancer Prostatic Dis* 2011; **14**: 46-52 [PMID: 20498680 DOI: 10.1038/pcan.2010.16]
- 13 **Ahmed HU**, Freeman A, Kirkham A, Sahu M, Scott R, Allen C, Van der Meulen J, Emberton M. Focal therapy for localized prostate cancer: a phase I/II trial. *J Urol* 2011; **185**: 1246-1254 [PMID: 21334018 DOI: 10.1016/j.juro.2010.11.079]
- 14 **Ahmed HU**, Pendse D, Illing R, Allen C, van der Meulen JH, Emberton M. Will focal therapy become a standard of care for men with localized prostate cancer? *Nat Clin Pract Oncol* 2007; **4**: 632-642 [PMID: 17965641 DOI: 10.1038/npcn0959]
- 15 **Emiliozzi P**, Corsetti A, Tassi B, Federico G, Martini M, Pansadoro V. Best approach for prostate cancer detection: a prospective study on transperineal versus transrectal six-core prostate biopsy. *Urology* 2003; **61**: 961-966 [PMID: 12736016 DOI: 10.1016/S0090-4295(02)02551-7]
- 16 **Kojima M**, Hayakawa T, Saito T, Mitsuya H, Hayase Y. Transperineal 12-core systematic biopsy in the detection of prostate cancer. *Int J Urol* 2001; **8**: 301-307 [PMID: 11389746]
- 17 **Emiliozzi P**, Longhi S, Scarpone P, Pansadoro A, DePaula F, Pansadoro V. The value of a single biopsy with 12 transperineal cores for detecting prostate cancer in patients with elevated prostate specific antigen. *J Urol* 2001; **166**: 845-850 [PMID: 11490231 DOI: 10.1016/S0022-5347(05)65849-1]
- 18 **Barzell WE**, Melamed MR. Appropriate patient selection in the focal treatment of prostate cancer: the role of transperineal 3-dimensional pathologic mapping of the prostate--a 4-year experience. *Urology* 2007; **70**: 27-35 [PMID: 18194708 DOI: 10.1016/j.urology.2007.06.1126]
- 19 **Crawford ED**, Rove KO, Barqawi AB, Maroni PD, Werahera PN, Baer CA, Koul HK, Rove CA, Lucia MS, La Rosa FG. Clinical-pathologic correlation between transperineal mapping biopsies of the prostate and three-dimensional reconstruction of prostatectomy specimens. *Prostate* 2013; **73**: 778-787 [PMID: 23169245 DOI: 10.1002/pros.22622]
- 20 **Zhang FB**, Shao Q, Du Y, Tian Y. [Ultrasound-guided transperineal 24-core saturation prostate biopsy is superior to the 14-core scheme in detecting prostate cancer in patients with PSA < 10; 20 microg/L]. *Zhonghua Nankexue* 2012; **18**: 306-309 [PMID: 22574363]
- 21 **Takenaka A**, Hara R, Hyodo Y, Ishimura T, Sakai Y, Fujioka H, Fujii T, Jo Y, Fujisawa M. Transperineal extended biopsy improves the clinically significant prostate cancer detection rate: a comparative study of 6 and 12 biopsy cores. *Int J Urol* 2006; **13**: 10-14 [PMID: 16448425 DOI: 10.1111/j.1442-2042.2006.01221.x]
- 22 **Vis AN**, Boerma MO, Ciatto S, Hoedemaeker RF, Schröder FH, van der Kwast TH. Detection of prostate cancer: a comparative study of the diagnostic efficacy of sextant transrectal versus sextant transperineal biopsy. *Urology* 2000; **56**: 617-621 [PMID: 11018617 DOI: 10.1016/S0090-4295(00)00681-6]
- 23 **Ficarra V**, Novella G, Novara G, Galfano A, Pea M, Martignoni G, Artibani W. The potential impact of prostate volume in the planning of optimal number of cores in the systematic transperineal prostate biopsy. *Eur Urol* 2005; **48**: 932-937 [PMID: 16202510 DOI: 10.1016/j.eururo.2005.08.008]
- 24 **Furuno T**, Demura T, Kaneta T, Gotoda H, Muraoka S, Sato T, Nagamori S, Shinohara N, Koyanagi T. Difference of cancer core distribution between first and repeat biopsy: In patients diagnosed by extensive transperineal ultrasound guided template prostate biopsy. *Prostate* 2004; **58**: 76-81 [PMID: 14673955 DOI: 10.1002/pros.10298]
- 25 **Nafie S**, Mellon JK, Dormer JP, Khan MA. The role of transperineal template prostate biopsies in prostate cancer diagnosis in biopsy naïve men with PSA less than 20 ng/ml (-1.). *Prostate Cancer Prostatic Dis* 2014; **17**: 170-173 [PMID: 24590360 DOI: 10.1038/pcan.2014.4]
- 26 **Klatte T**, Swietek N, Schatzl G, Waldert M. Transperineal template-guided biopsy for diagnosis of prostate cancer in patients with at least two prior negative biopsies. *Wien Klin Wochenschr* 2013; **125**: 669-673 [PMID: 24061696 DOI: 10.1007/s00508-013-0421-4]
- 27 **Bittner N**, Merrick GS, Bennett A, Butler WM, Andreini HJ, Taubenslag W, Adamovich E. Diagnostic Performance of Initial Transperineal Template-guided Mapping Biopsy of the Prostate Gland. *Am J Clin Oncol* 2013 Jun 11; Epub ahead of print [PMID: 23764680 DOI: 10.1097/COC.0b013e31829a2954]
- 28 **Pinkstaff DM**, Igel TC, Petrou SP, Broderick GA, Wehle MJ, Young PR. Systematic transperineal ultrasound-guided template biopsy of the prostate: three-year experience. *Urology* 2005; **65**: 735-739 [PMID: 15833518 DOI: 10.1016/j.urology.2004.10.067]
- 29 **Vyas L**, Acher P, Kinsella J, Challacombe B, Chang RT, Sturch P, Cahill D, Chandra A, Popert R. Indications, results and safety profile of transperineal sector biopsies (TPSB) of the prostate: a single centre experience of 634 cases. *BJU Int* 2014; **114**: 32-37 [PMID: 24053629 DOI: 10.1111/bju.12282]
- 30 **Hossack T**, Patel MI, Huo A, Brenner P, Yuen C, Spernat D, Mathews J, Haynes AM, Sutherland R, del Prado W, Stricker P. Location and pathological characteristics of cancers in radical prostatectomy specimens identified by transperineal biopsy compared to transrectal biopsy. *J Urol* 2012; **188**: 781-785 [PMID: 22819419 DOI: 10.1016/j.juro.2012.05.006]
- 31 **Mabjeesh NJ**, Lidawi G, Chen J, German L, Matzkin H. High detection rate of significant prostate tumours in anterior zones using transperineal ultrasound-guided template saturation biopsy. *BJU Int* 2012; **110**: 993-997 [PMID: 22394668 DOI: 10.1111/j.1464-410X.2012.10972.x]
- 32 **Taira AV**, Merrick GS, Galbreath RW, Andreini H, Taubenslag W, Curtis R, Butler WM, Adamovich E, Wallner KE. Performance of transperineal template-guided mapping biopsy in detecting prostate cancer in the initial and repeat biopsy setting. *Prostate Cancer Prostatic Dis* 2010; **13**: 71-77 [PMID: 19786982 DOI: 10.1038/pcan.2009.42]
- 33 **Shen PF**, Zhu YC, Wei WR, Li YZ, Yang J, Li YT, Li DM, Wang J, Zeng H. The results of transperineal versus transrectal prostate biopsy: a systematic review and meta-analysis. *Asian J Androl* 2012; **14**: 310-315 [PMID: 22101942 DOI: 10.1038/aja.2011.130]
- 34 **Satoh T**, Matsumoto K, Fujita T, Tabata K, Okusa H, Tsuboi T, Arakawa T, Irie A, Egawa S, Baba S. Cancer core distribution in patients diagnosed by extended transperineal prostate biopsy. *Urology* 2005; **66**: 114-118 [PMID: 15992910 DOI: 10.1016/j.urology.2005.01.051]
- 35 **Merrick GS**, Gutman S, Andreini H, Taubenslag W, Lindert DL, Curtis R, Adamovich E, Anderson R, Allen Z, Butler W, Wallner K. Prostate cancer distribution in patients diagnosed by transperineal template-guided saturation biopsy. *Eur Urol* 2007; **52**: 715-723 [PMID: 17337114 DOI: 10.1016/j.eururo.2007.02.041]
- 36 **Bott SR**, Henderson A, Halls JE, Montgomery BS, Laing R, Langley SE. Extensive transperineal template biopsies of prostate: modified technique and results. *Urology* 2006; **68**: 1037-1041 [PMID: 17095067 DOI: 10.1016/j.urology.2006.05.033]
- 37 **Ekwueme K**, Simpson H, Zakhour H, Parr NJ. Transperineal template-guided saturation biopsy using a modified technique: outcome of 270 cases requiring repeat prostate biopsy. *BJU Int* 2013; **111**: E365-E373 [PMID: 23714648 DOI: 10.1111/bju.12134]
- 38 **Bittner N**, Merrick GS, Butler WM, Bennett A, Galbreath RW. Incidence and pathological features of prostate cancer detected on transperineal template guided mapping biopsy after negative transrectal ultrasound guided biopsy. *J Urol* 2013; **190**: 509-514 [PMID: 23416641 DOI: 10.1016/j.juro.2013.02.021]
- 39 **Nafie S**, Pal RP, Dormer JP, Khan MA. Transperineal template prostate biopsies in men with raised PSA despite two previous sets of negative TRUS-guided prostate biopsies. *World J Urol* 2014; **32**: 971-975 [PMID: 24337167 DOI: 10.1007/s00345-013-1225-x]
- 40 **Abdollah F**, Novara G, Briganti A, Scattoni V, Raber M, Roscigno M, Suardi N, Gallina A, Artibani W, Ficarra V, Cestari A, Guazzoni G, Rigatti P, Montorsi F. Trans-rectal versus trans-perineal saturation rebiopsy of the prostate: is there a difference in cancer detection rate? *Urology* 2011; **77**: 921-925 [PMID: 21131034 DOI: 10.1016/j.urology.2010.08.048]
- 41 **Hara R**, Jo Y, Fujii T, Kondo N, Yokoyama T, Miyaji Y, Nagai A. Optimal approach for prostate cancer detection as initial biopsy: prospective randomized study comparing transperineal versus transrectal systematic 12-core biopsy. *Urology* 2008; **71**: 191-195

- [PMID: 18308081 DOI: 10.1016/j.urology.2007.09.029]
- 42 **Takenaka A**, Hara R, Ishimura T, Fujii T, Jo Y, Nagai A, Fujisawa M. A prospective randomized comparison of diagnostic efficacy between transperineal and transrectal 12-core prostate biopsy. *Prostate Cancer Prostatic Dis* 2008; **11**: 134-138 [PMID: 17533394 DOI: 10.1038/sj.pcan.4500985]
 - 43 **Kawakami S**, Yamamoto S, Numao N, Ishikawa Y, Kihara K, Fukui I. Direct comparison between transrectal and transperineal extended prostate biopsy for the detection of cancer. *Int J Urol* 2007; **14**: 719-724 [PMID: 17681062 DOI: 10.1111/j.1442-2042.2007.01810.x]
 - 44 **Demura T**, Hioka T, Furuno T, Kaneta T, Gotoda H, Muraoka S, Sato T, Mochizuki T, Nagamori S, Shinohara N. Differences in tumor core distribution between palpable and nonpalpable prostate tumors in patients diagnosed using extensive transperineal ultrasound-guided template prostate biopsy. *Cancer* 2005; **103**: 1826-1832 [PMID: 15756653 DOI: 10.1002/cncr.21020]
 - 45 **Emiliozzi P**, Scarpone P, DePaula F, Pizzo M, Federico G, Pansadoro A, Martini M, Pansadoro V. The incidence of prostate cancer in men with prostate specific antigen greater than 4.0 ng/ml: a randomized study of 6 versus 12 core transperineal prostate biopsy. *J Urol* 2004; **171**: 197-199 [PMID: 14665875 DOI: 10.1097/01.ju.0000099824.73886.f3]
 - 46 **Yamamoto S**, Kin U, Nakamura K, Hamano M, Nishikawa Y, Takenouchi T, Maruoka M. Transperineal ultrasound-guided 12-core systematic biopsy of the prostate for patients with a prostate-specific antigen level of 2.5-20 ng/ml in Japan. *Int J Clin Oncol* 2005; **10**: 117-121 [PMID: 15864697 DOI: 10.1007/s10147-004-0464-7]
 - 47 **Eichler K**, Hempel S, Wilby J, Myers L, Bachmann LM, Kleijnen J. Diagnostic value of systematic biopsy methods in the investigation of prostate cancer: a systematic review. *J Urol* 2006; **175**: 1605-1612 [PMID: 16600713 DOI: 10.1016/S0022-5347(05)00957-2]
 - 48 **Bigliocchi M**, Marini M, Nofroni I, Perugia G, Shahabadi H, Ciccariello M. Prostate cancer detection rate of transrectal ultrasonography, digital rectal examination, and prostate-specific antigen: results of a five-year study of 6- versus 12-core transperineal prostate biopsy. *Minerva Urol Nefrol* 2007; **59**: 395-402; 403-406 [PMID: 17947956]
 - 49 **Emiliozzi P**, Maymone S, Paterno A, Scarpone P, Amini M, Proietti G, Cordahi M, Pansadoro V. Increased accuracy of biopsy Gleason score obtained by extended needle biopsy. *J Urol* 2004; **172**: 2224-2226 [PMID: 15538236 DOI: 10.1097/01.ju.0000144456.67352.63]
 - 50 **Huo AS**, Hossack T, Symons JL, PeBenito R, Delprado WJ, Brenner P, Stricker PD. Accuracy of primary systematic template guided transperineal biopsy of the prostate for locating prostate cancer: a comparison with radical prostatectomy specimens. *J Urol* 2012; **187**: 2044-2049 [PMID: 22498226 DOI: 10.1016/j.juro.2012.01.066]
 - 51 **Pepe P**, Aragona F. Prostate needle biopsy: 12 vs. 18 cores -- is it necessary? *Urol Int* 2005; **74**: 19-22 [PMID: 15711103 DOI: 10.1159/000082703]
 - 52 **Takeshita H**, Numao N, Kijima T, Yokoyama M, Ishioka J, Matsuoka Y, Koga F, Saito K, Masuda H, Kawakami S, Yamamoto S, Yonese J, Fujii Y, Kihara K. Diagnostic performance of initial transperineal 14-core prostate biopsy to detect significant cancer. *Int Urol Nephrol* 2013; **45**: 645-652 [PMID: 23529272 DOI: 10.1007/s11255-013-0416-0]
 - 53 **Puech P**, Potiron E, Lemaitre L, Leroy X, Haber GP, Crouzet S, Kamoi K, Villers A. Dynamic contrast-enhanced-magnetic resonance imaging evaluation of intraprostatic prostate cancer: correlation with radical prostatectomy specimens. *Urology* 2009; **74**: 1094-1099 [PMID: 19773038 DOI: 10.1016/j.urology.2009.04.102]
 - 54 **Park BK**, Park JW, Park SY, Kim CK, Lee HM, Jeon SS, Seo SI, Jeong BC, Choi HY. Prospective evaluation of 3-T MRI performed before initial transrectal ultrasound-guided prostate biopsy in patients with high prostate-specific antigen and no previous biopsy. *AJR Am J Roentgenol* 2011; **197**: W876-W881 [PMID: 22021535 DOI: 10.2214/AJR.11.6829]
 - 55 **Engelhausen DG**, Engelhard K, Schwab SA, Uder M, Wach S, Wullich B, Krause FS. Magnetic resonance image-guided biopsies with a high detection rate of prostate cancer. *ScientificWorldJournal* 2012; **2012**: 975971 [PMID: 22489209 DOI: 10.1100/2012/975971]
 - 56 **Hambrock T**, Somford DM, Hoeks C, Bouwense SA, Huisman H, Yakar D, van Oort IM, Witjes JA, Fütterer JJ, Barentsz JO. Magnetic resonance imaging guided prostate biopsy in men with repeat negative biopsies and increased prostate specific antigen. *J Urol* 2010; **183**: 520-527 [PMID: 20006859 DOI: 10.1016/j.juro.2009.10.022]
 - 57 **Kasivisvanathan V**, Dufour R, Moore CM, Ahmed HU, Abd-Alazeez M, Charman SC, Freeman A, Allen C, Kirkham A, van der Meulen J, Emberton M. Transperineal magnetic resonance image targeted prostate biopsy versus transperineal template prostate biopsy in the detection of clinically significant prostate cancer. *J Urol* 2013; **189**: 860-866 [PMID: 23063807 DOI: 10.1016/j.juro.2012.10.009]
 - 58 **Chang DT**, Challacombe B, Lawrentschuk N. Transperineal biopsy of the prostate--is this the future? *Nat Rev Urol* 2013; **10**: 690-702 [PMID: 24061531 DOI: 10.1038/nrurol.2013.195]
 - 59 **Walz J**, Graefen M, Chun FK, Erbersdobler A, Haese A, Steuber T, Schlomm T, Huland H, Karakiewicz PI. High incidence of prostate cancer detected by saturation biopsy after previous negative biopsy series. *Eur Urol* 2006; **50**: 498-505 [PMID: 16631303 DOI: 10.1016/j.eururo.2006.03.026]
 - 60 **Rabets JC**, Jones JS, Patel A, Zippe CD. Prostate cancer detection with office based saturation biopsy in a repeat biopsy population. *J Urol* 2004; **172**: 94-97 [PMID: 15201745 DOI: 10.1097/01.ju.0000132134.10470.75]
 - 61 **Stewart CS**, Leibovich BC, Weaver AL, Lieber MM. Prostate cancer diagnosis using a saturation needle biopsy technique after previous negative sextant biopsies. *J Urol* 2001; **166**: 86-91; discussion 91-92 [PMID: 11435830 DOI: 10.1016/S0022-5347(05)66083-1]
 - 62 **Moran BJ**, Braccioforte MH. Stereotactic transperineal prostate biopsy. *Urology* 2009; **73**: 386-388 [PMID: 19027936 DOI: 10.1016/j.urology.2008.03.022]
 - 63 **Lane BR**, Zippe CD, Abouassaly R, Schoenfield L, Magi-Galluzzi C, Jones JS. Saturation technique does not decrease cancer detection during followup after initial prostate biopsy. *J Urol* 2008; **179**: 1746-1750; discussion 1750 [PMID: 18343412 DOI: 10.1016/j.juro.2008.01.049]
 - 64 **Davis M**, Sofer M, Kim SS, Soloway MS. The procedure of transrectal ultrasound guided biopsy of the prostate: a survey of patient preparation and biopsy technique. *J Urol* 2002; **167**: 566-570 [PMID: 11792920 DOI: 10.1097/00005392-200202000-00026]
 - 65 **Jeon SS**, Woo SH, Hyun JH, Choi HY, Chai SE. Bisacodyl rectal preparation can decrease infectious complications of transrectal ultrasound-guided prostate biopsy. *Urology* 2003; **62**: 461-466 [PMID: 12946747 DOI: 10.1016/S0090-4295(03)00470-9]
 - 66 **Prayer-Galetti T**, Ficarra V, Franceschini R, Liguori G, Martino P, Schiavina R. [When to carry out prostate biopsy]. *Arch Ital Urol Androl* 2005; **77**: 3-16 [PMID: 16402724]
 - 67 **Valerio M**, Ahmed HU, Emberton M, Lawrentschuk N, Lazzeri M, Montironi R, Nguyen PL, Trachtenberg J, Polascik TJ. The role of focal therapy in the management of localised prostate cancer: a systematic review. *Eur Urol* 2014; **66**: 732-751 [PMID: 23769825 DOI: 10.1016/j.eururo.2013.05.048]
 - 68 **de la Rosette J**, Ahmed H, Barentsz J, Johansen TB, Brausi M, Emberton M, Frauscher F, Greene D, Harisinghani M, Haustermans K, Heidenreich A, Kovacs G, Mason M, Montironi R, Mouraviev V, de Reijke T, Taneja S, Thuroff S, Tombal B, Trachtenberg J, Wijkstra H, Polascik T. Focal therapy in prostate cancer-report from a consensus panel. *J Endourol* 2010; **24**: 775-780 [PMID: 20477543 DOI: 10.1089/end.2009.0596]
 - 69 **Buskirk SJ**, Pinkstaff DM, Petrou SP, Wehle MJ, Broderick GA, Young PR, Weigand SD, O'Brien PC, Igel TC. Acute urinary retention after transperineal template-guided prostate biopsy. *Int J Radiat Oncol Biol Phys* 2004; **59**: 1360-1366 [PMID: 15275721 DOI: 10.1016/j.ijrobp.2004.01.045]
 - 70 **Merrick GS**, Taubenslag W, Andreini H, Brammer S, Butler WM, Adamovich E, Allen Z, Anderson R, Wallner KE. The morbidity of transperineal template-guided prostate mapping biopsy. *BJU Int* 2008; **101**: 1524-1529 [PMID: 18325064 DOI: 10.1111/j.1464-

- 410X.2008.07542.x]
- 71 **Li H**, Yan W, Zhou Y, Ji Z, Chen J. Transperineal ultrasound-guided saturation biopsies using 11-region template of prostate: report of 303 cases. *Urology* 2007; **70**: 1157-1161 [PMID: 18158038 DOI: 10.1016/j.urology.2007.07.072]
 - 72 **Miller J**, Perumalla C, Heap G. Complications of transrectal versus transperineal prostate biopsy. *ANZ J Surg* 2005; **75**: 48-50 [PMID: 15740517 DOI: 10.1111/j.1445-2197.2005.03284.x]
 - 73 **Grummet JP**, Weerakoon M, Huang S, Lawrentschuk N, Frydenberg M, Moon DA, O'Reilly M, Murphy D. Sepsis and 'superbugs': should we favour the transperineal over the transrectal approach for prostate biopsy? *BJU Int* 2014; **114**: 384-388 [PMID: 24612341 DOI: 10.1111/bju.12536]
 - 74 **Taira AV**, Merrick GS, Bennett A, Andreini H, Taubenslag W, Galbreath RW, Butler WM, Bittner N, Adamovich E. Transperineal template-guided mapping biopsy as a staging procedure to select patients best suited for active surveillance. *Am J Clin Oncol* 2013; **36**: 116-120 [PMID: 22307210 DOI: 10.1097/COC.0b013e31823fe639]
 - 75 **Pepe P**, Aragona F. Prostate biopsy: results and advantages of the transperineal approach--twenty-year experience of a single center. *World J Urol* 2014; **32**: 373-377 [PMID: 23743734 DOI: 10.1007/s00345-013-1108-1]
 - 76 **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**: 1142-1146 [PMID: 23726443 DOI: 10.1016/j.urology.2013.02.019]

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Adherence to immunosuppressor medication in renal transplanted patients

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timing, wrong dose and/or wrong pill, but may also refer to missing appointments, not booking appointments, not doing blood work, not returning calls and/or refusal to follow the treatment regimen. In renal transplantation, adherence to immunosuppressive medication is a fundamental requisite in order to preserve graft function, since non-adherence is one of the main causes for late acute rejection, incomplete recovery after rejection treatment, chronic graft dysfunction, graft loss, and death. Transplantation failure due to treatment non-adherence is economically, socially, ethically and morally unjustifiable. This is a very prevalent issue: in some studies, its incidence is as high as 70% of patients. The self-reported nonadherence levels found in certain studies, including those performed immediately after transplantation show the need for early and continued intervention after kidney transplantation in order to maximise adherence and consequently clinical outcomes. There is not a single method to assess non adherence, thus combining several measures increases diagnostic accuracy. Electronic monitoring with a microdevice that records each time a pill bottle is opened is considered the "gold standard" for measuring adherence, but self-report at a confidential interview was the best measure of adherence. Thus non-adherence risk can be effectively assessed using clinically available assessment tools. Medication Adherence Scale, Brief Medical Questionnaire, Immunosuppressant Therapy Adherence Scale, Immunosuppressant Therapy Barrier Scale, Long-Term Medication Behavior Self-Efficacy Scale and Simplified Medication Adherence Questionnaire are some of the self-reported questionnaires. There are multiple factors associated with non-adherence in immunosuppressant therapy: Younger patients (adolescent, especially), poor health coverage, poor social support, unmarried, no family, non-Caucasian, immigrant, lower income, lower socioeconomic class, greater parental distress and lower family cohesion; complex medical regimens, higher number of drugs, longer time after transplant, toxicity, side effects, poor tolerance to medication, higher number of physicians involved, poor provider-patient rapport; psychological

Abstract

Non-adherence is a priority public health concern. Non-adherence means not taking medications, missing medications, taking too much, not taking enough, wrong

(dependency, high levels of anxiety and hostility, poorer behavioral functioning and greater distress in children) and psychiatric (depression) illnesses, low self-efficacy with medicine intake, perception of immunosuppressive therapy as not been necessary to preserve kidney function, forgetfulness, rebelliousness, poor perception of health, poor satisfaction, low Health-related quality of life, addictions, lack of coping strategies and avoidance behavior; patient morbidity: comorbidity, receiving a transplant from a live donor, retransplantation, and non-insulin-dependent diabetes. The most frequent strategies to promote medication-taking must focus on modifiable risk factors. Reasons for non-adherence are complex and diverse and any successful intervention aimed at improving adherence must be multidimensional. Although effective intervention strategies are needed to improve immunosuppressant therapy adherence, few intervention studies have been conducted in the adult renal transplant population. In this study, we perform an exhaustive review of the different strategies reported in the literature. A number of key reasons for non-adherence are also provided.

Key words: Adherence; Transplantation outcomes; Renal transplantation; Immunosuppressive medication; Health-related quality of life

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Core tip: Non-adherence is a priority public health concern. In renal transplantation, adherence is crucial to preserve graft functioning. Non-adherence rates of up to 70% of patients, including immediately after transplantation demonstrate the need for early and continued interventions after transplantation to maximise clinical outcomes. To increase the diagnostic accuracy of non-adherence, several measures must be combined. Multiple risk-factors exist. The strategies to foster medication-taking must focus on modifiable risk-factors and be of multidimensional nature. The strategies reported in the literature, some keys to understand non-adherence, and a few intervention studies are reviewed in this paper.

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INTRODUCTION

Non-adherence is a priority public health concern. Following the World Health Organization, the definition of adherence would be: "the extent to which a person's behavior-taking medication, following a diet, and/or executing lifestyle changes-corresponds with agreed recommendations from a health care

Table 1 Health effects of non-adherence^[2]

Increased morbidity
Treatment failures
Exacerbation of disease
More frequent physician visits
Increased hospitalizations
Decreased HRQoL
Decreased survival
Death
Economic impact: lost wages, sick time

HRQoL: Health-related quality of life.

provider"^[1]. According to cochrane review^[2]: (1) adherence is intended to be a non-judgmental term, and a statement of fact rather than blame of the prescriber, patient, or treatment; (2) compliance infers conformity to medical or health recommendations; and (3) concordance is a consensual agreement about treatment taking established between patient and practitioner.

Non-adherence means not taking medications, missing medications, taking too much, not taking enough, wrong timing, wrong dose, and/or wrong pill, but also may refer to missing appointments, not booking appointments, not doing blood work, not returning calls, and/or refusal to follow the treatment regimen.

Non-adherence implies major consequences. In Table 1, there is a list of health effects of non-adherence.

Furthermore this is a very prevalent problem. A cochrane review^[2] shows benchmark of non-adherence rates were: epilepsy 30% to 50%, arthritis 50% to 71%, hypertension 40% (average), diabetes 40% to 50%, oral contraceptives 8% and asthma 20%.

A complete review to update the results of randomized controlled trials of interventions to help patients follow prescriptions for medications for medical problems was achieved in January 2007^[3]. The authors' conclusions were: "for short-term treatments several quite simple interventions increased adherence and improved patient outcomes, but the effects were inconsistent from study to study with less than half of studies showing benefits. Current methods of improving adherence for chronic health problems are mostly complex and not very effective, so that the full benefits of treatment cannot be realized".

In a previous review by these authors, interventions for Medication Adherence in cochrane review Oct 2005^[2] can be seen in Table 2.

IMPORTANCE OF ADHERENCE/ NON-ADHERENCE AND RENAL TRANSPLANTATION

In renal transplantation, adherence to immunosuppressor medication is an indispensable requirement in order to preserve graft function. The concept of adherence

Table 2 Interventions categories^[2]

More instruction of patients
Counseling about target disease, compliance with therapy, side-effects
Automated telephone, computer-assisted patient monitoring and counseling
Manual telephone
Family interventions
Increasing convenience of care
Simplified dosing
Different formulations
Self-monitoring strategies
Reminders
Dose-dispensing units/charts
Appointments and refill reminders
Reinforcement or rewards for improved adherence in reduced frequency of visits
Crisis intervention
Direct observation
Lay health mentoring
Comprehensive pharmaceutical care
Psychological therapy

refers mostly to the compliance with the instructions regarding prescribed timing and doses. Adherence can be also assessed in other domains as blood work, clinical attendance, diet, exercise, and other healthcare requirements.

Some solid organ recipients do not take their treatment as prescribed, and thus they fail to reach the desired outcomes. Furthermore, this is one of the main cause of late acute rejection, incomplete recovery after rejection treatment, chronic graft dysfunction, graft loss, and death. It should be stressed that it is also a potential modifiable risk factor for poor outcomes. The negative consequences of non-adherence are numerous, and may complicate the management of the disease, due to the need of additional time, a reduction in the benefits of the treatment, a loss of medication cost-effectiveness, the need of higher doses or stronger medicines, intoxication and other undesirable effects, as well as an increase in sanitary costs, which translates into a loss of money at the expense of budget allocation for other health services.

Transplantation is the best renal replacement therapy in terms of health-related quality of life (HRQoL). According to some studies, HRQoL can be similar to that of the general population^[4]. Many studies confirm that improvement in HRQoL^[5-9], even in elderly patients^[10] or up to five different scenarios of transplant evolution^[11].

There also exist three meta-analyses which are in agreement with the evidence of an improved HRQoL after receiving a renal transplant: the first was carried out by Dew *et al*^[5] with 66 articles and 6726 patients selected, another by Cameron *et al*^[12] included 49 articles selected and, lastly, one by Tonelli *et al*^[13], in which 110 studies are selected, comprised an astounding 1922300 patients. In fact, most of the studies reported a statistically significant improvement after transplantation with respect to the pre-transplant physical, mental (in over 70% of the studies equal to

or superior and the global HRQoL in almost 100% than that of the healthy population) and social dimensions of HRQoL. So there is a confirmation of the generalised clinical impressions of improvement, but the unpublished studies without findings of improvement in HRQoL after renal transplantation, and the variability of the case-mix variables in the different samples and groups of treatment, should counsel prudence.

Renal transplantation improves considerably the patient's autonomy, who does not depend on a machine, and reduces morbi-mortality, since the risk of death is lower in transplanted patients than in those on waiting lists^[14]. Nevertheless, it must be noted that not all the required transplantations can be performed due to the lack of organs, which leads to waiting lists for kidneys. Yet another aspect that has to be taken into consideration is the yearly per-patient cost of dialysis (around 50000 EUR per year and patient on average), as opposed to the cost of transplantation. Even though the cost of the first year is roughly similar to that of dialysis, it is reduced to 10000 EUR per year from the second year post-transplantation^[15].

All these reasons make the later failure of transplantation due to non-adherence to treatment economically, socially, ethically and morally unjustifiable.

PREVALENCE OF NON-ADHERENCE IN RENAL TRASPLANTEES

Despite the devastating consequences of non-adherence, including a decrease of HRQoL, an increase in sanitary costs, the need for dialysis, an increase in morbidity and mortality, *etc.*, a study to determine the percentage of non-adherent patients carried out in Italy^[16] with 7206 patients revealed that 267 non-adherent patients lost the graft. The study identified three main profiles or non-adherent transplanted patients: "accidental" non-adherents (47%), which are those who forget to take their medications from time to time; "invulnerable" non-adherents (28%), which believe they do not need to take immunosuppressors regularly, and "decisive" non-adherents (25%), who decide which treatment to take for themselves.

Rosenberger *et al*^[17] find a 54% rate of non-adherence and Chisholm *et al*^[18] refer non-adherence ranges between 5% and 68%. Other authors^[19] who used the "gold standard" measure (eletronic monitoring) in a cohort of 58 renal transplantees found that 12% of the patients forgot their medication at least 20% of the days, and 26% forgot to take their medication at least 10% of the days. Denhaerynck *et al*^[20] present a prevalence range of adherence between 2% and 67% and a weighted prevalence of 28% in a literature search of 38 articles measuring non-adherence. A cross sectional study^[21] in a Swedish population with 250 renal transplant recipients showed only 46% never failed to follow the medical treatment with respect to drug intakes, dosage or timing. Timing

was the most frequently reported deviation (48%). Sixteen percent of them had failed taking at least one dose of the prescribed immunosuppressants during the previous four weeks. Four individuals had reduced the prescribed doses. Only one reported taking a "drug holiday". Nine participants reported stronger concerns than the need for immunosuppressive medication. In a cross-sectional sample of 218 patients recruited in London, United Kingdom (1999-2002), adherence was measured. The results were: low intentional non-adherence (13.8%) although 62.4% admitted unintentional non-adherence and 25.4% presented sub-target immunosuppressant levels^[22]. As evidenced, non-adherence is common in kidney transplantation, especially in younger patients, but in older patients too. A project^[23] was undertaken to examine outcomes of medication adherence in 37 renal transplant recipients. The Medication Event Monitoring System was implemented for one year. Eighty-six percent of the participants were non-adherent with medications. Similar percentages of non-adherence are seen in children and adolescent patients. For instance, a cross-sectional study showed that expression of Quality of Life of the adolescents was satisfactory, but parents told serious problems as a 75% of them were non-adherent with their immunosuppressive drugs and had other problematic health behaviors (smoking, illicit drug use, dietary non-adherence, and suboptimal exercise levels)^[24].

The self-reported nonadherence levels found in studies, including immediately after transplantation prove the need for early and continued interventions after kidney transplantation in order to maximise adherence and consequently clinical outcomes^[25].

However, caution must be exercised since in a prospective, non-interventional cohort, French study with a total of 312 kidney transplant recipients from eight French transplantation centers, it was observed that physicians underestimated the prevalence of adverse events when compared to patient self-reporting^[26].

RELATIONSHIP BETWEEN NON-ADHERENCE AND CLINICAL OUTCOMES

Another issue medical literature reveals is the relationship between non-adherence and clinical outcomes and the costs of transplanted renal patients. Non-adherence to immunosuppressive medication is in fact one of the main causes of transplant failure, and it may potentially explain why kidney survival does not improve as expected despite the development of new immunosuppressors. Data clearly show how graft survival is significantly worse in non-adherent patients. A meta-analysis by Butler *et al.*^[27] of 325 studies published between 1980 and 2001 to measure the frequency and impact of non-adherence in renal failure revealed that non-adherence to immunosuppressants

is a major cause of renal transplant failure. In cross-sectional studies ($n = 15$), a median (interquartile range) of 22% (18%-26%) of recipients were non-adherent. Cohort studies ($n = 10$) indicated that non-adherence contributes substantially to graft loss; a median of 36% (14%-65%) of graft losses were associated with non-adherence. Meta-analysis of these studies showed that the odds of graft failure increased sevenfold (4%-12%) in non-adherent subjects compared with adherent subjects. This is in keeping with the data compiled by other authors^[28] who, in a study featuring 24.5% of non-adherent patients (7.7% "casual" non-adherents and 16.8% "severe" non-adherents), proved that the most severe non-adherent recipients experienced a higher number of acute rejection episodes and higher graft dysfunction. In a prospective study, Vlamincx *et al.*^[29] studied one hundred and forty-six adult renal transplant recipients during a 5-year period in order to know differences between the incidence of late acute rejections and changes in serum-creatinine between compliers and non-compliers (22.6%) with immunosuppressive therapy after 1 year of receiving transplantation. Twenty-one point two percent of non-compliers patients had an acute rejection vs 8% in the group of compliers. Conclusion was that non-compliance in renal transplant patients is associated with a 3.2 higher risk for late acute rejections and a higher increase in serum-creatinine. Another randomized trial^[30] involving 150 kidney transplant recipients with a median follow-up of 8 years post-transplantation found that patient non-compliance seemed responsible for 45% (13/29) of observed graft failures, with 11 of these occurring after 36 mo. Non-compliance as a cause of graft failure may become more prominent as immunosuppression trials achieve longer-term follow-up.

In conclusion, non-compliance with immunosuppressive medications in renal transplant recipients results in higher rate of acute rejection episodes, allograft dysfunction, graft loss and patient death.

As for costs, another study^[31] examining the relationships between compliance with allograft outcomes and costs in 15525 renal transplant recipients showed that adolescent recipients aged 19-24 years were more likely to be persistently non-compliant than patients aged 24-44 years. Poor and fair compliant recipients were associated with increased risks of allograft loss compared to the excellent compliant recipients. Persistent low compliance was associated with a \$12840 increase in individual 3-year medical costs. Similar findings appear in pediatric patients: Chisholm-Burns *et al.*^[32], using data reported by the United States Renal Data System (USRDS), which contains Medicare prescription claims, suggested that greater adherence was significantly associated with longer time to graft failure ($P = 0.009$). Cleemput *et al.*^[33] examined economic evaluation by means of a Markov model and found that the mean cost per QALY

(Quality-Adjusted Life-Year) gained in adherent patients relative to non-adherent patients was eur 35021 per QALY. A specialty pharmacy program (in addition to medication dispensing, it includes adherence and clinical management programs, patient education, and counseling services provided by transplant pharmacology experts) was implemented by Tschida *et al.*^[34] and it was associated with lower transplant-related medical costs (the mean transplant-related medical cost was 42% lower in the specialty pharmacy program group: \$5960 vs \$8486; $P=0.04$), as well as higher transplant medication adherence within the first year of evaluation.

HOW TO MEASURE ADHERENCE IN RENAL TRANSPLANTATION PATIENTS

When it comes to assessing adherence, Butler *et al.*^[27] point out in their meta-analysis that only 2 of the 325 studies published from 1980 to 2001 used the "gold standard" measure of electronic monitoring with a microdevice that records each time a pill bottle is opened. Currently, this is the most accurate measure for prospective studies, since transversal studies used to employ self-report questionnaires. Butler *et al.*^[35] also studied the sensitivity and specificity of these measures in comparison with electronic monitoring. Their conclusion was that self-report at a confidential interview was the best measure of adherence for the detection of both missed doses and erratic timing of medication. Thus non-adherence risk can be effectively assessed by means of clinically available assessment tools.

The clinical methods more frequently used are self-reported questionnaires and interviews, clinician rating, plasma levels of immunosuppressants and their variability, pill counts, refill records, clinical outcomes, and biological and chemical markers ("white coat adherence").

For instance, the variation of serum drug levels was employed as a potential objective tool to monitor medication nonadherence. Hsiao *et al.*^[36] studied variations of tacrolimus and mycophenolic acid trough levels in 46 pediatric patients who underwent renal transplantation between 2002 and 2003 from 1 to 12 mo post-transplant, and standard deviation (SD) and percent coefficient of variation (%CV) were calculated. The tacrolimus %CV seems to be a useful and better marker, compared with SD alone.

The best methods for using self-report and trough levels to predict non-adherence likely differ based on the medication for which adherence is being assessed^[37]. Medication Adherence Scale^[38], Brief Medical Questionnaire^[39], Immunosuppressant Therapy Adherence Scale^[40], Immunosuppressant Therapy Barrier Scale^[41], Long-Term Medication Behavior Self-Efficacy Scale^[42] and Simplified Medication Adherence Questionnaire^[43] are some of the self-reported questionnaires.

naires.

On the other hand, 73 older adult renal transplanted patients expressed their perceptions with the Medication Event Monitoring System [MEMS[®]] TrackCaps for 12 mo. They perceived that the MEMS had a neutral effect on their medication-taking routine (65%), believed it was practical (56%), and could not describe any instances in which using the MEMS was difficult (56%). No significant difference in medication adherence was found between those who perceived the MEMS' influence negatively/neutrally and those who perceived the MEMS' positively^[44]. However Israni *et al.*^[45] also utilized microelectronic cap monitors to determine the association of adherence with a single immunosuppressive medication and kidney allograft outcomes post-transplantation in a prospective cohort study (243 patients from eight transplant centers) and conclusion was non-adherence was not associated with kidney allograft outcomes. Other more sophisticated electronic monitoring systems are being used but there is not sufficient experience yet. For instance, the Ingestible Sensor System, a novel technology for directly assessing the ingestion of oral medications and treatment adherence that provides highly reliable measurements of intake^[46].

A general conclusion for achieving a diagnosis of non-adherence would be that combining measures increase diagnostic accuracy, and it's relevant for clinical and research purposes^[47].

DETERMINANTS AND FACTORS INVOLVED IN NON-ADHERENCE

Regarding the determinants which lead to medication non-compliance, there are many, including ignorance, forgetfulness (awareness of memory impairment significantly affected adherence to immunosuppressive drugs^[48] and following Schmid-Mohler *et al.*^[49] "forgetfulness is the most powerful barrier against adherence. Intention to adhere plays a minor role in non-adherence in renal transplant recipients"), lack of understanding of the instructions provided by the health practitioner, disbelief or doubts concerning the need or benefits, treatment costs, unpleasant side effects, rebelliousness, presence of psychiatric illness, depression, comorbidity, medication tolerance, number of drugs^[50] and the complexity of the treatment, poor patient-physician communication which explains the "center effect"^[51], the lack of social support and not having family^[51,52].

According to studies on factors which may condition adherence, it seems that being female (or having a male partner, or being unmarried^[53,54]), a poor perception of one's health and a poor satisfaction predict a low HRQoL and low adherence^[55]. There also appears to be a relationship with time from the date of transplantation, both in the case of recent transplantation^[18] and the longer its duration^[28,54], as well as in cases of retransplantation^[54].

One obvious factor is younger age, as confirmed

in several studies; furthermore, Dobbels *et al.*^[56] found 36 studies, with a prevalence of non-adherence of 31.8%. Adolescents had more risk than younger patients and they had a 44% of all graft losses and a 23% of late acute rejection episodes associated with non adherence. Dew *et al.*^[57] found 61 papers in a meta-analysis in pediatric solid organ transplantation. Non-adherence to clinic appointments and tests was at 12.9 cases per 100 patients per year, the immunosuppression non-adherence six cases and other (substance use restrictions, diet, exercise, *etc.*) 0.6 to 8 cases. Age, family functioning (parental distress and family cohesion), and the child's psychological status significantly correlated with poorer adherence. Similar findings were obtained by Gerson *et al.*^[58].

Other important factors are socioeconomics, such as lower income^[18,51,54], lower socioeconomic class^[28] and poor socioeconomic background^[51] as well as addiction^[28] and psychiatric illnesses^[28] such as depression^[27,54,59] and higher stress levels^[54]. Other, more debated factors include lower education levels, receiving a transplant from a live donor^[27], non- insulin-dependent^[54] and to what extent may be related with a lower adherence to the immunosuppressive treatment.

On the other hand, there are several reviews on the determinants and factors associated with non-adherence. While reviewing the literature, Jindal *et al.*^[60] found that out of all renal transplantees, the patients with a higher risk of non-adherence were younger, women, single and non-Caucasian, in addition to patients receiving a transplant from a live donor, those who had been transplanted for more time and those with a previous transplant. They also discovered that patients exhibiting emotional issues such as anxiety, hostility, depression, distress, lack of coping strategies and avoidance behavior also showed a higher risk of non-adherence after renal transplantation.

Loghman-Adham^[51] also point as factors some identified in certain studies on poor adherence, such as: frequent doses (regarding this, several works prove the beneficial effect on self-reported adherence and treatment satisfaction in renal transplant patients taking tacrolimus once daily vs twice daily^[61-64], including in the long-term^[65]), the patient's perception of the benefits of the treatment^[27], poor provider-patient rapport, lack of motivation, belonging to a lower social class, lack of familiar or social support and being younger.

PSYCHOLOGICAL FACTORS, UNDERSTANDING NON-ADHERENCE, REPRESENTATIONS OF THE DISEASE

How can non-adherence in renal transplantation patients be properly understood? Renal transplantation is a therapy which comprises a set of beliefs and issues. In order to provide meaning and answers to the disease, patients create their own models or "representations"

of the disease, which may incorporate doubts or false beliefs about the disease, the benefits of the treatment and the adherence to immunosuppressive medication. Different representations may have different effects on clinical outcomes, since they modulate the relationship between the patient and the disease. In recent years, the study of the role of beliefs about the disease and how they may impact health-related outcomes has become one of the most productive areas within Health Psychology. One of the most rewarding theoretical frameworks is the self-regulatory or "common sense" model proposed by Leventhal and his group^[66]. Leventhal formulated a model which emphasizes the role of the theories the patient develops around his or her own health status; they are called "common sense" theories, as opposed to the scientific theories which direct the performance of the practitioner, and whose value lies in their ability to determine the behavior of the individual^[67,68]. The model stems from the understanding of individuals as active "troubleshooters" who organize the processing of perceptive and conceptual information about threats against health, self-regulated by a feedback system^[69]. Thus, initially, people process external information, such as a message from a health professional, or internal, such as the detection of a symptom, and elaborate a cognitive representation of the issue, as well as the associated emotions. As a second step, plans of action or coping procedures (such as seeking support or taking medicines) are developed. Lastly, the third step entails assessing the consequences which may affect the previous stages and then modify accordingly any subsequent episodes against future health threats. The potential practical usefulness lies in the possibility of handling representations in order to modify the impact of these cognitive/emotional representations of the disease on the health-disease outcomes: physical condition, stress, psychological well-being, social functioning, *etc.*, and thus this may be a chance to identify the representation as a means to intervene and enable adaptation and recovery. There are very few studies which properly convey the cognitions of renal transplantation patients and their behavior related to medication and rejection. Data yielded by cognitive behavioral models stress the importance of representations on the disease regarding the persistence of a given disorder or upset. Terminal chronic renal failure is associated with a remarkable loss of personal control and the lifelong challenge of modifying behavior^[70]. Regarding compliance in chronic diseases, Phatak *et al.*^[71] state that the beliefs of patients about medication are associated to non-adherence. There are associations between certain beliefs, such as perceiving more uncomfortable side effects and that the patient is taking more medicines than needed. Beliefs about medication explain on their own the 22.4% of variance in chronic diseases. Along the same lines, other authors have recently published a study in which perceptions of the disease explain between 6% and 26% of variance in psychological distress averages, and

disease strategies explain between 12% and 25%. The more symptoms patients have, which they attribute to the disease, and the greater emotional load they provoke, the higher the psychological distress and the less they use adaptative strategies, such as focusing on problems and easing their emotions.

However, to think that one has a more personal control over the disease and the use of adaptative coping strategies, such as positive reinterpretation and growth, are associated with reduced distress levels. It appears that coping strategies act as mediators between the perceptions about the disease and the outcomes. These findings support the role disease perceptions and coping strategies play when explaining the levels of psychological distress in patients^[44].

It would also appear that labeling a disease as chronic is associated with a reduction in the belief of personal control and treatment efficacy, as well as an increase in the perception of the consequences of the disease on daily functioning. Besides, a lower coherence with respect to the disease is linked to an increase in psychological distress. Resorting to psychoeducation before implementing a therapy or treatment helps patients to better understand their disease and the treatment, and it is also effective in reducing psychological distress and may possibly improve future well-being^[72]. Table 3 shows a summary of non-adherence risk factors.

Relationship between disease representations, HRQoL, psychological factors and adherence

Only a few studies have assessed the psychological factors which may be having an impact on patients' adherence. Butler *et al.*^[19] tried to analyze the relationship between disease representations, HRQoL, depression and adherence. They found that factors more associated to noncompliance are a lesser belief in the need for medication and receiving a transplant from a living donor. Suffering from depression was also common, but it was not strongly linked to non-adherence. These authors share and confirm the worrisome situation of finding a higher rate of non-adherence in renal transplantees from living donors because of the emphasis nephrologists are currently putting on spreading the use of this technique. A relatively recent study^[73] informed that younger patients, those who perceived less autonomy when dealing with the treatment, resorted to more active coping strategies and those who perceived a higher degree of interference of the treatment with their normal lives exhibited a worse adherence to treatment. In addition, there is a relationship between disease representations and HRQoL in renal patients. Covic *et al.*^[74] found that the adaptation of a patient to a chronic disease is determined by their beliefs about the disease and about the treatment. Between 15% and 31% of the variance rate in Physical Component Summary and Mental Component Summary can be explained by three

dimensions of the disease representation: the perception of the evolution of the disease, personal control, and the emotional response to the disease. The HRQoL of these patients is the result of a complex interrelation of clinical and personal factors. We believe that the two key components of the self-regulation model (beliefs and strategies) do explain HRQoL outcomes of the patient and adherence to medication. Furthermore, the perceptual framework about disease perceptions may be useful to make explicit and understand the ideas patients have about the disease^[75].

After receiving a transplanted organ, patients live with the uncertainty and the fear their body will reject the organ and with the need of acquiring new strategies and resources to look after themselves, such as recognizing the signs and symptoms to avoid infections and rejection. This suggests that after transplantation and being discharged from hospital, the patient has to carry on with his or her life as if having a chronic disease. The success of most therapies always depends to a great extent on a patient's disposition; thus, managing the active implication of the patient is of utmost importance. Managing the disease is a process for which the specialists and the patients are all responsible. If patients forget to follow their prescribed treatment, refuse the medication or, conversely, self-medicate, this may limit or prevent the proper management of the disease, which in turn will always compromise the benefits of the treatment.

STRATEGIES FOR MINIMIZING NON-ADHERENCE IN RENAL TRANSPLANTATION

Intimately linked to the previous section on determinants and factors, the most frequent strategies to promote medication-taking need to focus on the modifiable risk factors. Reasons for non-adherence are complex and a successful intervention to improve adherence must be multidimensional. Although effective intervention strategies are needed to improve immunosuppressant therapy adherence, few intervention studies have been conducted in the adult renal transplanted population. Chisholm-Burns *et al.*^[76] implemented a randomized controlled trial of a patient-specific behavioral contracts intervention to improve immunosuppressant therapy adherence among adult with a renal transplantation. Researchers developed a toolbox that included simple, practical, accessible mechanisms and strategies to improve immunosuppressant therapy adherence. One hundred and fifty renal transplant patients were enrolled in the study: the 76 in the intervention group had higher adherence than 74 in control group. Furthermore, 76.1% of patients in the intervention group compared with 42.7% in the control group were not hospitalized during the 1-year study period, resulting in cost savings. Thus, evidence supports

Table 3 Factors associated with non-adherence to immunosuppressive therapy

Age of patients: Younger (specially adolescent) and older patients (> 55 yr)
Gender: Male (or female), not having a female partner
Socioeconomics and cultural: Poor health coverage, poor health access, costs of treatment, difficulty in transportation, poor social support, unmarried, no family, non caucasian, immigrant, lack of general education and specific education about renal transplantation, lower income, lower socioeconomic class, poor socioeconomic background, greater parental distress and lower family cohesion in family functioning
Medication: Complex medical regimens, higher number of drugs, longer post-transplant, toxicity and side effects, poor tolerance of medication, higher number of doctors, poor provider-patient rapport, patient implicitly seen as defaulter
Psychological: Psychological (dependency, high levels of anxiety and hostility; in children, poorer behavioral functioning and greater distress) and psychiatric illness (depression), low self-efficacy with med intake, perceptions of immunosuppressive therapy as not needed to keep the kidney, significant positive relationship between pre-tx non-adherence and post-tx non-adherence (past behaviour predicts future behaviour), evolution of disease is a matter of chance, forgetfulness, rebelliousness, poor perception of health, poor satisfaction, low health-related quality of life, addictions, lack of coping strategies and avoidance behavior
Patient morbidity: Comorbidity, receiving a transplant from a live donor, retransplant, non-insulin-dependent diabetes
Other: No research, opportunities for improving adherence through optimizing the health care system or training the health care work remain hidden

using behavioral contracts as an effective adherence intervention that may improve healthcare outcomes and lower costs. Through a randomized controlled trial design, Russell *et al*^[77] screened 30 adult renal transplant recipients for medication non-adherence using electronic monitoring. Fifteen non-adherent participants were randomized to receive either a 6-mo continuous self-improvement intervention or attention control management. The mean medication adherence score for the continuous self-improvement intervention group ($n = 8$) was statistically significantly higher than the attention control group's ($n = 5$) mean medication adherence score. Participants' perceptions of the intervention were highly favorable. De Bleser *et al*^[78] reviewed 12 intervention studies and found that only 5 used randomized control designs. No single intervention was superior, so authors concluded that a combination of interventions with a team approach may be the most useful long-term strategy. O'Grady *et al*^[79] propose multidisciplinary insights too. A good minireview is that by Prendergast *et al*^[80]. Gordon *et al*^[81] found the barriers were: forgetting to refill prescriptions (13%), changes in prescriptions or doses (13%), being busy (10%), forgetting to bring medicines with them (10%), and being away from home (10%). Thus the strategies to avoid non-adherence were: having a schedule of medication-taking (60%), using devices as pillboxes (42%), bringing medicines with them (34%), distributing pills according to routine (32%), and using other people to remind them (26%). There are findings which suggest that strategies using social support to avoid forgetfulness and other to improve affectionate and instrumental support related to daily routine may be useful tools^[52]. And more particularly the prevalence and consequences of cost-related immunosuppressive medication non adherence among kidney transplant recipients have now been documented (continuous insurance coverage for outpatient immunosuppressive medications remains a major issue)^[82]. As for the "how" these strategies may be implemented, new technologies are already being used. For instance, mobile phone based remote monitoring of medication

adherence improves long-term graft outcomes in kidney transplants. This is a relatively no expensive technology and it may offer a close patient monitoring in a non-intrusive manner. Some recent studies demonstrate that kidney transplant recipients have a positive overall attitude toward mobile phone and they were comfortable with the idea of being monitored using it and confident that their privacy can be protected^[83]. Other paper^[84] shows that a new smartphone application in order to support drug adherence, was used by 11688 chronically ill users with a wide range of diseases over a longer period of time. Thirteen percent (292) had a previous history of transplantation and the results were positive.

However, to sum up, there are no definitive methods in place to properly measure adherence, it is not well studied and there are no single sufficiently supported effective interventions.

REFERENCES

- 1 World Health Organization Report. Adherence to long-term therapies, evidence for action. Geneva: World Health Organization. Available from: URL: http://www.who.int/chronic_conditions/en/adherence_report.pdf
- 2 Haynes RB, Yao X, Degani A, Kripalani S, Garg A, McDonald HP. Interventions to enhance medication adherence. *Cochrane Database Syst Rev* 2005; (4): CD000011 [PMID: 16235271]
- 3 Haynes RB, Ackloo E, Sahota N, McDonald HP, Yao X. Interventions for enhancing medication adherence. *Cochrane Database Syst Rev* 2008; (2): CD000011 [PMID: 18425859 DOI: 10.1002/14651858]
- 4 Rebollo P, Ortega F, Baltar JM, Alvarez-Ude F, Alvarez Navascués R, Alvarez-Grande J. Is the loss of health-related quality of life during renal replacement therapy lower in elderly patients than in younger patients? *Nephrol Dial Transplant* 2001; 16: 1675-1680 [PMID: 11477173 DOI: 10.1093/ndt/16.8.1675]
- 5 Dew MA, Switzer GE, Goycoolea JM, Allen AS, DiMartini A, Kormos RL, Griffith BP. Does transplantation produce quality of life benefits? A quantitative analysis of the literature. *Transplantation* 1997; 64: 1261-1273 [PMID: 9371666 DOI: 10.1097/00007890-19971150-00006]
- 6 Jofré R, López-Gómez JM, Moreno F, Sanz-Guajardo D, Valderrábano F. Changes in quality of life after renal transplantation. *Am J Kidney Dis* 1998; 32: 93-100 [PMID: 9669429 DOI: 10.1053/

- ajkd.1998.v32.pm9669429]
- 7 **Rebollo P**, Ortega F, Baltar JM, Badia X, Alvarez-Ude F, Díaz-Corte C, Naves M, Navascués RA, Ureña A, Alvarez-Grande J. Health related quality of life (HRQOL) of kidney transplanted patients: variables that influence it. *Clin Transplant* 2000; **14**: 199-207 [PMID: 10831077 DOI: 10.1034/j.1399-0012.2000.140304.x]
- 8 **Rebollo P**, Ortega F, Baltar JM, Díaz-Corte C, Navascués RA, Naves M, Ureña A, Badia X, Alvarez-Ude F, Alvarez-Grande J. Health-related quality of life (HRQOL) in end stage renal disease (ESRD) patients over 65 years. *Geriatr Nephrol Urol* 1998; **8**: 85-94 [PMID: 9893216 DOI: 10.1023/A: 1008338802209]
- 9 **Hathaway DK**, Winsett RP, Johnson C, Tolley EA, Hartwig M, Milstead J, Wicks MN, Gaber AO. Post kidney transplant quality of life prediction models. *Clin Transplant* 1998; **12**: 168-174 [PMID: 9642506]
- 10 **Evans RW**, Manninen DL, Garrison LP, Hart LG, Blagg CR, Gutman RA, Hull AR, Lowrie EG. The quality of life of patients with end-stage renal disease. *N Engl J Med* 1985; **312**: 553-559 [PMID: 3918267]
- 11 **Laupacis A**, Keown P, Pus N, Krueger H, Ferguson B, Wong C, Muirhead N. A study of the quality of life and cost-utility of renal transplantation. *Kidney Int* 1996; **50**: 235-242 [PMID: 8807593 DOI: 10.1038/ki.1996.307]
- 12 **Cameron JI**, Whiteside C, Katz J, Devins GM. Differences in quality of life across renal replacement therapies: a meta-analytic comparison. *Am J Kidney Dis* 2000; **35**: 629-637 [PMID: 10739783 DOI: 10.1016/S0272-6386(00)70009-6]
- 13 **Tonelli M**, Wiebe N, Knoll G, Bello A, Browne S, Jadhav D, Klarenbach S, Gill J. Systematic review: kidney transplantation compared with dialysis in clinically relevant outcomes. *Am J Transplant* 2011; **11**: 2093-2109 [PMID: 21883901 DOI: 10.1111/j.1600-6143.2011.03686.x]
- 14 **Wolfe RA**, Ashby VB, Milford EL, Ojo AO, Ettenger RE, Agodoa LY, Held PJ, Port FK. Comparison of mortality in all patients on dialysis, patients on dialysis awaiting transplantation, and recipients of a first cadaveric transplant. *N Engl J Med* 1999; **341**: 1725-1730 [PMID: 10580071 DOI: 10.1056/NEJM199912023412303]
- 15 **Kaplan B**, Meier-Kriesche HU. Renal transplantation: a half century of success and the long road ahead. *J Am Soc Nephrol* 2004; **15**: 3270-3271 [PMID: 15579532 DOI: 10.1097/01.ASN.0000146569.59482.8C]
- 16 **Rapisarda F**, Tarantino A. [Non compliance predictive factors in renal transplantation]. *G Ital Nefrol* 2004; **21**: 51-56 [PMID: 15356848]
- 17 **Rosenberger J**, Geckova AM, van Dijk JP, Nagyova I, Roland R, van den Heuvel WJ, Groothoff JW. Prevalence and characteristics of noncompliant behaviour and its risk factors in kidney transplant recipients. *Transpl Int* 2005; **18**: 1072-1078 [PMID: 16101729 DOI: 10.1111/j.1432-2277.2005.00183.x]
- 18 **Chisholm MA**, Lance CE, Mulloy LL. Patient factors associated with adherence to immunosuppressant therapy in renal transplant recipients. *Am J Health Syst Pharm* 2005; **62**: 1775-1781 [PMID: 16120736 DOI: 10.2146/ajhp040541]
- 19 **Butler JA**, Roderick P, Mullee M, Mason JC, Peveler RC. Frequency and impact of nonadherence to immunosuppressants after renal transplantation: a systematic review. *Transplantation* 2004; **77**: 769-776 [PMID: 15021846 DOI: 10.1097/01.TP.0000110408.83054.88]
- 20 **Denhaerynck K**, Dobbels F, Cleemput I, Desmyttere A, Schäfer-Keller P, Schaub S, De Geest S. Prevalence, consequences, and determinants of nonadherence in adult renal transplant patients: a literature review. *Transpl Int* 2005; **18**: 1121-1133 [PMID: 16162098 DOI: 10.1111/j.1432-2277.2005.00176.x]
- 21 **Lennerling A**, Forsberg A. Self-reported non-adherence and beliefs about medication in a Swedish kidney transplant population. *Open Nurs J* 2012; **6**: 41-46 [PMID: 22509233 DOI: 10.2174/1874434601206010041]
- 22 **Griva K**, Davenport A, Harrison M, Newman SP. Non-adherence to immunosuppressive medications in kidney transplantation: intent vs. forgetfulness and clinical markers of medication intake. *Ann Behav Med* 2012; **44**: 85-93 [PMID: 22454221 DOI: 10.1007/s12160-012-9359-4]
- 23 **Russell CL**, Cetingok M, Hamburger KQ, Owens S, Thompson D, Hathaway D, Winsett RP, Conn VS, Madsen R, Sittler L, Wakefield MR. Medication adherence in older renal transplant recipients. *Clin Nurs Res* 2010; **19**: 95-112 [PMID: 20185804 DOI: 10.1177/1054773810362039]
- 24 **Dobbels F**, Decorte A, Roskams A, Van Damme-Lombaerts R. Health-related quality of life, treatment adherence, symptom experience and depression in adolescent renal transplant patients. *Pediatr Transplant* 2010; **14**: 216-223 [PMID: 19497017 DOI: 10.1111/j.1399-3046.2009.01197.x]
- 25 **Massey EK**, Tielen M, Laging M, Beck DK, Khemai R, van Gelder T, Weimar W. The role of goal cognitions, illness perceptions and treatment beliefs in self-reported adherence after kidney transplantation: a cohort study. *J Psychosom Res* 2013; **75**: 229-234 [PMID: 23972411 DOI: 10.1016/j.jpsychores]
- 26 **Couzi L**, Moulin B, Morin MP, Albano L, Godin M, Barrou B, Alamartine E, Morelon E, Girardot-Seguin S, Mendes L, Misdrabi D, Cassuto E, Merville P. Factors predictive of medication nonadherence after renal transplantation: a French observational study. *Transplantation* 2013; **95**: 326-332 [PMID: 23149477 DOI: 10.1097/TP.0b013e318271d7c1]
- 27 **Butler JA**, Peveler RC, Roderick P, Smith PW, Horne R, Mason JC. Modifiable risk factors for non-adherence to immunosuppressants in renal transplant recipients: a cross-sectional study. *Nephrol Dial Transplant* 2004; **19**: 3144-3149 [PMID: 15479748 DOI: 10.1093/ndt/gfh505]
- 28 **Ghods AJ**, Nasrollahzadeh D. Noncompliance with immunosuppressive medications after renal transplantation. *Exp Clin Transplant* 2003; **1**: 39-47 [PMID: 15859906]
- 29 **Vlaminck H**, Maes B, Evers G, Verbeke G, Lerut E, Van Damme B, Vanrenterghem Y. Prospective study on late consequences of subclinical non-compliance with immunosuppressive therapy in renal transplant patients. *Am J Transplant* 2004; **4**: 1509-1513 [PMID: 15307839 DOI: 10.1111/j.1600-6143.2004.00537.x]
- 30 **Guerra G**, Ciancio G, Gaynor JJ, Zarak A, Brown R, Hanson L, Sageshima J, Roth D, Chen L, Kupin W, Tueros L, Ruiz P, Livingstone AS, Burke GW. Randomized trial of immunosuppressive regimens in renal transplantation. *J Am Soc Nephrol* 2011; **22**: 1758-1768 [PMID: 21807891 DOI: 10.1681/ASN.2011010006]
- 31 **Pinsky BW**, Takemoto SK, Lentine KL, Burroughs TE, Schnitzler MA, Salvalaggio PR. Transplant outcomes and economic costs associated with patient noncompliance to immunosuppression. *Am J Transplant* 2009; **9**: 2597-2606 [PMID: 19843035 DOI: 10.1111/j.1600-6143.2009.02798.x]
- 32 **Chisholm-Burns MA**, Spivey CA, Rehfeld R, Zawadeh M, Roe DJ, Gruessner R. Immunosuppressant therapy adherence and graft failure among pediatric renal transplant recipients. *Am J Transplant* 2009; **9**: 2497-2504 [PMID: 19681814 DOI: 10.1111/j.1600-6143.2009.02793.x]
- 33 **Cleemput I**, Kesteloot K, Vanrenterghem Y, De Geest S. The economic implications of non-adherence after renal transplantation. *Pharmacoeconomics* 2004; **22**: 1217-1234 [PMID: 15606228 DOI: 10.2165/00019053-200422180-00006]
- 34 **Tschida S**, Aslam S, Khan TT, Sahli B, Shrank WH, Lal LS. Managing specialty medication services through a specialty pharmacy program: the case of oral renal transplant immunosuppressant medications. *J Manag Care Pharm* 2013; **19**: 26-41 [PMID: 23383705]
- 35 **Butler JA**, Peveler RC, Roderick P, Horne R, Mason JC. Measuring compliance with drug regimens after renal transplantation: comparison of self-report and clinician rating with electronic monitoring. *Transplantation* 2004; **77**: 786-789 [PMID: 15021850 DOI: 10.1097/01.TP.0000110412.20050.36]
- 36 **Hsiao M**, Fernandez HE, Gjertson D, Ettenger RB, Tsai EW. Monitoring nonadherence and acute rejection with variation in blood immunosuppressant levels in pediatric renal transplantation. *Transplantation* 2011; **92**: 918-922 [PMID: 21857278 DOI: 10.1097/TP.0b013e31822dc34f]
- 37 **Pai AL**, Rausch J, Tackett A, Marsolo K, Drotar D, Goebel J. System for integrated adherence monitoring: real-time non-

- adherence risk assessment in pediatric kidney transplantation. *Pediatr Transplant* 2012; **16**: 329-334 [PMID: 22353189 DOI: 10.1111/j.1399-3046.2012.01657.x]
- 38 **Wu JR**, Chung M, Lennie TA, Hall LA, Moser DK. Testing the psychometric properties of the Medication Adherence Scale in patients with heart failure. *Heart Lung* 2008; **37**: 334-343 [PMID: 18790334 DOI: 10.1016/j.hrtlng.2007.10.001]
- 39 **Svarstad BL**, Chewning BA, Sleath BL, Claesson C. The Brief Medication Questionnaire: a tool for screening patient adherence and barriers to adherence. *Patient Educ Couns* 1999; **37**: 113-124 [PMID: 14528539 DOI: 10.1016/S0738-3991(98)00107-4]
- 40 **Chisholm MA**, Lance CE, Williamson GM, Mulloy LL. Development and validation of the immunosuppressant therapy adherence instrument (ITAS). *Patient Educ Couns* 2005; **59**: 13-20 [PMID: 16198214]
- 41 **Chisholm MA**, Lance CE, Williamson GM, Mulloy LL. Development and validation of an immunosuppressant therapy adherence barrier instrument. *Nephrol Dial Transplant* 2005; **20**: 181-188 [PMID: 15572384 DOI: 10.1093/ndt/ghf576]
- 42 **De Geest S**, Abraham I, Gemoets H, Evers G. Development of the long-term medication behaviour self-efficacy scale: qualitative study for item development. *J Adv Nurs* 1994; **19**: 233-238 [PMID: 8188953 DOI: 10.1111/j.1365-2648.1994.tb01076.x]
- 43 **Ortega Suárez FJ**, Sánchez Plumed J, Pérez Valentín MA, Pereira Palomo P, Muñoz Cepeda MA, Lorenzo Aguiar D. Validation on the simplified medication adherence questionnaire (SMAQ) in renal transplant patients on tacrolimus. *Nefrologia* 2011; **31**: 690-696 [PMID: 22130285 DOI: 10.3265/Nefrologia.pre2011.Aug]
- 44 **Russell CL**, Owens S, Hamburger KQ, Thompson DA, Leach RR, Cetingok M, Hathaway D, Conn VS, Ashbaugh C, Peace L, Madsen R, Winsett RP, Wakefield MR. Medication adherence and older renal transplant patients' perceptions of electronic medication monitoring. *J Gerontol Nurs* 2009; **35**: 17-21 [PMID: 19772223 DOI: 10.3928/00989134-20090903-06]
- 45 **Israni AK**, Weng FL, Cen YY, Joffe M, Kamoun M, Feldman HI. Electronically measured adherence to immunosuppressive medications and kidney function after deceased donor kidney transplantation. *Clin Transplant* 2011; **25**: E124-E131 [PMID: 20977496 DOI: 10.1111/j.1399-0012.2010.01340.x]
- 46 **Eisenberger U**, Wüthrich RP, Bock A, Ambühl P, Steiger J, Intondi A, Kuranoff S, Maier T, Green D, DiCarlo L, Feutren G, De Geest S. Medication adherence assessment: high accuracy of the new Ingestible Sensor System in kidney transplants. *Transplantation* 2013; **96**: 245-250 [PMID: 23823651 DOI: 10.1097/TP.0b013e31829b7571]
- 47 **Schäfer-Keller P**, Steiger J, Bock A, Denhaerynck K, De Geest S. Diagnostic accuracy of measurement methods to assess non-adherence to immunosuppressive drugs in kidney transplant recipients. *Am J Transplant* 2008; **8**: 616-626 [PMID: 18294158 DOI: 10.1111/j.1600-6143.2007.02127.x]
- 48 **Cheng CY**, Lin BY, Chang KH, Shu KH, Wu MJ. Awareness of memory impairment increases the adherence to immunosuppressants in kidney transplant recipients. *Transplant Proc* 2012; **44**: 746-748 [PMID: 22483484 DOI: 10.1016/j.transproceed.2011.11.030]
- 49 **Schmid-Mohler G**, Thut MP, Wüthrich RP, Denhaerynck K, De Geest S. Non-adherence to immunosuppressive medication in renal transplant recipients within the scope of the Integrative Model of Behavioral Prediction: a cross-sectional study. *Clin Transplant* 2010; **24**: 213-222 [PMID: 19674014 DOI: 10.1111/j.1399-0012.2009.01056.x]
- 50 **Weng FL**, Israni AK, Joffe MM, Hoy T, Gaughan CA, Newman M, Abrams JD, Kamoun M, Rosas SE, Mange KC, Strom BL, Brayman KL, Feldman HI. Race and electronically measured adherence to immunosuppressive medications after deceased donor renal transplantation. *J Am Soc Nephrol* 2005; **16**: 1839-1848 [PMID: 15800121]
- 51 **Loghman-Adham M**. Medication noncompliance in patients with chronic disease: issues in dialysis and renal transplantation. *Am J Manag Care* 2003; **9**: 155-171 [PMID: 12597603]
- 52 **Chisholm-Burns MA**, Spivey CA, Wilks SE. Social support and immunosuppressant therapy adherence among adult renal transplant recipients. *Clin Transplant* 2010; **24**: 312-320 [PMID: 19694770 DOI: 10.1111/j.1399-0012.2009.01060.x]
- 53 **Scholz U**, Klaghofer R, Dux R, Roellin M, Boehler A, Muellhaupt B, Noll G, Wüthrich RP, Goetzmann L. Predicting intentions and adherence behavior in the context of organ transplantation: gender differences of provided social support. *J Psychosom Res* 2012; **72**: 214-219 [PMID: 22325701 DOI: 10.1016/j.jpsychores.2011.10.008]
- 54 **Frazier PA**, Davis-Ali SH, Dahl KE. Correlates of noncompliance among renal transplant recipients. *Clin Transplant* 1994; **8**: 550-557 [PMID: 7865918]
- 55 **Ortega F**, Otero A, Crespo JF, Delgado JF, Borro JM, Cuervo J. Satisfaction and adherence with immunosuppressant treatment in renal transplant patients living with a working graft. *J Nephrol* 2013; **26**: 297-305 [PMID: 22684646 DOI: 10.5301/jn.5000132]
- 56 **Dobbels F**, Ruppert T, De Geest S, Decorte A, Van Damme-Lombaerts R, Fine RN. Adherence to the immunosuppressive regimen in pediatric kidney transplant recipients: a systematic review. *Pediatr Transplant* 2010; **14**: 603-613 [PMID: 20214741 DOI: 10.1111/j.1399-3046.2010.01299.x]
- 57 **Dew MA**, Dabbs AD, Myaskovsky L, Shyu S, Shellmer DA, DiMartini AF, Steel J, Unruh M, Switzer GE, Shapiro R, Greenhouse JB. Meta-analysis of medical regimen adherence outcomes in pediatric solid organ transplantation. *Transplantation* 2009; **88**: 736-746 [PMID: 19741474 DOI: 10.1097/TP.0b013e3181b2a0e0]
- 58 **Gerson AC**, Furth SL, Neu AM, Fivush BA. Assessing associations between medication adherence and potentially modifiable psychosocial variables in pediatric kidney transplant recipients and their families. *Pediatr Transplant* 2004; **8**: 543-550 [PMID: 15598321 DOI: 10.1111/j.1399-3046.2004.00215.x]
- 59 **Cukor D**, Rosenthal DS, Jindal RM, Brown CD, Kimmel PL. Depression is an important contributor to low medication adherence in hemodialyzed patients and transplant recipients. *Kidney Int* 2009; **75**: 1223-1229 [PMID: 19242502 DOI: 10.1038/ki.2009.51]
- 60 **Jindal RM**, Joseph JT, Morris MC, Santella RN, Baines LS. Noncompliance after kidney transplantation: a systematic review. *Transplant Proc* 2003; **35**: 2868-2872 [PMID: 14697924 DOI: 10.1016/j.transproceed.2003.10.052]
- 61 **van Boekel GA**, Kerkhofs CH, Hilbrands LB. Treatment satisfaction in renal transplant patients taking tacrolimus once daily. *Clin Ther* 2013; **35**: 1821-1829.e1 [PMID: 24135441 DOI: 10.1016/j.clinthera.2013.09.014]
- 62 **Albano L**, Banas B, Klemptner JL, Glyda M, Viklicky O, Kamar N. OSAKA trial: a randomized, controlled trial comparing tacrolimus QD and BD in kidney transplantation. *Transplantation* 2013; **96**: 897-903 [PMID: 23982340 DOI: 10.1097/TP.0b013e3182a203bd]
- 63 **Kuypers DR**, Peeters PC, Sennesael JJ, Kianda MN, Vrijens B, Kristanto P, Dobbels F, Vanrenterghem Y, Kanaan N. Improved adherence to tacrolimus once-daily formulation in renal recipients: a randomized controlled trial using electronic monitoring. *Transplantation* 2013; **95**: 333-340 [PMID: 23263559 DOI: 10.1097/TP.0b013e3182725532]
- 64 **Dharancy S**, Giral M, Tetaz R, Fatras M, Dubel L, Pageaux GP. Adherence with immunosuppressive treatment after transplantation: results from the French trial PREDICT. *Clin Transplant* 2012; **26**: E293-E299 [PMID: 22686953 DOI: 10.1111/j.1399-0012.2012.01652.x]
- 65 **Obi Y**, Ichimaru N, Kato T, Kaimori JY, Okumi M, Yazawa K, Rakugi H, Nonomura N, Isaka Y, Takahara S. A single daily dose enhances the adherence to immunosuppressive treatment in kidney transplant recipients: a cross-sectional study. *Clin Exp Nephrol* 2013; **17**: 310-315 [PMID: 23089939 DOI: 10.1007/s10157-012-0713-4]
- 66 **Leventhal H**, Meyer DY, Nerenz DR. The common sense representation of illness danger. In: Rachman S, editor. *Contributions to Medical Psychology*. New York: Pergamon Press, 1980: 7-30
- 67 **Leventhal H**, Nerenz DR. The assessment of illness cognition. In: Karoly P, editor. *Measurement strategies in Health Psychology*. New York: Wiley, 1985: 517-554
- 68 **Leventhal H**, Leventhal EA, Cameron L. Representations, procedures and affect in illness self-regulation: a perceptual-

- cognitive model. In: Baum A, Revenson TA, Singer JE, editors. *Handbook of Health Psychology*. Mahwah NJ: Lawrence Erlbaum Associates, 2001: 19-47
- 69 **Leventhal H**, Nerenz DR, Steele DJ. Illness representations and coping with health threats. In: Baum A, Taylor SE, Singer JE, editors. *Handbook of Psychology and Health*. Hillsdale NJ: Lawrence Erlbaum Associates, 1984: 219-252
- 70 **Rapisarda F**, Tarantino A, De Vecchi A, Baggio G, Ghezzi F, Nicodemo D, Resega R, Li Vecchi M. Dialysis and kidney transplantation: similarities and differences in the psychological aspects of noncompliance. *Transplant Proc* 2006; **38**: 1006-1009 [PMID: 16757246 DOI: 10.1016/j.transproceed.2006.02.143]
- 71 **Phatak HM**, Thomas J. Relationships between beliefs about medications and nonadherence to prescribed chronic medications. *Ann Pharmacother* 2006; **40**: 1737-1742 [PMID: 16985088 DOI: 10.1345/aph.1H153]
- 72 **Hermele S**, Olivo EL, Namerow P, Oz MC. Illness representations and psychological distress in patients undergoing coronary artery bypass graft surgery. *Psychol Health Med* 2007; **12**: 580-591 [PMID: 17828678 DOI: 10.1080/13548500601162705]
- 73 **Gremigni P**, Bacchi F, Turrini C, Cappelli G, Albertazzi A, Bitti PE. Psychological factors associated with medication adherence following renal transplantation. *Clin Transplant* 2007; **21**: 710-715 [PMID: 17988263]
- 74 **Covic A**, Seica A, Gusbeth-Tatomir P, Gavrilovici O, Goldsmith DJ. Illness representations and quality of life scores in haemodialysis patients. *Nephrol Dial Transplant* 2004; **19**: 2078-2083 [PMID: 15213317 DOI: 10.1093/ndt/gfh254]
- 75 **Llewellyn C**, McGurk M, Weinman J. The relationship between the Patient Generated Index (PGI) and measures of HR-QoL following diagnosis with head and neck cancer: are illness and treatment perceptions determinants of judgment-based outcomes? *Br J Health Psychol* 2007; **12**: 421-437 [PMID: 17726768 DOI: 10.1348/135910706X118422]
- 76 **Chisholm-Burns MA**, Spivey CA, Sredzinski E, Butler SL. Intervention toolbox to promote immunosuppressant therapy adherence in adult renal transplant recipients. *J Am Pharm Assoc* (2003) 2012; **52**: 816-822 [PMID: 23229970 DOI: 10.1331/JAPhA.2012.11083]
- 77 **Russell C**, Conn V, Ashbaugh C, Madsen R, Wakefield M, Webb A, Coffey D, Peace L. Taking immunosuppressive medications effectively (TIMELink): a pilot randomized controlled trial in adult kidney transplant recipients. *Clin Transplant* 2011; **25**: 864-870 [PMID: 21077956 DOI: 10.1111/j.1399-0012.2010.01358.x]
- 78 **De Bleser L**, Matteson M, Dobbels F, Russell C, De Geest S. Interventions to improve medication-adherence after transplantation: a systematic review. *Transpl Int* 2009; **22**: 780-797 [PMID: 19386076 DOI: 10.1111/j.1432-2277.2009.00881.x]
- 79 **O'Grady JG**, Asderakis A, Bradley R, Burnapp L, McPake DM, Perrin M, Russell S, Watson AR, Watson CJ, Wray J, Wilson LC. Multidisciplinary insights into optimizing adherence after solid organ transplantation. *Transplantation* 2010; **89**: 627-632 [PMID: 20124952 DOI: 10.1097/TP.0b013e3181ca87b0]
- 80 **Prendergast MB**, Gaston RS. Optimizing medication adherence: an ongoing opportunity to improve outcomes after kidney transplantation. *Clin J Am Soc Nephrol* 2010; **5**: 1305-1311 [PMID: 20448067 DOI: 10.2215/CJN.07241009]
- 81 **Gordon EJ**, Gallant M, Sehgal AR, Conti D, Siminoff LA. Medication-taking among adult renal transplant recipients: barriers and strategies. *Transpl Int* 2009; **22**: 534-545 [PMID: 19175560 DOI: 10.1111/j.1432-2277.2008.00827.x]
- 82 **Evans RW**, Applegate WH, Briscoe DM, Cohen DJ, Rorick CC, Murphy BT, Madsen JC. Cost-related immunosuppressive medication nonadherence among kidney transplant recipients. *Clin J Am Soc Nephrol* 2010; **5**: 2323-2328 [PMID: 20847093 DOI: 10.2215/CJN.04220510]
- 83 **McGillicuddy JW**, Weiland AK, Frenzel RM, Mueller M, Brunner-Jackson BM, Taber DJ, Baliga PK, Treiber FA. Patient attitudes toward mobile phone-based health monitoring: questionnaire study among kidney transplant recipients. *J Med Internet Res* 2013; **15**: e6 [PMID: 23305649 DOI: 10.2196/jmir.2284]
- 84 **Becker S**, Kribben A, Meister S, Diamantidis CJ, Unger N, Mitchell A. User profiles of a smartphone application to support drug adherence--experiences from the iNephro project. *PLoS One* 2013; **8**: e78547 [PMID: 24194946 DOI: 10.1371/journal.pone.0078547]

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Genetics and male infertility

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Abstract

The goal of this review is to explain the requirement for understanding the genetic structure of infertility arising from male factor and to discuss the essentials of these genetic elements (2). The majority of the population is affected by this disorder caused by male factor infertility (1); but the etiologies are still unknown. After the primary genetic structure in infertile phenotypes is searched, an evaluation can be made. Thus the reasons causing infertility can be discovered and patients can benefit from effective therapies (1). Publications about male infertility within the recent 10 years in the Pubmed database were discussed (1). There are some approachments for describing the function of specific

genes, but no adequate study is present to be useful for diagnosing and treating male infertility (1). Male fertility and fertility in offspring of males are considerably affected by the exact transition of epigenetic information (1). When the genetic factors playing a role in male infertility were analysed, significant steps will be taken for treating patients and determining the reasons of idiopathic infertility (1). Developments in technology associated with the impact of genetics may enable to specify the etiology of male infertility by determining specific infertile phenotype marks (1).

Key words: Male infertility; Chromosomal abnormality; Y chromosome microdeletion; Genetics; Azoospermia factor

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Core tip: In the case of being unable to be pregnant after regular unprotected intercourse for one year (6), it is defined as infertility, affecting about 10%-15% of all the couples. Male factor is responsible for about half of cases (6). Genes playing a role in testicular differentiation and full spermatogenesis are found in human Y chromosome (6). The main goal of this study is to mention the various chromosomal abnormalities and deletions of Y chromosome, which cause infertility; for this reason (14) it is important to know the genetic mechanisms that are responsible from the infertility especially for the clinicians.

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GENETICS AND MALE INFERTILITY

Infertility is mentioned when a female is unable to be pregnant after 1 year of unprotected regular intercourse, and this problem is encountered in

10%-15% of couples^[1] (4). Male infertility is seen in about 30%-55% of cases of infertility^[2,3] (4). If there is no pregnancy before, it is called as primary infertility; it results in live birth or not, if there is at least one pregnancy before, it is named as secondary infertility^[1]. Infertility is encountered in 10%-15% of couples in the reproductive age as a significant health problem^[2,3] (16). Approximately one third of infertility cases arise from pathologies due to the male, one third due to female, and one third due to both partners. Therefore the male factor is responsible for at least 50% of infertile couples^[4]. Medical treatment for infertility is requested by only 1 in 13 men of reproductive age^[4] (4). According to data created using standard diagnostic protocols of the World Health Organization (WHO), the female factor has been found in 37% of infertile partners, the male factor in 8%, both factors together in 35% and the cause is unknown in 5%^[5].

Male infertility

Infertility (infertility with male factor) occurs in approximately 50% of infertile couples due to causes associated with male partner being unable to produce spermatozoa in adequate number to enable fertility^[6]. In 40% of infertile population, qualitative and quantitative sperm production abnormalities are detected. In 60%-70% of cases, the source of reduced testicular sperm function is unclear^[3]. The sources of male infertility can be classified as follows: (1) Idiopathic; (2) Mechanic urogenital obstruction (vas deferens, ductal system, etc.); (3) Physical trauma; (4) Infection; (5) Life style (obesity, psychological problems, age, exercise, drugs, smoking)^[7]; (6) Varicocele; (7) Endocrine disorders^[3,8]; (8) Malignity^[9]; (9) Cryptorchidism^[10-12]; and (10) Genetic causes.

Spermatogenesis changes may occur due to many reasons such as systemic diseases, cryptorchidism, endocrinological diseases, obstruction in the seminal tract, and infections. Human spermatogenesis disorders frequently (50%) occur idiopathically and because of genetic causes. Mutations in genes under hypothalamic/pituitary control of spermatogenesis are described and these mutations are responsible for some types of hypogonadotropic hypogonadism^[10-12].

Azoospermia is observed in 1% of all men, 10%-15% of infertile men^[4,13]. Idiopathic non-obstructive azoospermia or serious oligospermia is a private group in male infertility. Idiopathic non-obstructive azoospermic men (INOA) is one of the primary causes of unperceived infertility; these are eugonadal and have primary infertility, low testicular volume, and high FSH levels; all of these are suggestive of testicular lesion to be likely congenital^[14]. If azoospermia is due to severe intrinsic testicular defect, a prominent increase is seen at serum FSH level while serum FSH level is lower than normalcy in hypogonadotropic hypogonadism.

Genetic reasons in male infertility

Genetic disorders, such as chromosomal anomalies

and monogenic diseases, have been established to be responsible from 10%-15% of infertility conditions^[15]. A great number of genetic reasons causing male infertility are defined in humans^[16]. Genetic alterations in infertile men usually lead to reduced spermatogenesis, genital structural abnormalities, decreased testicular size, hypogonadism and sperm dysfunction^[17].

Genetic anomalies can be categorized in four main groups: (1) Y chromosome microdeletions; (2) Chromosomal abnormalities; (3) Gene mutations and polymorphisms; and (4) Epigenetic disorders^[18].

Y chromosome and fertility: Human Y chromosome includes the genes which are necessary for spermatogenesis and development of gonadal differentiation in favor of testis^[19-21]. Although human Y chromosome incorporates nucleotides over 60 billion, it is the chromosome with the lowest number of gene in proportion to other chromosomes. Y chromosome plays a role as genetic marker of male characteristic properties and demonstrates many interesting biologic features^[22]. While the proximal site of the short arm (Yp) and the long arm (Yq) of Y chromosome is euchromatic site, the distal site of Y chromosome is heterochromatin site and the length of this site is variable^[23]. Male specific site forming 85% of Y chromosome carries MSY (male specific site of Y), 3 euchromatic (x-transposed, x degenerated, ampliconic), and a heterochromatic mosaic chain. To date, 156 transcription units, 78 protein-coding genes, and 27 different proteins associated with Y chromosome have been defined^[22]. There are pseudoautosomal border site, PABY1 and PABY2 pseudoautosomal sites on Yp and Yq arms, respectively, and homologues on X chromosome. Sites other than these sites do not participate to meiotic recombination. Accordingly, this situation leaves 95% of Y chromosome as non-recombinant^[22,24].

Human Y chromosome, so as its majority consists of repetition elements, includes a limited number of functional genes; additionally some alphoid repetitions incorporate major human short interspersed nuclear element (SINE) and a few satellite sequence family. Alphoid sequences are conglomerated near the Y chromosome centromere and can be distinguished from other chromosomes. The majority of Alu repetitions of Y chromosome show quite less similarity with genomic Alu sequence. Alu sequence is the most found repetition element in human genome^[22]. As non-coding repetitive DNA is more, deletions are frequently seen in Y chromosome^[7]. Some different spermatogenic differences are caused by Y chromosome microdeletions. These include hypospermatogenesis, maturation arrest, Sertoli cell only syndrome (SCOS)^[23,25,26]. Infertility may also occur with autosomal genes controlling mutations or paracrine systems in protooncogenes in the infertility signal mechanism as well as Y-linked sequences^[22].

Y chromosome and testis determining factor:

Numerous genes have been examined during researching

factor or factors determining testis development. H-Y antigen (Histocompatibility Antigen) and ZFY (Zinc Finger Protein, Y-linked) gene are among these. Today, however, these factors are accepted not to have a role in determining testis. The gene which is required for differentiation of bipotential gonad in favor of testis is testis determining factor (TDF). This gene is not adequate, although it is necessary for differentiation. Proteins produced by 1.1 kb-length transcripts formed by single exon of SRY defined in Yp11.3 band and having no intron have a length of 204 amino acids and include homologue sequences related to HMG-BOX. HMG (high mobility group)-BOX is a DNA-binding motif that is composed of 79-amino acids which is strongly protected. It enables acceleration or deceleration of transcription in gene and suppression or activation of the target gene by helping DNA bending. SRY gene can suppress the only active copy of SRVX in normal 46 XY men and 47 XXY men with Klinefelter syndrome; thus freed autosomal locus can carry out testis formation. SRVX is active in 46 XX females and enables differentiation of bipotential gonad in favor of ovary by suppressing autosomal genes. If SRVX is in case of two active copies, SRY will be unable to adequately decrease functions of SRVX and testis formation will be prevented. This model explains that X, Y, and autosomal genes work together in gonadal differentiation^[5,19-21].

Y chromosome and azoospermia factor: Many genes on the autosomal and Y chromosome control germ cell development. Gene and gene families involving in spermatogenesis are available in the long arm of Y chromosome and have a crucial importance in germ cell development and differentiation^[27,28]. In infertile men, microdeletions in the long arm of Y chromosome (Yq) can be morbid cause^[3]. Y chromosome is separated into 7 deletion periods. Each of these spaces is also separated into subperiods. The hypothesis that one or one group gene on Y chromosome exists, having a place in human spermatogenesis, has been reported by Tiepolo *et al.*^[27] for the first time in 1976. Genes which are crucial in spermatogenesis are localized on 11.23 band in the long arm of Y chromosome. This band is at the 5th and 6th deletion interval. This site is known as azoospermic factor sites (AZF). While AZFa is on the proximal Yq11, AZFb and AZFc are on the distal Yq11. These sites do not conflict with each other. RNA-binding proteins are encoded by these AZF genes. They take part in gene expression, RNA metabolism, packaging, transport to cytoplasm, and splicing regulation^[27]. In 1992, Vollrath *et al.*^[29] arranged a deletion map with 43 intervals of Y chromosome; these sites also contain the sites extending along Y chromosome and called "sequence tagged sites" (STS)^[3,20,26,28-30]. In male infertility and spermatogenic disorder after Klinefelter syndrome, Y chromosome microdeletions are the second closest reason^[21,31,32]. Therefore, genetic screening of AZF deletions must

be absolutely performed in studies of male infertility. With discovery of human Y chromosome sequence, molecular mechanism of Y chromosome microdeletions has been understood to carry out as a result of homologue recombination between similar pieces in palindromic sequences. This also results in deletions or rearrangements of Y chromosome^[21,33]. Some patients with idiopathic male infertility may be caused by microdeletions on the long arm of Y chromosome (11). Y chromosome microdeletions usually are not found in karyotype and responsible for loss of genes forming AZF factor^[14,33]. Furthermore, microdeletions in these AZF sites are related with different testicular histology exchanging from Sertoli cell only syndrome to hypospermatogenesis as well as azoospermia^[3].

Each AZF site deletion causes different phenotypic effects^[8]. In the study performed by Sargent *et al.*^[34], AZFa site in 4 infertile men have been examined, and deletion has been detected in one only^[34]. Deletions in the AZFb site have been found to be related to azoospermia, oligospermia, and normospermia. Deletions of the AZFc site have been shown to be associated with azoospermia and serious oligospermia^[35]. In many cases, deletions in the AZF site have been demonstrated to lead to loss of spermatogenesis. AZFc is the site where the most deletion is found among three AZF sites; AZFb site follows that^[36].

Y chromosome microdeletion has been defined in 9% of azoospermic infertile men and 11.6% of severe oligospermic men. In other words, although Y chromosome microdeletions are the closest molecular hereditary reason in infertile men, there is no deletion in 85% of azoospermic men and 90% of oligospermic men because other Y chromosome-dependent factors, for example some re-arrangements such as changes in repetition sequences in gene families with multicopy, polymorphism or mutations in Y chromosome-specific genes, and duplication, contribute to infertile phenotype^[37]. That triggering AZF site deletions may be a Y chromosome haplotype. For this reason, some individuals may prone to more novo deletion. Advanced paternal age may also trigger loss of Y sequences^[38].

Y chromosome deletion mechanism: In clinical and molecular studies performed since 1994, the role of Y chromosome genes and Y chromosome microdeletions in male infertility have been examined^[37]. Analysis of microdeletions in patients tries to reveal the roles of gene or gene families in spermatogenesis regulation^[22]. Frequently seeing *de novo* Y deletions is attributed to impetuous decrement of genetic material. Y chromosome's structural difference may be associated with elements repeated alongside chromosome to be more and these repetitions to be seen in the site (homologue site between X and Y chromosomes) where recombination is done. Furthermore, specific Y chromosome sequences increasing AZF deletion sites are available, and consequently some individuals are

able to be predisposed for *de novo* deletions more than the others. High fatherly age is also considered to increase Y chromosome gene sequence loss^[39].

Y chromosome molecular screening indications:

Y chromosome microdeletion screening helps to understand the reason for azoospermia or oligospermia in patients and to determine prognosis. Which patients need for Y chromosome molecular screening can be determined as follows: according to world literature, deletions are clinically seen in those who are azoospermic or have a spermiogram counts of 1×10^6 /mL. Infrequently, deletion can be seen in infertile patients who have a sperm concentration of $1-5 \times 10^6$ /mL (3). Although microdeletion is more frequent in patients selected by testicular histology, for example, in patients with Sertoli cell only syndrome (SCOS), it is unable to give certain selection criteria about which patients are a nominee for molecular analysis^[23,40]. Deletion screening must be suggested for severe oligospermic or azoospermic patients being a candidate for intracytoplasmic sperm injection (ICSI) or TESE/ICSI because TESE should not be performed in patients who have (3) complete deletion in the AZFa site or in cases with complete deletion in the AZFb site or AZFb+c site. Additionally, deletions in the AZFc site can pass male offspring if an assisted reproductive method is used^[29,41]. Therefore, detection of deletion has a prognostic importance and is crucial in therapeutic approach^[32,42]. To date, it has been reported that only 17 male and 18 female ICSI babies were borned from fathers with Yq microdeletion; while these babies are phenotypically normal, one male baby only has been diagnosed with pulmonary atresia and left ventricular hypoplasia. Generally, molecular diagnosis indication for Y chromosome microdeletion is a crucial clinical decision varying from case to case, and it is quite important that clinicians approve this diagnosis for which patients^[31]. Diagnostic evaluations of deletions are carried out by polymerase chain reaction of selected sites on Y chromosome. MSY-specific sequence tagged sites (STS) primers imply nameless genes, in other words common genes, in chromosome or genes^[43]. That being important in diagnosis of Y chromosome microdeletion is which STS primers in Y chromosome will be used. The sites where STS primers used are found should not be polymorphic; they should be the sites where deletions are specifically known in men influenced by oligo/azoospermia with respect to microdeletion clinically certain^[31].

Deletions found in the Y chromosome site where deletion events are less frequently seen have been reported to result in severe infertility as in AZFa. Increasing the number of STS in sites where deletions are mostly found, for example as in AZFc, will inform about the dimensions of deletion. Based on these principles, well screening of the important sites of

Y chromosome can be achieved by 20-30 STS. In the study performed by Pryor *et al.*^[44] (1997), only one STS deletion found in oligozoospermic patients has been revealed to represent a polymorphism not leading to infertility of patient. However, it is suggested in this study that these STSs should not be excluded from STS panel while evaluating Y chromosome in an infertile patient as these deletions are also found in infertile patients^[44].

Other Y chromosome genes: Another gene that takes part in spermatogenesis is CDY, the chromodomain protein Y-linked gene. It is located on Yq. It is explicated in the testis. It can be involved in enabling the exchange of histones in spermatogenesis. It also helps the proteins which adjust transcription easier accession to the postmeiotic sperm DNA. This is occurred by the acetylation of histones^[34]. During evolution, functional separation from CDY gene's autosomal homologue and migration to the Y chromosome are considered (CDYL, located on chromosome 6) (1). Thus the gene becomes interesting to study^[45] (1). The TSPY gene is located on the short arm of the Y chromosome; it also has transcripts on the long arm of the chromosome^[46]. Protein of the gene expressed in the testis has been identified in spermatogonia^[47] (1). The TSPY gene signals spermatogonia in order to enter meiosis, thus it may regulate the timing of spermatogenesis^[48] (1). In a study about copy number diversity of the TSPY gene, it was reported that there were more copies in infertile patients^[49] (1). This stands for further investigation of TSPY to specify its position in infertility (1).

Chromosomes in fertility and chromosomal abnormalities

Condensed chromosomes involve in gamete formation, also in premeiotic divisions, meiosis, fertilization, and all consecutive mitotic divisions. So, chromosomal errors can also be a ground of investigation to identify the role of genetics in male factor infertility^[50]. Chromosomal abnormalities are accountable from nearly 5% of male infertility. The prevalence rises to 15% azoospermic cases^[51]. Chromosomal abnormalities found in infertile men are classified as numerical abnormalities (gonosomal aneuploidy) and structural abnormalities^[7,10]. While sex chromosomal abnormalities are more frequently encountered in azoospermic patients, autosomal abnormalities are mostly seen in oligospermic patients. The frequency of reciprocal translocation, Robertsonian translocation and inversion is increased in infertile men compared to newborn population^[52].

Numerical chromosome abnormalities: The most common reason of chromosomal abnormalities in infertile men is aneuploidy, or alterations in chromosome number^[50]. The rate of aneuploidy in men with nonobstructive azoospermia is exclusively high^[53] (1),

especially in their sexuality chromosomes. Despite different quantity of genetic material from normal sperms in aneuploid sperm, these sperms can prosperously fertilize the oocyte (1). Ultimately, their offspring gain an incorrect chromosome number^[54] (1). Classical trisomies (trisomy 21) and sex chromosome trisomies (XXY or XYY) are within numeral abnormalities that can be mosaic or non-mosaic. Another kind of numeric abnormalities is aneuploidy seen in sperm^[7,10]. The most seen numerical chromosome abnormalities are emphasized below.

Klinefelter syndrome: Klinefelter syndrome is the most prevalent chromosomal abnormality induced by aneuploidy. It is present in 5% of men with severe oligozoospermia and in 10% of azoospermia^[55]. The syndrome usually gives rise to the arrest of spermatogenesis at the primary spermatocyte stage, but rarely later stages of sperm growth are detected^[3]. Klinefelter syndrome has two types (1): nonmosaic, 47, XXY; and mosaic, 47, XXY/46, XY. Although formerly believed to be infertile, it has been predicted that 25% of nonmosaic Klinefelter syndrome cases have sperm in their ejaculate^[2]. Patients with Klinefelter syndrome may become pregnant using ICSI, but there is a risk for producing offspring with chromosomal abnormalities^[10,11] (1). This syndrome is characterized by the presence of one or more X chromosome. Extra X chromosome can come paternally or maternally. In 67% of studies, both X chromosomes have been reported to come maternally. Maternal and paternal ages are high. Even if extra X chromosome originates either maternally or paternally, clinic of patients does not change^[5]. Extra X chromosome occurs with nondisjunction in the paternal meiosis I by a possibility over 50%, in the maternal meiosis I or II by a possibility of 40%; the rest ensues postzygotically^[8]. A male prototype with Klinefelter syndrome is usually characterized by a long height, narrow shoulder, wide hip, rare body hair, gynecomastia, small penis, androgen failure, azoospermia, and decreased verbal intelligence. A little part of them is diagnosed before puberty^[55]. Variably spermatogenic disorders are present in these patients, but men are generally sterile unless karyotype is not mosaic. Even in non-mosaic cases, germ cells which function and have 46 XY karyotype have been encountered; this is because patients are gonadal mosaic. Therefore, reproductive men with Klinefelter syndrome are predisposed to have an aneuploidic child^[8]. Men with Klinefelter syndrome are under more risk in terms of breast cancer and osteoporosis. Therefore, diagnosing the syndrome is not important only for reproductive health, but also for long term general health of patient^[56]. In treatment of patients with Klinefelter syndrome, androgen replacement must be done for cases where especially puberty is delayed or not seen and for patients whose testosterone levels are under normalcy according their ages^[5].

47, XYY syndrome: It is seen by 0.1%-0.4% in newborns. They have no other phenotypic characteristic except their typical long height. They have aggressive and antisocial characteristic by 1%-2%. Even if spermatogenic evaluation varies between normalcy and azoospermia, they are generally fertile. The results varying from various maturation arrest forms to complete germinal aplasia are obtained from testicular biopsies of those who are infertile. Though LH and testosterone levels are normal in a bulk of patients, FSH level is detected as normal or high similar with germ cell injury^[5]. Through Y chromosome non-disjunction in the paternal meiosis II, 47 XYY syndrome is considered to occur. This syndrome causes hormonal imbalance, affecting human chorionic gonadotropin function. Fertility may occur as a result of gonadal mosaicism. Marker chromosome carriers are under high infertility risk due to meiotic arrest and instability^[7].

Mixed gonadal dysgenesis: Phenotypically, mixed gonadal dysgenetic patients can be male, female, or ambiguous genitalia. Sex is identified according to the appearance of sexual organs at birth. There is normal karyotype in approximately 33% of these patients. This situation is suggestive of that there are disorders also apart from sex chromosome aneuploidy. There is normal Leydig cell population if a unilateral testis is in scrotum; however, no germ cells are present in seminiferous tubules. If testis is intraabdominal, there is a tendency to malignancies belonging to male and female^[16].

Structural chromosome abnormalities: Inversions (paracentric or pericentric), balanced translocations (Robertsonian/reciprocal, autosomal/gonosomal) and Y chromosome deletions are among structural abnormalities that cause male infertility^[7,10].

Robertsonian and reciprocal translocations: Chromosomal translocations are also a type of aneuploidy^[18]. Genetic material at the break points of genes can be lost because of translocations (1). Autosomal translocations are 4-10 times more frequent in infertile males when compared with normal males. In infertile males, the prevalence of Robertsonian translocations is only 0.8%, but in general population it is nearly 9 times lower than in the infertile males^[45].

Robertsonian translocations are generally seen in 1.6% and 0.09% of oligozoospermic and azoospermic men, respectively^[45]. Those who carry Robertsonian translocations can have a normal phenotype but they could be infertile due to an absence of gamete production (2) (1). Fluorescent *in situ* hybridization, with probes added for prevalent translocations, is proposed to detect the chromosomal composition of the sperm^[57]. As patients with translocation between Y chromosome and autosomal chromosomes transmit azoospermia into their male children,

they can also cause male gamete deformities or idiopathic sterility^[58]. Reciprocal translocations can cause diminished fertility, spontaneous abortions, and birth defects according to the site of translocation. Inter-chromosome translocations can cause meiotic mistake and cell death. Severe spermatogenic arrest and azoospermia can be seen in men with reciprocal X-autosomal translocation^[8]. Reciprocal Y-autosomal translocations cause abnormal spermatogenesis because of abnormal sex chromosome matching. The most common reciprocal translocation in infertile men is the translocation between 13q and 14q [t(13q14q)]. Meiotic studies were performed in infertile men carrying t(13q14q) and t(14q21q) and these studies showed that rearranged autosomes can lead to infertility during spermatogenesis in meiosis. Nucleolar organizer regions (NOR) are found on the short heterochromatic arms of acrocentric chromosomes. These regions are needed in RNA synthesis. Therefore, Robertsonian translocations which lost their NORs cause cell disturbance, germ cell death, and decrease in fertility^[7]. Translocations seen in infertile men are mostly reciprocal and such translocations are seen mostly in oligospermic men (1.7%) more frequent than azoospermic men (0.6%)^[59].

Autosomal inversions: The site of polymorphic chromosomal alternatives in infertile men should be specified. The relationship between a great number of normal variant and undermined spermatogenesis is not certain yet. The incidence of polymorphic chromosomal variants in infertile men spread over a quite wide area (3.46%-35.7%). The most frequently occurring heterochromatic version is the pericentric inversion of chromosome with number 9 by a frequency of 1%-1.65% in normal population and 1.17%-5% in infertile men [inv(9)(p11q13)]^[59]. These inversions are related to azoospermia and severe oligoasthenoteratospermia. Accordingly, translocations and inversions transmit into child at a higher rate than normalcy as hereditary in pregnancies *via* ICSI or IVF^[16]. Y chromosome heterochromatin region corresponds to the distal Yq12. This region is genetically inactive and its length varies in normal population^[60]. Raised length of the heterochromatin region of the long arm of Y chromosome has been declared by 7.14% and 1.4% in infertile men in normal population, respectively. Polymorphisms of Y chromosome are considered to be one of the reasons affecting spermatogenesis^[61,62].

46, XX male syndrome: It is encountered in 20000 live births. Generally, phenotypic appearance, sexual and psychosocial identities are in favor of male; however, semen analyses indicate azoospermia. Even if most cases are sporadic, autosomal recessive inheritance has been also reported. In 10% cases, phenotypically ambiguous genital and hypospadias can be encountered. In 33% of cases, gynecomastia and tubular hyalinization in testis biopsy, tubular

fibrosis and pseudoadenomatous conglomeration in Leydig cells are detected. While FSH is found high as secondary to spermatogenesis disorder, testosterone level is low or at the bottom level of normalcy. Despite XX genotype as a result of translocation of *SRY* gene between Xp and Yp tips during paternal meiosis, primitive gonad differentiates in favor of testis. Translocation of the distal Yp tip carrying *SRY* gene to any autosome can also cause a similar phenotype. Another alternative is, with a mutation in *SRVX* gene, removal of inhibition of this gene on another gene with autosomal localization. In conclusion, *AZF* gene is lack in patients and azoospermia is in question^[5].

Gene mutations and polymorphisms

As patients with obstructive azoospermia may carry cystic fibrosis mutation, in patients with severe oligospermia or non-obstructive azoospermia, microdeletion may be present in the long arm of Y chromosome^[63]. It is known that specific gene mutations affect testicular formation, internal and external genitalia development, and spermatogenesis negatively. Syndromes affecting genitourinary tract may also affect ductal function and/or ejaculation. A great number of genetic reasons causing male infertility are defined in humans^[45].

X-linked genes: There are numerous X-linked genes represented in the testis and it is considered that they take role in gametogenesis (1). The androgen receptor (*AR*) gene is localised on Xq (the long arm of the X chromosome)^[48,64]. In meiosis, its act is the conversion of spermatocytes, so it can round spermatids during spermatogenesis^[65]. In a current study, it has been detected that while mutations are present in *AR* gene of approximately 2% of infertile men, the controls had none^[45] (1). The *AR* gene mutations can also cause (1) androgen insensitivity syndrome. The *AR* gene has also two polymorphisms. These polymorphisms are important in the studies for their part in male factor infertility. The CAG and GGC polymorphisms are established on exon 1. They code for polyglutamine and polyglycine stretches, respectively^[51]. The CAG polymorphism has been investigated more extensively than the GGC polymorphism. It has been determined that longer lengths of the CAG polymorphisms are related with diminished transcriptional activity of the *AR* gene in infertile men, so this means that longer polyglutamine tracts are concerned with male factor infertility^[51]. In some studies, it has been observed that shorter CAG polymorphisms can be in relationship with higher quality sperm and altered levels of spermatogenesis^[66]. Both of these polymorphisms may be affected by ethnical impacts, because studies in Europe couldn't find a relationship between the CAG polymorphism and infertility, but studies in men from Asia, Singapore and Australia detected a relationship between infertility and these polymorphisms^[67,68].

USP26 is another gene that is found on the long arm of the X chromosome. It is expressed in the

early stages of spermatogenesis^[69]. It takes part in histone disposal during spermatogenesis and also the corruption and rebuilding of proteins^[45]. It has been found that there is an intercourse between the gene and infertility^[70].

The *TAF7L* gene has also been studied to find if it is a probable participant to infertility in men. The *TAF7L* gene is expressed in the testis and related with the autosomal *TAF7* gene which is a transcription factor^[45]. As transcription factor regulators control the spatial and temporal aspects, they are important in spermatogenesis^[71] (1). Kallmann syndrome (KS), another genetic disorder, is inherited as both X-linked and autosomal that can also lead to infertility in males. It is also called as idiopathic hypogonadotropic hypogonadism and is combined with anosmia or hyposmia. A defect in the migration of the GnRH neurons causes this disorder^[72] (1). It is characterized with low levels of sex steroids and low to normal levels of FSH and LH^[73].

Epigenetic errors

There are some epigenetic regulatory mechanisms that are necessary for normal embryogenesis. These are: (1) functional role of centrosome; (2) DNA methylation; (3) histone modifications; (4) chromatin remodeling; and (5) RNA transcripts and telomere length.

The best example of the sperm epigenetic contribution to the embryo is methylation. Because if paternal methylation is abnormal, the human embryos cannot develop. DNA methylation, also called as "imprinting", is important in the choice of which genes, from parental or maternal genomes will be expressed in the embryo^[50].

In epigenetics, there are some clinical methods such as direct methods (*i.e.*, single-cell gel electrophoresis) or indirect methods (*i.e.*, sperm chromatin integrity assays). All of these methods are used to detect the quality of sperm DNA. But, existing data haven't verified any correlation between DNA unity and pregnancy outcomes in ART and natural conception. So, no evidence is present for functional role of DNA integrity testing as a previsor of fertility^[74] (1).

Genotype/phenotype correlation: As there is no deletion in the majority of normospermic men, Y microdeletions have been reported to be specific for spermatogenic disorder^[37]. Although fertility is concordant with Y deletions, it reveals the fact that proper fertilization can carry out even in the less number of sperm, depending on fertility status of female partner. Therefore, considering Y deletions as the reason for oligo/azoospermia rather than infertility will be more appropriate. Deletion of the entire AZFa region results in complete SCOS and azoospermia. Deletion of isolated genes in the AZFa region such as *USP9Y* or *DBY* is associated with a variable testicular phenotype. Such deletions have

been defined sporadically only to date. AZFb and AZFb+c complete deletions (P5/proximal P1, P5/distal P1, P4/distal P1) are descriptive of spermatogenic arrest or SCOS resulted in azoospermia. In patients with AZFa region complete deletion, no any sperm has been encountered in the procedure of testicular sperm extraction (TESE). As in AZFa deletion complete deletion, the diagnosis of AZFb or AZFb+c complete deletions is incompatible with correction of the number of sperm, and ICSI should not be suggested for these patients^[31]. AZFc region deletions are in relationship with a variable clinic and histological phenotype^[31,41,75]. Generally, AZFc deletions are appropriate with residual spermatogenesis. AZFc deletions can be available in azoospermic or vigorous oligospermic men and rarely transmit into male offspring. The possibility to obtain sperm with TESE is high in men with azoospermia and AZFc deletion; so they can have a child with ICSI. Male children of these patients will be those with AZFc deletion^[31]. Phenotypes related to deletions are variable, and generally there is no connection between clinic phenotype and localization of deletion^[11].

Treatment in male infertility

Intracytoplasmic sperm injection: ICSI has been propounded by Palermo *et al.*^[76] for the first time in 1992 and achieved a new breakthrough in treatment of serious infertility with male factor. But the ICSI pregnancy rates obtained from IVF centers around the world is lower (30%-50%)^[76,77]. With definition of ICSI, although there is oligospermia or azoospermia, men with Y chromosome microdeletion have a possibility to have a child, using spermatozoa obtained surgically or from ejaculate. When diagnosed with Y chromosome microdeletion, couples should be informed about reproductive methods. The majority (79%) of infertile partners with Y chromosome microdeletion choose ICSI in terms of fertility problem. But, when ICSI is used, if child becomes a male, he will likely experience the same microdeletion and fertility problems^[11,26,38]. While the success rate in infertile couples treated with ICSI is 76%, this ratio is 15% in those who receive standard IVF therapy, for example intrauterine insemination^[78]. Due to the development of assisted reproductive techniques (ART), clinicians are in need of understanding how genetics is crucial in male factor infertility cases (1) because new technologies, such as ICSI, permit the men with suboptimal sperm quality to cope with natural selection mechanisms and produce a viable zygote^[51]. As ART, such as *in vitro* fertilization (IVF) and ICSI, includes relatively new procedures, the frequency of the inheritance of mutations *via* these procedures and their impact on future generations are not yet exactly comprehended^[57] (1) As a result, it is essential to identify the underlying genetic structure of male infertility to develop appropriate screens for abnormal phenotypes and to discover more effective

solutions for infertile couples' problems^[54] (1).

CONCLUSION

Numerous genes are responsible for male fertility, including spermatogenesis and sperm function. Because men who have undigested infertility can hold genetic abnormalities that may accommodate their reproductive potential, further researches are needed to determine such cases (2).

REFERENCES

- 1 **Barbieri RL.** Female infertility. In: Strauss FJ, Barbieri RL, editors. Reproductive endocrinology. 5th ed. Pennsylvania: Elsevier Inc., 2004: 633-668
- 2 **Tuarnaye H.** Gamete source and manipulation. In: Vayana E, Rowe PS, Griffin PD, editors. Current practices and controversies in assisted reproduction: report of a WHO meeting. Geneva: WHO, 2002: 83-101
- 3 **Mittal RD,** Singh G, Srivastava A, Pradhan M, Kesari A, Makker A, Mittal B. Y chromosome micro-deletions in idiopathic infertility from Northern India. *Ann Genet* 2004; **47**: 331-337 [PMID: 15581830 DOI: 10.1016/j.anngen.2004.05.003]
- 4 **O'Connell M,** McClure N, Lewis SE. Mitochondrial DNA deletions and nuclear DNA fragmentation in testicular and epididymal human sperm. *Hum Reprod* 2002; **17**: 1565-1570 [PMID: 12042279 DOI: 10.1093/humrep/17.6.1565]
- 5 **Özdiler E,** Aydos K. Klinik Androloji. Ankara: Ankara Üniversitesi Basımevi, 2000
- 6 **Bienvenu T,** Patrat C, Jouannet P. [Molecular detection of Y chromosome microdeletions: a new approach based on the denaturing gradient gel electrophoresis]. *Gynecol Obstet Fertil* 2003; **31**: 639-646 [PMID: 14563610 DOI: 10.1016/s1297-9589(03)00176-0]
- 7 **Griffin DK,** Finch KA. The genetic and cytogenetic basis of male infertility. *Hum Fertil (Camb)* 2005; **8**: 19-26 [PMID: 15823847 DOI: 10.1080/14647270400016407]
- 8 **Thangaraj K,** Gupta NJ, Pavani K, Reddy AG, Subramanian S, Rani DS, Ghosh B, Chakravarty B, Singh L. Y chromosome deletions in azoospermic men in India. *J Androl* 2003; **24**: 588-597 [PMID: 12826698 DOI: 10.1002/j.1939-4640.2003.tb02710.x]
- 9 **Richard SM,** Bianchi NO, Bianchi MS, Peltomäki P, Lothe RA, Pavicic W. Ethnic variation in the prevalence of AZF deletions in testicular cancer. *Mutat Res* 2004; **554**: 45-51 [PMID: 15450403]
- 10 **Siffroi JP,** Chantot-Bastaraud S, Ravel C. [Genetic origin of spermatogenesis impairments: clinical aspects and relationships with mouse models of infertility]. *Gynecol Obstet Fertil* 2003; **31**: 504-515 [PMID: 12865188 DOI: 10.1016/S1297-9589(03)00133-4]
- 11 **García Rodríguez J,** Martín Benito JL, Rodríguez Martínez JJ, Jalón Monzón A, Rodríguez Faba O, Fernández Gómez JM, Regadera Sejas J. [Infertility caused by AZF microdeletions. A new case of azoospermia]. *Actas Urol Esp* 2002; **26**: 801-803 [PMID: 12645377 DOI: 10.1016/s0210-4806(02)72859-3]
- 12 **Bar-Shira Maymon B,** Yogev L, Yavetz H, Lifschitz-Mercer B, Schreiber L, Kleiman SE, Botchan A, Hauser R, Paz G. Spermatogonial proliferation patterns in men with azoospermia of different etiologies. *Fertil Steril* 2003; **80**: 1175-1180 [PMID: 14607570 DOI: 10.1016/s0015-0282(03)02161-7]
- 13 **Hu Z,** Xia Y, Guo X, Dai J, Li H, Hu H, Jiang Y, Lu F, Wu Y, Yang X, Li H, Yao B, Lu C, Xiong C, Li Z, Gui Y, Liu J, Zhou Z, Shen H, Wang X, Sha J. A genome-wide association study in Chinese men identifies three risk loci for non-obstructive azoospermia. *Nat Genet* 2012; **44**: 183-186 [PMID: 22197933 DOI: 10.1038/ng.1040]
- 14 **Giannouli C,** Goulis DG, Lambropoulos A, Lissens W, Tarlatzis BC, Bontis JN, Papadimas J. Idiopathic non-obstructive azoospermia or severe oligozoospermia: a cross-sectional study in 61 Greek men. *Int J Androl* 2004; **27**: 101-107 [PMID: 15149468 DOI: 10.1046/j.1365-2605.2003.00456.x]
- 15 **Bailey JA,** Gu Z, Clark RA, Reinert K, Samonte RV, Schwartz S, Adams MD, Myers EW, Li PW, Eichler EE. Recent segmental duplications in the human genome. *Science* 2002; **297**: 1003-1007 [PMID: 12169732 DOI: 10.1126/science.1072047]
- 16 **Kadioğlu A,** Çayan S, Semerci B, Orhan İ, Aşçı R, Yaman MÖ, Usta MF, Kendirci M. Erkek Reprodüktif Sistem hastalıkları ve Tedavisi. İstanbul: Acar Matbaacılık, 2004
- 17 **Hargreave TB.** Genetic basis of male fertility. *Br Med Bull* 2000; **56**: 650-671 [PMID: 11255552]
- 18 **Esteves SC,** Agarwai A. The azoospermic male: current knowledge and future perspectives. *Clinics (Sao Paulo)* 2013; **68** Suppl 1: 1-4 [PMID: 23503949 DOI: 10.6061/clinics/2013(sup01)01]
- 19 **Lipshultz LI,** Howards SS. Infertility in the male. 3rd ed. USA: Mosby, 1997
- 20 **Girardi SK,** Mielnik A, Schlegel PN. Submicroscopic deletions in the Y chromosome of infertile men. *Hum Reprod* 1997; **12**: 1635-1641 [PMID: 9308784 DOI: 10.1093/humrep/12.8.1635]
- 21 **Hucklenbroich K,** Gromoll J, Heinrich M, Hohoff C, Nieschlag E, Simoni M. Partial deletions in the AZFc region of the Y chromosome occur in men with impaired as well as normal spermatogenesis. *Hum Reprod* 2005; **20**: 191-197 [PMID: 15498781 DOI: 10.1093/humrep/deh558]
- 22 **Ali S,** Hasnain SE. Genomics of the human Y-chromosome. 1. Association with male infertility. *Gene* 2003; **321**: 25-37 [PMID: 14636989 DOI: 10.1016/j.gene.2003.08.006]
- 23 **Foresta C,** Moro E, Ferlin A. Y chromosome microdeletions and alterations of spermatogenesis. *Endocr Rev* 2001; **22**: 226-239 [PMID: 11294825 DOI: 10.1210/edrv.22.2.0425]
- 24 **Ali S,** Hasnain SE. Molecular dissection of the human Y-chromosome. *Gene* 2002; **283**: 1-10 [PMID: 11867207 DOI: 10.1016/s0378-1119(01)00860-5]
- 25 **Gudeloglu A,** Parekattil SJ. Update in the evaluation of the azoospermic male. *Clinics (Sao Paulo)* 2013; **68** Suppl 1: 27-34 [PMID: 23503952 DOI: 10.6061/clinics/2013(sup01)04]
- 26 **van Golde RJ,** Wetzels AM, de Graaf R, Tuerlings JH, Braat DD, Kremer JA. Decreased fertilization rate and embryo quality after ICSI in oligozoospermic men with microdeletions in the azoospermia factor c region of the Y chromosome. *Hum Reprod* 2001; **16**: 289-292 [PMID: 11157822 DOI: 10.1093/humrep/16.2.289]
- 27 **Tiepolo L,** Zuffardi O. Localization of factors controlling spermatogenesis in the nonfluorescent portion of the human Y chromosome long arm. *Hum Genet* 1976; **34**: 119-124 [PMID: 1002136 DOI: 10.1007/bf00278879]
- 28 **Dada R,** Gupta NP, Kucheria K. Yq microdeletions--azoospermia factor candidate genes and spermatogenic arrest. *J Biomol Tech* 2004; **15**: 176-183 [PMID: 15331583]
- 29 **Vollrath D,** Foote S, Hilton A, Brown LG, Beer-Romero P, Bogan JS, Page DC. The human Y chromosome: a 43-interval map based on naturally occurring deletions. *Science* 1992; **258**: 52-59 [PMID: 1439769 DOI: 10.1126/science.1439769]
- 30 **El Awady MK,** El Shater SF, Ragaa E, Atef K, Shaheen IM, Megiud NA. Molecular study on Y chromosome microdeletions in Egyptian males with idiopathic infertility. *Asian J Androl* 2004; **6**: 53-57 [PMID: 15064835]
- 31 **Krausz C,** Hoefsloot L, Simoni M, Tüttelmann F. EAA/EMQN best practice guidelines for molecular diagnosis of Y-chromosomal microdeletions: state-of-the-art 2013. *Andrology* 2014; **2**: 5-19 [PMID: 24357628 DOI: 10.1111/j.2047-2927.2013.00173.x]
- 32 **Eloualid A,** Rhaissi H, Reugu A, Bounaceur S, El Houate B, Abidi O, Charif M, Louanjli N, Chadli E, Barakat A, Bashamboo A, McElreavey K, Rouba H. Association of spermatogenic failure with the b2/b3 partial AZFc deletion. *PLoS One* 2012; **7**: e34902 [PMID: 22514689 DOI: 10.1371/journal.pone.0034902]
- 33 **Vogt PH.** Genomic heterogeneity and instability of the AZF locus on the human Y chromosome. *Mol Cell Endocrinol* 2004; **224**: 1-9 [PMID: 15353175 DOI: 10.1016/j.mce.2004.06.008]
- 34 **Sargent CA,** Boucher CA, Kirsch S, Brown G, Weiss B, Trundley A, Burgoyne P, Saut N, Durand C, Levy N, Terriou P, Hargreave T, Cooke H, Mitchell M, Rappold GA, Affara NA. The critical region

- of overlap defining the AZFa male infertility interval of proximal Yq contains three transcribed sequences. *J Med Genet* 1999; **36**: 670-677 [PMID: 10507722]
- 35 **Affara NA**. The role of the Y chromosome in male infertility. *Expert Rev Mol Med* 2001; **2001**: 1-16 [PMID: 14987368 DOI: 10.1017/s1462399401002319]
 - 36 **Layman LC**. Human gene mutations causing infertility. *J Med Genet* 2002; **39**: 153-161 [PMID: 11897813 DOI: 10.1136/jmg.39.3.153]
 - 37 **Krausz C**, Forti G, McElreavey K. The Y chromosome and male fertility and infertility. *Int J Androl* 2003; **26**: 70-75 [PMID: 12641824 DOI: 10.1046/j.1365-2605.2003.00402.x]
 - 38 **Raicu F**, Popa L, Apostol P, Cimponeriu D, Dan L, Ilinca E, Dracea LL, Marinescu B, Gavrilă L. Screening for microdeletions in human Y chromosome--AZF candidate genes and male infertility. *J Cell Mol Med* 2003; **7**: 43-48 [PMID: 12767260 DOI: 10.1111/j.1582-4934.2003.tb00201.x]
 - 39 **Krausz C**, McElreavey K. Y chromosome and male infertility. *Front Biosci* 1999; **4**: E1-E8 [PMID: 9889182 DOI: 10.2741/krausz]
 - 40 **Kamp C**, Huellen K, Fernandes S, Sousa M, Schlegel PN, Mielnik A, Kleiman S, Yavetz H, Krause W, Küpker W, Johannisson R, Schulze W, Weidner W, Barros A, Vogt PH. High deletion frequency of the complete AZFa sequence in men with Sertoli-cell-only syndrome. *Mol Hum Reprod* 2001; **7**: 987-994 [PMID: 11574668 DOI: 10.1093/molehr/7.10.987]
 - 41 **Oates RD**, Silber S, Brown LG, Page DC. Clinical characterization of 42 oligospermic or azoospermic men with microdeletion of the AZFc region of the Y chromosome, and of 18 children conceived via ICSI. *Hum Reprod* 2002; **17**: 2813-2824 [PMID: 12407032 DOI: 10.1093/humrep/17.11.2813]
 - 42 **Hamada AJ**, Esteves SC, Agarwal A. A comprehensive review of genetics and genetic testing in azoospermia. *Clinics (Sao Paulo)* 2013; **68** Suppl 1: 39-60 [PMID: 23503954 DOI: 10.6061/clinics/2013(sup01)06]
 - 43 **Skaletsky H**, Kuroda-Kawaguchi T, Minx PJ, Cordum HS, Hillier L, Brown LG, Repping S, Pyntikova T, Ali J, Bieri T, Chinwalla A, Delehaunty A, Delehaunty K, Du H, Fewell G, Fulton L, Fulton R, Graves T, Hou SF, Latrielle P, Leonard S, Mardis E, Maupin R, McPherson J, Miner T, Nash W, Nguyen C, Ozersky P, Pepin K, Rock S, Rohlfling T, Scott K, Schultz B, Strong C, Tin-Wollam A, Yang SP, Waterston RH, Wilson RK, Rozen S, Page DC. The male-specific region of the human Y chromosome is a mosaic of discrete sequence classes. *Nature* 2003; **423**: 825-837 [PMID: 12815422 DOI: 10.1038/nature01722]
 - 44 **Pryor JL**, Kent-First M, Muallem A, Van Bergen AH, Nolten WE, Meisner L, Roberts KP. Microdeletions in the Y chromosome of infertile men. *N Engl J Med* 1997; **336**: 534-539 [PMID: 9023089 DOI: 10.1056/nejm199702203360802]
 - 45 **O'Flynn O'Brien KL**, Varghese AC, Agarwal A. The genetic causes of male factor infertility: a review. *Fertil Steril* 2010; **93**: 1-12 [PMID: 20103481 DOI: 10.1016/j.fertnstert.2009.10.045]
 - 46 **Lardone MC**, Parodi DA, Valdevenito R, Ebensperger M, Piottante A, Madariaga M, Smith R, Pommer R, Zambrano N, Castro A. Quantification of DDX3Y, RBMY1, DAZ and TSPY mRNAs in testes of patients with severe impairment of spermatogenesis. *Mol Hum Reprod* 2007; **13**: 705-712 [PMID: 17881721 DOI: 10.1093/molehr/gam057]
 - 47 **Schnieders F**, Dörk T, Arnemann J, Vogel T, Werner M, Schmidtke J. Testis-specific protein, Y-encoded (TSPY) expression in testicular tissues. *Hum Mol Genet* 1996; **5**: 1801-1807 [PMID: 8923009 DOI: 10.1093/hmg/5.11.1801]
 - 48 **Nuti F**, Krausz C. Gene polymorphisms/mutations relevant to abnormal spermatogenesis. *Reprod Biomed Online* 2008; **16**: 504-513 [PMID: 18413059 DOI: 10.1016/s1472-6483(10)60457-9]
 - 49 **Vodicka R**, Vrtel R, Dusek L, Singh AR, Krizova K, Svacinova V, Horinova V, Dostal J, Oborna I, Brezinova J, Sobek A, Santavy J. TSPY gene copy number as a potential new risk factor for male infertility. *Reprod Biomed Online* 2007; **14**: 579-587 [PMID: 17509197 DOI: 10.1016/s1472-6483(10)61049-8]
 - 50 **Emery BR**, Carrell DT. The effect of epigenetic sperm abnormalities on early embryogenesis. *Asian J Androl* 2006; **8**: 131-142 [PMID: 16491264 DOI: 10.1111/j.1745-7262.2006.00127.x]
 - 51 **Ferlin A**, Raicu F, Gatta V, Zuccarello D, Palka G, Foresta C. Male infertility: role of genetic background. *Reprod Biomed Online* 2007; **14**: 734-745 [PMID: 17579990 DOI: 10.1016/s1472-6483(10)60677-3]
 - 52 **Quilter CR**, Svennevik EC, Serhal P, Ralph D, Bahadur G, Stanhope R, Sütterlin M, Delhanty JD, Taylor KE. Cytogenetic and Y chromosome microdeletion screening of a random group of infertile males. *Fertil Steril* 2003; **79**: 301-307 [PMID: 12568838 DOI: 10.1016/s0015-0282(02)04692-7]
 - 53 **Palermo GD**, Colombero LT, Hariprasad JJ, Schlegel PN, Rosenwaks Z. Chromosome analysis of epididymal and testicular sperm in azoospermic patients undergoing ICSI. *Hum Reprod* 2002; **17**: 570-575 [PMID: 11870105 DOI: 10.1093/humrep/17.3.570]
 - 54 **Carrell DT**. Contributions of spermatozoa to embryogenesis: assays to evaluate their genetic and epigenetic fitness. *Reprod Biomed Online* 2008; **16**: 474-484 [PMID: 18413055 DOI: 10.1016/s1472-6483(10)60454-3]
 - 55 **Visoosak J**, Graham JM. Klinefelter syndrome and other sex chromosomal aneuploidies. *Orphanet J Rare Dis* 2006; **1**: 42 [PMID: 17062147 DOI: 10.1186/1750-1172-1-42]
 - 56 **Bojesen A**, Gravholt CH. Klinefelter syndrome in clinical practice. *Nat Clin Pract Urol* 2007; **4**: 192-204 [PMID: 17415352 DOI: 10.1038/ncpuro0775]
 - 57 **Georgiou I**, Syrrou M, Pardalidis N, Karakitsios K, Mantzavinos T, Giotitsas N, Loutradis D, Dimitriadis F, Saito M, Miyagawa I, Tzoumis P, Sylakos A, Kanakas N, Moustakareas T, Baltogiannis D, Touloupides S, Giannakis D, Fatouros M, Sofikitis N. Genetic and epigenetic risks of intracytoplasmic sperm injection method. *Asian J Androl* 2006; **8**: 643-673 [PMID: 17111067 DOI: 10.1111/j.1745-7262.2006.00231.x]
 - 58 **Conte RA**, Kleyman SM, Klein V, Bialer MG, Verma RS. Characterization of a de novo t(Y; 9)(q11.2; q22) by FISH technique. *Ann Genet* 1996; **39**: 10-15 [PMID: 9297438]
 - 59 **Lissitsina J**, Mikelsaar R, Punab M. Cytogenetic analyses in infertile men. *Arch Androl* 2006; **52**: 91-95 [PMID: 16443584 DOI: 10.1080/01485010500316030]
 - 60 **Akkari Y**, Lawce H, Kelson S, Smith C, Davis C, Boyd L, Magenis RE, Olson S. Y chromosome heterochromatin of differing lengths in two cell populations of the same individual. *Prenat Diagn* 2005; **25**: 304-306 [PMID: 15849801 DOI: 10.1002/pd.1119]
 - 61 **Penna Videau S**, Araujo H, Ballesta F, Balleca JL, Vanrell JA. Chromosomal abnormalities and polymorphisms in infertile men. *Arch Androl* 2001; **46**: 205-210 [PMID: 11339646 DOI: 10.1080/01485010151096504]
 - 62 **Wiland E**, Wojda A, Kamieniczna M, Szczygiel M, Kurpisz M. Infertility status of male individuals with abnormal spermogram evaluated by cytogenetic analysis and in vitro sperm penetration assay. *Med Sci Monit* 2002; **8**: CR394-CR400 [PMID: 12016421]
 - 63 **Levron J**, Aviram-Goldring A, Madgar I, Raviv G, Barkai G, Dor J. Sperm chromosome abnormalities in men with severe male factor infertility who are undergoing in vitro fertilization with intracytoplasmic sperm injection. *Fertil Steril* 2001; **76**: 479-484 [PMID: 11532468 DOI: 10.1016/s0015-0282(01)01957-4]
 - 64 **Wang PJ**, McCarrey JR, Yang F, Page DC. An abundance of X-linked genes expressed in spermatogonia. *Nat Genet* 2001; **27**: 422-426 [PMID: 11279525 DOI: 10.1038/86927]
 - 65 **De Gendt K**, Swinnen JV, Saunders PT, Schoonjans L, Dewerchin M, Devos A, Tan K, Atanassova N, Claessens F, Lécureuil C, Heyns W, Carmeliet P, Guillouf F, Sharpe RM, Verhoeven G. A Sertoli cell-selective knockout of the androgen receptor causes spermatogenic arrest in meiosis. *Proc Natl Acad Sci USA* 2004; **101**: 1327-1332 [PMID: 14745012 DOI: 10.1073/pnas.0308114100]
 - 66 **Lazaros L**, Xita N, Kaponis A, Zikopoulos K, Sofikitis N, Georgiou I. Evidence for association of sex hormone-binding globulin and androgen receptor genes with semen quality. *Andrologia* 2008; **40**: 186-191 [PMID: 18477206 DOI: 10.1111/j.1439-0272.2008.00835.x]
 - 67 **Rajpert-De Meyts E**, Leffers H, Petersen JH, Andersen AG, Carlsen E, Jørgensen N, Skakkebaek NE. CAG repeat length in androgen-receptor gene and reproductive variables in fertile and

- infertile men. *Lancet* 2002; **359**: 44-46 [PMID: 11809188 DOI: 10.1016/s0140-6736(02)07280-x]
- 68 **Yong EL**, Loy CJ, Sim KS. Androgen receptor gene and male infertility. *Hum Reprod Update* 2003; **9**: 1-7 [PMID: 12638777 DOI: 10.1093/humupd/dmg003]
- 69 **Stouffs K**, Lissens W, Tournaye H, Van Steirteghem A, Liebaers I. Possible role of USP26 in patients with severely impaired spermatogenesis. *Eur J Hum Genet* 2005; **13**: 336-340 [PMID: 15562280 DOI: 10.1038/sj.ejhg.5201335]
- 70 **Paduch DA**, Mielnik A, Schlegel PN. Novel mutations in testis-specific ubiquitin protease 26 gene may cause male infertility and hypogonadism. *Reprod Biomed Online* 2005; **10**: 747-754 [PMID: 15970005 DOI: 10.1016/s1472-6483(10)61119-4]
- 71 **Kimmins S**, Kotaja N, Davidson I, Sassone-Corsi P. Testis-specific transcription mechanisms promoting male germ-cell differentiation. *Reproduction* 2004; **128**: 5-12 [PMID: 15232059 DOI: 10.1530/rep.1.00170]
- 72 **Bhagavath B**, Layman LC. The genetics of hypogonadotropic hypogonadism. *Semin Reprod Med* 2007; **25**: 272-286 [PMID: 17594608 DOI: 10.1055/s-2007-980221]
- 73 **Burris AS**, Rodbard HW, Winters SJ, Sherins RJ. Gonadotropin therapy in men with isolated hypogonadotropic hypogonadism: the response to human chorionic gonadotropin is predicted by initial testicular size. *J Clin Endocrinol Metab* 1988; **66**: 1144-1151 [PMID: 3372679 DOI: 10.1210/jcem-66-6-1144]
- 74 **Practice Committee of American Society for Reproductive Medicine**. The clinical utility of sperm DNA integrity testing. *Fertil Steril* 2008; **90**: S178-S180 [PMID: 19007622 DOI: 10.1016/j.fertnstert.2008.08.054]
- 75 **Luetjens CM**, Gromoll J, Engelhardt M, Von Eckardstein S, Bergmann M, Nieschlag E, Simoni M. Manifestation of Y-chromosomal deletions in the human testis: a morphometrical and immunohistochemical evaluation. *Hum Reprod* 2002; **17**: 2258-2266 [PMID: 12202411 DOI: 10.1093/humrep/17.9.2258]
- 76 **Palermo G**, Joris H, Devroey P, Van Steirteghem AC. Pregnancies after intracytoplasmic injection of single spermatozoon into an oocyte. *Lancet* 1992; **340**: 17-18 [PMID: 1351601 DOI: 10.1016/0140-6736(92)92425-f]
- 77 **Ryu HM**, Lin WW, Lamb DJ, Chuang W, Lipshultz LI, Bischoff FZ. Increased chromosome X, Y, and 18 nondisjunction in sperm from infertile patients that were identified as normal by strict morphology: implication for intracytoplasmic sperm injection. *Fertil Steril* 2001; **76**: 879-883 [PMID: 11704105 DOI: 10.1016/s0015-0282(01)02827-8]
- 78 **Lewis-Jones I**, Aziz N, Seshadri S, Douglas A, Howard P. Sperm chromosomal abnormalities are linked to sperm morphologic deformities. *Fertil Steril* 2003; **79**: 212-215 [PMID: 12524092 DOI: 10.1016/s0015-0282(02)04411-4]

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Vasectomy reversal: A review of the evaluation, techniques, and outcomes

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Core tip: This review highlights the evaluation and treatment of men who have undergone vasectomy and desire vasectomy reversal to father children. For surgeons offering this treatment, appropriate evaluation and treatment are crucial for acceptable outcomes. Although variations on surgical approaches have evolved over the years, one constant is the need for a high level of training and skill in microsurgical techniques.

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INTRODUCTION

Approximately 500000 men in the United States undergo vasectomy every year. With a divorce rate of around 50%, up to 6% of men who have undergone vasectomy will elect to have the vasectomy reversed sometime in their lifetime^[1,2]. Vasectomy reversal (VR) was described in the 1930's and the use of the operative microscope for magnification to assist in the anastomosis was applied in the 1970's and significantly improved patency rates^[3-5].

ANATOMY

Understanding the anatomy of the vas deferens and the epididymis is paramount to successful outcomes with VR. The vas deferens, which is also known as the

Abstract

This review highlights the evaluation and treatment of men who have undergone vasectomy and desire vasectomy reversal to father children. For surgeons offering this treatment, the appropriate evaluation and treatment are crucial for acceptable outcomes. Although variations on surgical approaches have evolved over the years, one constant is the need for a high level of training and skill in microsurgical techniques.

ductus deferens, extends from the distal end of the cauda of the epididymis. Its embryological origin is the mesonephric (wolffian) duct. It is a tubular structure, and the segment leaving the epididymis for the first two to three centimeters is known as the convoluted vas deferens, which is tortuous. The vas deferens measures between 30 and 35 cm in length from the cauda epididymis to the ejaculatory duct, where it terminates. The vas deferens travels behind the vessels in the spermatic cord, posteriorly. Depending on the segment, the lumen of the vas deferens ranges between 0.2 and 0.7 mm in diameter^[6]. The deferential artery, a branch off of the superior vesical artery supplies the vas deferens^[7]. The scrotal vas deferens' venous drainage is *via* the deferential vein which drains into the pampiniform plexus. The venous drainage of the pelvic vas deferens is *via* the pelvic venous plexus. The vas deferens' lymphatic drainage travels to the external and internal iliac nodes.

Sperm travel through the epididymis from the testis to reach the vas deferens. If the tightly coiled tubule known as the epididymis is uncoiled it would stretch the length of 12 to 15 feet long. The three regions of the epididymis are characterized as the caput (head), the corpus (body), and the cauda (tail). The caput epididymis is comprised of 8-12 ductuli efferentes from the testis. The most distal portion of the cauda epididymis is continuous with vas deferens. The arterial supply of the caput and corpus epididymis is from a branch of the testicular artery, which further divides to supply the superior and inferior epididymal branches^[8]. Branches from the deferential artery provide vascular supply to the cauda epididymis. Venous drainage of the corpus and cauda epididymis are *via* the vena marginalis of Haberer, draining into the pampiniform plexus *via* the vena marginalis of the testis, or through cremasteric or deferential veins^[8]. Lymphatic drainage of the caput and corpus epididymis is through channels that travel with the internal spermatic vein, draining to the preaortic nodes. Lymphatic channels from the cauda epididymis join those leaving the vas deferens to drain into the external iliac nodes.

PREOPERATIVE EVALUATION/PHYSICAL EXAMINATION

Prior to undergoing VR, the level of spermatogenesis in the patient should be assessed. A history of fertility from prior to the vasectomy is typically considered sufficient. A full physical examination should be performed prior to VR with special attention to the genital examination. Testicular volumes and consistency should be assessed. Firm, normal volume testicles are indicators of good spermatogenesis whereas small or soft testes may indicate some spermatogenic deficiency. It is not uncommon for the epididymis to feel dilated in men who have undergone vasectomy. Epididymal induration may indicate the need for

vasoepididymostomy (VE). When a large vasectomy defect or gap can be palpated, this should prompt counseling for a more extensive dissection to perform a tension free anastomosis. When a sperm granuloma is palpated at the testicular end of the vas deferens, this indicates leaking of sperm as a result of a pop-off valve like mechanism to decrease intra-epididymal pressures. Sperm granuloma are associated with better outcomes with VRs suggesting that the epididymis has protected itself by decreasing intraluminal pressures^[9]. When physical examination reveals a very long vasectomy defect, a segment that has been removed, the surgeon should consider a non-standard incision approach^[10]. As more men are being diagnosed and treated with testosterone replacement for hypogonadism, impacting the level of spermatogenesis, medical management must be considered prior to performing VR in these men. Testosterone replacement should be discontinued, testicular salvage therapy with clomiphene citrate or human chorionic gonadotropin should be implemented for approximately three months, and then VR can be performed with good outcomes^[11].

The obstructive interval since the vasectomy has a significant impact on the type of VR required, vasovasostomy (VV) vs VE. This has been shown to affect patency rates in many studies and generally the longer the interval since vasectomy, the more challenging the candidate is considered to be for VR^[12,13]. However, in the hands of a surgeon who is proficient in both VV and VE, VR should still be offered to men with longer obstructive intervals. In technically skilled hands, success rates remain high regardless of the type of VR performed in men with obstructive intervals over 10 years^[14]. Multiple nomograms have been constructed to predict the type of VR required and patency rates. Factors evaluated to assess these outcomes include patient age, testicular volume, the presence of sperm granuloma, and obstructive interval^[15,16]. There is a question of the accuracy of the nomograms and their utility with inconsistent data^[17,18]. As it is not typically possible to predict preoperatively if VE will be required, VR should only be performed by surgeons skilled in both VV and VE^[19,20].

Before a man undergoes VR, his female partner should undergo a fertility evaluation with counseling on female age and ovarian reserve on fertility potential^[10].

PREOPERATIVE LABORATORY TESTING

Semen analysis with a centrifuged evaluation of the pellet may be performed prior to VR. Ten percent of these centrifuged pellets will reveal whole sperm suggesting good outcomes indicating that sperm will be found in the vas deferens at least unilaterally at the time of VR^[21]. When the semen analysis reveals low semen volume, transrectal ultrasound should be performed to rule out the possibility of a concomitant

ejaculatory duct obstruction.

When the physical examination indicates potential spermatogenic deficiency with findings such as small, soft testicles, a serum follicle stimulating hormone (FSH) should be obtained. An elevated FSH indicates spermatogenic failure, potentially poor outcome with VR, and requiring higher assisted reproduction use^[22]. Serum antisperm antibody (ASA) testing is not recommended as a routine preoperative test prior to VR. Approximately 60% of men develop circulating ASAs after bilateral vasectomy^[23]. Preoperative ASA testing is of unproven value, and the high postoperative conception rate after VR questions the impact of circulating ASAs on fecundability^[24-31].

ANESTHESIA

VR may be performed with local, regional, or general anesthesia^[10]. As meticulous microsurgical technique and tissue handling is mandated for superior outcomes, general anesthesia is the anesthesia of choice to minimize patient movement. Although VR can be performed with local anesthesia with sedation, this tends to result in more motion which makes a challenging operation more challenging. If a VE or a more difficult anastomosis is required, it may require lengthy operative times which can be difficult on the patient under local anesthesia or sedation.

INCISION APPROACHES

The scrotal incision provides the most direct access to the vasectomy defect to isolate the ends of the vas deferens for anastomosis. In scenarios with high vasectomy defects or long vasectomy defects, the incision may be extended toward the external inguinal ring. The testis may be delivered in cases with a very low vasectomy defect or when a VE is deemed necessary. Mini-incision VR using no-scalpel vasectomy principles has been evaluated with comparable patency rates with less postoperative pain and faster functional recovery^[32,33].

In men who have previously undergone varicocele repair or inguinal hernia repair, the surgical approach to VR will vary. If a man has undergone varicocele repair for orchialgia or for hypogonadism with a concomitant vasectomy, the VR should be approached through the prior subinguinal incision after confirming that the vasectomy was performed subinguinally by previous operative report. In men who have suspected vas deferens obstruction from previous inguinal herniorrhaphy, approaching the VR through the previous scar will lead to the site of the vas deferens obstruction.

PREPARING THE VAS DEFERENS

Once the vasectomy defect is isolated through the incision, the abdominal and testicular ends of the vasa may be isolated with the use of vessel loops. Care

should be taken to not strip the vas deferens of the perivasal adventitia to maintain the microvasculature to the vas deferens. The abdominal and testicular ends of the vas deferens should be adequately mobilized, with its adventitia, to allow for a tension free anastomosis. The obstructed segment of the vas deferens at the vasectomy defect site may be excised. Care should be taken to preserve the artery during this maneuver. After the testicular and abdominal ends of the vas deferens are isolated, the testicular end of the vas deferens is sharply divided at an exact 90 degrees. The divided end should have the muscularis and the mucosa inspected under microsurgical magnification to confirm that there is a healthy surface to anastomose without fibrosis or scar. Fluid from the testicular lumen of the vas deferens is then applied to a glass slide and is diluted with a drop of saline and is examined under the light microscope. The quality of the fluid from the testicular end of the vas deferens and the microscopic findings dictate whether a VV or a VE should be performed. If microscopic examination of the vasal fluid reveals whole sperm with tails or when there is copious, clear fluid from the vas deferens but no sperm are found in the fluid, VV should be performed. If fluid is not present, a 24 gauge angiocatheter sheath is cannulated into the lumen of the testicular end of the vas deferens and barbatage is performed with 0.1 mL of saline which is then microscopically examined. If there is no significant vasal fluid or sperm identified after this maneuver, a VE should be performed. When the vasal fluid appears thick and toothpaste like in quality, sperm are typically not found on microscopic examination of the fluid, and VE is indicated. Data has shown that greater than 90% of VRs will be successful when sperm fragments (sperm heads and/or short tails) are found in the vasal fluid intraoperatively regardless of the fluid quality. This success rate surpasses the expected success rate with VE^[34,35]. Sperm quality has been categorized in five grades to describe the findings in the vasal fluid. Grade 1 reveals mainly normal motile sperm, grade 2 mainly normal nonmotile sperm, grade 3 mainly sperm heads, grade 4 only sperm heads, and grade 5 no sperm^[36,37].

The abdominal end of the vas deferens is divided in a similar manner. The lumen is gently cannulated with a 24 gauge angiocatheter sheath and saline is injected into the lumen to demonstrate patency. The ends of the testicular and abdominal vas deferens are then approximated with the use of a Microspike approximating clamp, or with carefully placed 6-0 prolene adventitial sutures to approximate the ends with the help of an assistant. A penrose drain covered metal ruler or tongue blade is then placed beneath the approximated ends to provide a template for the anastomosis. In the circumstance when saline is injected into the lumen of the abdominal end of the vas deferens and it reveals that there is not patency, this suggests another obstruction. A 2-0 polypropylene suture is carefully passed through the lumen of the

abdominal vas deferens to encounter the site of distal obstruction. If this obstruction is isolated within 5 cm of the initial vasectomy site, the abdominal end of the vas deferens may be dissected to the obstruction site and excised to perform one anastomosis after further mobilization of both ends to allow for a tension free anastomosis. This may require extension of the incision. Performing multiple anastomoses on the vas deferens increases the risk for devascularization and failure.

ANASTOMOSIS PEARLS

A high level of microsurgical expertise is required for optimal VR outcomes. Prognostic advantages are gained by strict surgical principles during the anastomosis. The luminal mucosa of the abdominal and testicular ends of the vas deferens should be approximated meticulously. The anastomosis should be water-tight as sperm are antigenic and will stimulate an inflammatory response which can lead to fibrosis and obstruction of the anastomosis if they leak at the anastomosis^[38]. A tension free anastomosis is crucial for long term success. Mobilizing the abdominal and testicular ends of the vas deferens, and placing reinforcing, muscularis sutures to minimize tension on the anastomosis will improve long term patency rates. A minimal touch technique, with as little manipulation of the vasal ends for anastomosis is paramount to a successful outcome as is maintaining microvascular supply to the vas deferens by maintaining the vasal adventitia and not stripping the vas deferens.

MICROSURGICAL VASOVASOSTOMY

VV may be performed by a modified one-layer anastomosis, placing four to eight interrupted 9-0 nylon sutures through the full thickness of each end of the vas deferens lumens. Following the placement of these sutures, interrupted 9-0 nylon sutures are placed between these full thickness sutures in the muscular layer^[39]. Some surgeons prefer a two-layer anastomosis, which is performed by placing five to eight 10-0 nylon interrupted sutures to approximate the inner mucosal edges of the ends of the vas deferens. Following the placement of these mucosal sutures, seven to ten outer muscular layer interrupted sutures of 9-0 nylon are placed^[37]. Experienced microsurgeons compensate for the discrepancy in luminal diameters between the abdominal and testicular ends of the vas deferens during the anastomosis. Some place microdots with a microtip marking pen to preplan the suture placement prior to performing the anastomosis^[40]. This technique utilizes interrupted 10-0 monofilament nylon sutures for mucosal approximation and interrupted 9-0 monofilament nylon sutures deep in the muscularis in between the already placed mucosal sutures. When VV is performed in the convoluted vas deferens, very meticulous technique is mandated for a successful

outcome. Although this anastomosis is more technically demanding, patency rates are comparable to anastomosis in the straight portion of the vas deferens, when performed by skilled microsurgeons^[41,42]. A useful maneuver in difficult circumstances is the trans-scrotal crossed VV. This technique allows for anastomosis of one testicular end of the vas deferens to the contralateral abdominal end of the vas deferens. This maneuver is used when there is unilateral inguinal vas deferens obstruction associated with an atrophic testis on the contralateral side, or obstruction of inguinal vas deferens and epididymal obstruction on the contralateral side^[1,37,43,44]. Repeat VR is a valid option for men who failed an initial VR. The decision to perform a repeat VR should be based on the obstructive interval, the original VR, and the experience of the surgeon^[45,46].

When VVs are performed after sperm is found in the vasal fluid of at least one side, postoperative patency is demonstrated by the presence of sperm in the ejaculate in up to 99.5% of men^[40]. One-layer VV and two-layer VV have been shown to have similar patency rates^[47,48]. Pregnancy rates within two years of VR of 52% have been achieved and up to 63% with exclusion of female factor and when based on female partner age and the time since vasectomy^[9,49-53]. Postoperative semen quality and female factors and age of the female partner determine the rates of spontaneous conception in couples after VR^[47,54].

VASOEPIDIDYMOSTOMY

VE is a highly technically demanding operation, must be performed under magnification, and should only be performed by microsurgeons with appropriate training and experience in this operation who perform it frequently. When the decision to perform a VE is made, anastomoses are less technically challenging and more likely to succeed in the distal regions of the epididymis, as the epididymal wall thickens more distally with more smooth muscle cells. As the corpus and cauda of the epididymis is a single microscopic tubule, obstruction at any point will lead to a complete blockage of sperm from entering the vas deferens. The use of the operative microscope significantly improves VE patency rates^[55,56]. Multiple techniques have been employed to perform VE. VE may be performed by end-to end or end-to side anastomosis^[19,20]. The end-to end anastomosis has fallen out of favor for the most part. The end-to-side VE is performed by identifying the presence of markedly dilated epididymal tubules and approximating the muscularis and adventitia of the vas deferens to a specific opening in the tunica of the epididymis. This is a relatively bloodless and atraumatic technique^[20,56-60]. The testis is delivered through a scrotal incision. The vas deferens is isolated with a vessel loop at the junction of the straight and convoluted vas deferens. The vas deferens is transected sharply and is prepared as previously described above. The tunica vaginalis is incised and

the epididymis is inspected under magnification. The anastomotic site on the epididymis is identified where tubules are dilated, proximal to the suspected obstruction. A 3-4 mm incision is made in the tunica with microscissors overlying the dilated tubules. The epididymal tubules are gently dissected and exposed. The end of a 10-0 nylon needle is used to puncture the selected epididymal tubule and the fluid is examined microscopically to identify sperm. The vas deferens is secured to the epididymal tunica with 3-4 interrupted 6-0 polypropylene sutures with positioning allowing the vasal lumen to reach the opening of the epididymal tunica without tension. Under 25-32 magnification, interrupted 10-0 monofilament nylon sutures double armed with fishhook tapered needles are used to approximate the posterior mucosal edge of the epididymal tubule to the posterior vasal mucosa. Two to four additional 10-0 sutures are used for the anterior mucosal anastomosis. Six to ten additional interrupted 9-0 sutures are used to approximate the outer muscularis and adventitia of the vas deferens to the incised edge of the epididymal tunica. The testis and epididymis is carefully placed back in the tunica vaginalis and the scrotum is closed in layers.

The authors preferred technique for VE is the 2 stitch intussusceptions technique. Two parallel needles of double armed 10-0 nylon sutures are placed in the dilated epididymal tubule longitudinally without pulling them through to avoid leakage of tubular fluid and collapse of the dilated tubule. A microknife is used to make an opening longitudinally in the tubule between the parallel placed sutures. The fluid is examined microscopically for the presence of sperm. The needles are then passed inside out the vas deferens mucosa to perform the intussuscepted anastomosis^[56,60-62]. The muscularis and adventitia are anchored the epididymal tunica as described above (Figure 1).

In the hands of experienced, skilled microsurgeons, VE patency rates are reported between 50% and 85%^[61,63]. Men who underwent the classic end-to-side or older less commonly performed end-to-end anastomosis will have respective patency and pregnancy rates of approximately 70% and 43%^[55,64]. The intussuscepted techniques patency rates range between 70% and 90%^[56,60,65].

ROBOT ASSISTED VASECTOMY REVERSAL

VR has traditionally been performed with magnification through the use of the operative microscope. Recently, da Vinci robot assistance has been applied to VR. Robotic assistance was first utilized on *ex vivo* human vas deferens to perform VV with the findings of elimination of physiological tremor and comparable patency rates suggesting that the robot may be used as an alternative to the operative microscope^[66]. Robot assisted VV and VE were then performed in the rat

model. The findings were improved stability and motion reduction during suturing of the anastomosis^[67]. A multilayered robot assisted VV was performed in an *in vivo* rabbit model with comparable patency rates, reinforcing the suggested role of robotics in microsurgery^[68]. Robot assisted VR was performed in humans and resulted in shorter operative times and higher sperm counts in early postoperative semen analyses when compared to microsurgical VR^[69]. A validating human study on robot assisted VR compared to microsurgical VR demonstrated comparable patency rates, operative times, and early postoperative sperm concentrations and total motile counts. Although the mean anastomosis time in the robotic group was statistically significantly longer in the early robotic experience than the microsurgical group, this equated to a ten minute longer mean anastomosis time clinically^[70]. The suggested advantages of the use of the operative robot for such microsurgery include: elimination of physiologic tremor, improved stability, surgeon ergonomics/decreased surgeon fatigue, scalability of motion, three-dimensional high-definition visualization, the ability for the surgeon to manipulate three surgical instruments and the camera simultaneously, not requiring a specialty skilled microsurgical assistant, and the potential of improving operative times^[70]. This early data shows promise, however; large-scale prospective, randomized controlled trials are needed to validate the broader adoption of robot assistance for VR.

The robotic platform has provided advantages for more challenging scenarios such as use for intra-abdominal VR following laparoscopic vasectomy or in men with vasal obstruction due to inguinal hernia repair with mesh (Figure 2)^[71,72].

POSTOPERATIVE CARE

VR is performed as an outpatient surgery. Once the patient has recovered from anesthesia, he may ambulate. Immediately following VR, the patient should be placed in a tight fitting scrotal supporter with fluff gauze. An ice pack to the scrotum is recommended for the first one to two days postoperatively. Postoperative antibiotics are not indicated. Analgesics may be given, but are not always needed. Most men return to work three days postoperatively as long as they do not partake in heavy or physical activity at work. No intercourse, ejaculation, exercise, or strenuous activity is allowed for three weeks after surgery. Semen analysis is obtained at 6 wk, 3 mo, and 6 mo postoperatively and every 6 mo thereafter until the couple achieves a pregnancy or further assistance is required. If azoospermia persists at 6 mo postoperatively, this indicates a failure in the procedure, requiring a discussion of options including a repeat attempt at reconstruction vs sperm retrieval to be used with *in vitro* fertilization/intracytoplasmic sperm injection.

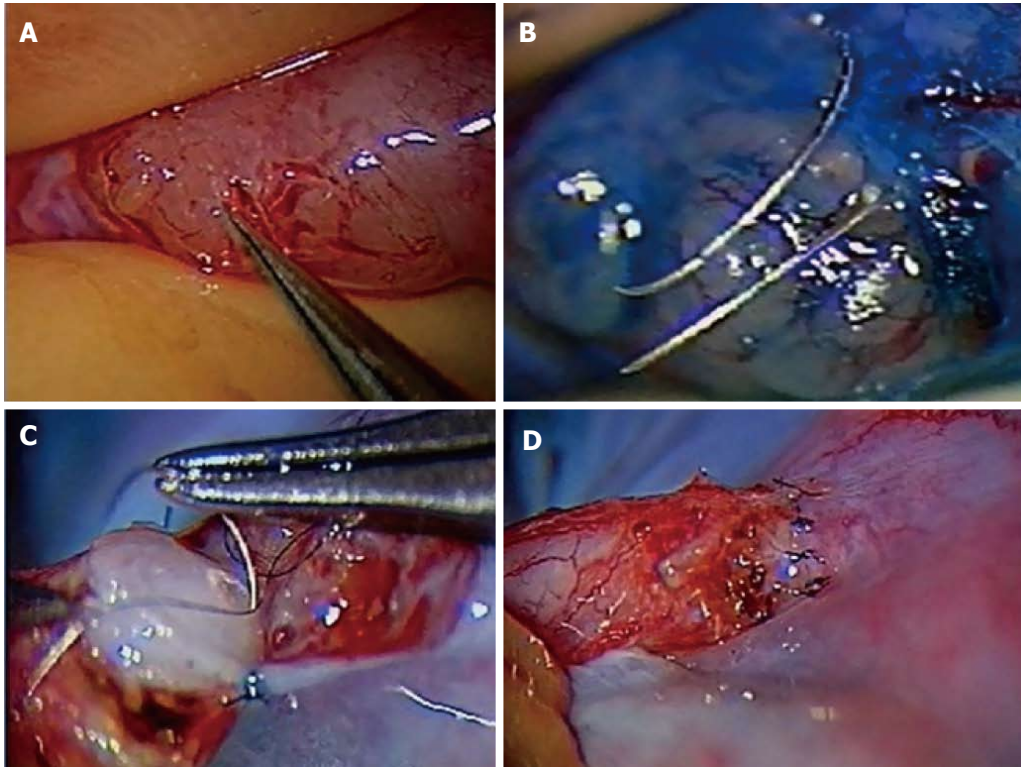


Figure 1 Microsurgical vasoepididymostomy. A: Dissection of dilated epididymal tubules; B: Placement of needles for the 2 stitch technique; C: Placement of mucosal vas deferens luminal stitch; D: Completed vasoepididymostomy anastomosis.

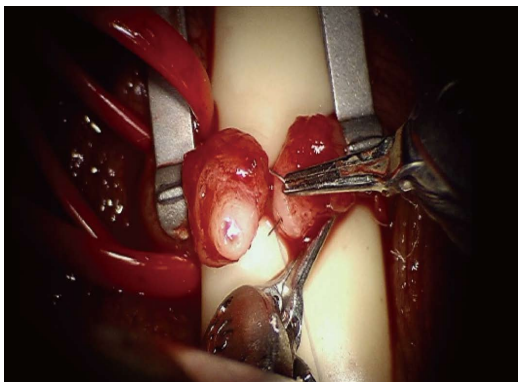


Figure 2 Placement of the full thickness transluminal stitch for a modified one-layer anastomosis with robot assistance.

COMPLICATIONS

Hematoma and infection are rare complications of VR. Damage to the deferential artery adjacent to the vas deferens is a potential intraoperative complication. Although there are two other arterial supplies to the testicle, the gonadal and cremasteric arteries, great care should be taken to preserve the deferential artery. Late stricture and obstruction are represented by progressive loss of sperm motility followed by decreasing sperm counts and eventually azoospermia in some men. Late obstruction has been reported to range between 5% and 12% at 18 mo following VR^[65,73]. As a precaution, it is recommended that men cryopreserve sperm once motile sperm are identified

in the ejaculate after VR.

CONCLUSION

VR is a very effective method of reestablishing fertility for men who have undergone vasectomy with extremely high success rates when performed by skilled, highly trained surgeons. Surgeons must not only be technically proficient with acceptable success rates with both VV and VE in order to provide this service; but they must have an in depth understanding in the evaluation, treatments, and post-operative management of these men. Different technical variations have developed over the years and continue to advance.

REFERENCES

1. Sheynkin YR, Hendin BN, Schlegel PN, Goldstein M. Microsurgical repair of iatrogenic injury to the vas deferens. *J Urol* 1998; **159**: 139-141 [PMID: 9400456 DOI: 10.1016/S0022-5347(01)64036-9]
2. Shin D, Lipshultz LI, Goldstein M, Barmé GA, Fuchs EF, Nagler HM, McCallum SW, Niederberger CS, Schoor RA, Brugh VM 3rd, Honig SC. Herniorrhaphy with polypropylene mesh causing inguinal vasal obstruction: a preventable cause of obstructive azoospermia. *Ann Surg* 2005; **241**: 553-558 [PMID: 15798455 DOI: 10.1097/01.sla.0000157318.13975.2a]
3. Twyman ED, Nelson CS. Vas deferens anastomosis: successful repair four years subsequent to bilateral vasectomy. *Urol Cutaneous Rev* 1938; **42**: 586
4. Boyarsky S. Operating microscope for vasovasostomy. *South Med J* 1973; **66**: 302-304 [PMID: 4691005 DOI: 10.1097/00007611-197303000-00004]

- 5 **Kim HH**, Goldstein M. History of vasectomy reversal. *Urol Clin North Am* 2009; **36**: 359-373 [PMID: 19643238 DOI: 10.1016/j.ucl.2009.05.001]
- 6 **Middleton WD**, Dahiya N, Naughton CK, Teefey SA, Siegel CA. High-resolution sonography of the normal extrapelvic vas deferens. *J Ultrasound Med* 2009; **28**: 839-846 [PMID: 19546325]
- 7 **Sjostrand NO**. The adrenergic innervation of the vas deferens and the accessory male genital glands. *Acta Physiol Scand* 1965; **65**: 7
- 8 **Macmillan EW**. The blood supply of the epididymis in man. *Br J Urol* 1954; **26**: 60-71 [PMID: 13149847 DOI: 10.1111/j.1464-410X.1954.tb04736.x]
- 9 **Wosnitzer MS**, Goldstein M. Relationship of sperm granuloma to obstructive interval and vasectomy reversal patency outcomes. *Fertility and Sterility* 2013; **100** Suppl: S213 [DOI: 10.1016/j.fertnstert.2013.07.1290]
- 10 **Practice Committee of the American Society for Reproductive Medicine**. Vasectomy reversal. *Fertil Steril* 2006; **86**: S268-S271 [PMID: 17055839 DOI: 10.1016/j.fertnstert.2006.08.046]
- 11 **Coward RM**, Mata DA, Smith RP, Kovac JR, Lipshultz LI. Vasectomy reversal outcomes in men previously on testosterone supplementation therapy. *Urology* 2014; **84**: 1335-1340 [PMID: 25307733 DOI: 10.1016/j.urology.2014.06.081]
- 12 **Shin YS**, Kim SD, Park JK. Preoperative factors influencing postoperative results after vasovasostomy. *World J Mens Health* 2012; **30**: 177-182 [PMID: 23596609 DOI: 10.5534/wjmh.2012.30.3.177]
- 13 **Magheli A**, Rais-Bahrami S, Kempkensteffen C, Weiske WH, Miller K, Hinz S. Impact of obstructive interval and sperm granuloma on patency and pregnancy after vasectomy reversal. *Int J Androl* 2010; **33**: 730-735 [PMID: 19906186 DOI: 10.1111/j.1365-2605.2009.01007.x]
- 14 **Grober ED**, Karpman E, Fanipour M. Vasectomy reversal outcomes among patients with vasal obstructive intervals greater than 10 years. *Urology* 2014; **83**: 320-323 [PMID: 24210560 DOI: 10.1016/j.urology.2013.09.016]
- 15 **Hsiao W**, Goldstein M, Rosoff JS, Piccorelli A, Kattan MW, Greenwood EA, Mulhall JP. Nomograms to predict patency after microsurgical vasectomy reversal. *J Urol* 2012; **187**: 607-612 [PMID: 22177169 DOI: 10.1016/j.juro.2011.10.044]
- 16 **Fenig DM**, Kattan MW, Mills JN, Gisbert M, Yu C, Lipshultz LI. Nomogram to preoperatively predict the probability of requiring epididymovasostomy during vasectomy reversal. *J Urol* 2012; **187**: 215-218 [PMID: 22099990 DOI: 10.1016/j.juro.2011.09.026]
- 17 **Kavoussi PK**, Bird ET. Validation of a vasoepididymostomy predictor model: is vasoepididymostomy truly predictable preoperatively? *Fertil Steril* 2009; **92**: 180-181 [PMID: 18835603 DOI: 10.1016/j.fertnstert.2008.04.058]
- 18 **Parekattil SJ**, Kuang W, Agarwal A, Thomas AJ. Model to predict if a vasoepididymostomy will be required for vasectomy reversal. *J Urol* 2005; **173**: 1681-1684 [PMID: 15821548 DOI: 10.1097/01.ju.0000154608.08496.f2]
- 19 **Silber SJ**. Microscopic vasoepididymostomy: specific microanastomosis to the epididymal tubule. *Fertil Steril* 1978; **30**: 565-571 [PMID: 720645]
- 20 **Thomas AJ**. Vasoepididymostomy. *Urol Clin North Am* 1987; **14**: 527-538 [PMID: 3303597]
- 21 **Lemack GE**, Goldstein M. Presence of sperm in the pre-vasectomy reversal semen analysis: incidence and implications. *J Urol* 1996; **155**: 167-169 [PMID: 7490823 DOI: 10.1097/00005392-199601000-00063]
- 22 **Hsiao W**, Sultan R, Lee R, Goldstein M. Increased follicle-stimulating hormone is associated with higher assisted reproduction use after vasectomy reversal. *J Urol* 2011; **185**: 2266-2271 [PMID: 21497850 DOI: 10.1016/j.juro.2011.02.011]
- 23 **Thomas AJ**, Pontes JE, Rose NR, Segal S, Pierce JM. Microsurgical vasovasostomy: immunologic consequences and subsequent fertility. *Fertil Steril* 1981; **35**: 447-450 [PMID: 7215571]
- 24 **Meinertz H**, Linnet L, Fogh-Andersen P, Hjort T. Antisperm antibodies and fertility after vasovasostomy: a follow-up study of 216 men. *Fertil Steril* 1990; **54**: 315-321 [PMID: 2379630]
- 25 **Vrijhof HJ**, Delaere KP. Vasovasostomy results in 66 patients related to obstructive intervals and serum agglutinin titres. *Urol Int* 1994; **53**: 143-146 [PMID: 7645141 DOI: 10.1159/000282656]
- 26 **Fuchs EF**, Alexander NJ. Immunologic considerations before and after vasovasostomy. *Fertil Steril* 1983; **40**: 497-499 [PMID: 6617911]
- 27 **Parslow JM**, Royle MG, Kingscott MM, Wallace DM, Hendry WF. The effects of sperm antibodies on fertility after vasectomy reversal. *Am J Reprod Immunol* 1983; **3**: 28-31 [PMID: 6859372 DOI: 10.1111/j.1600-0897.1983.tb00208.x]
- 28 **Collins JA**, Burrows EA, Yeo J, YoungLai EV. Frequency and predictive value of antisperm antibodies among infertile couples. *Hum Reprod* 1993; **8**: 592-598 [PMID: 8501191]
- 29 **Eggert-Kruse W**, Christmann M, Gerhard I, Pohl S, Klinga K, Runnebaum B. Circulating antisperm antibodies and fertility prognosis: a prospective study. *Hum Reprod* 1989; **4**: 513-520 [PMID: 2794011]
- 30 **Witkin SS**, David SS. Effect of sperm antibodies on pregnancy outcome in a subfertile population. *Am J Obstet Gynecol* 1988; **158**: 59-62 [PMID: 3337181 DOI: 10.1016/0002-9378(88)90776-4]
- 31 **Menge AC**, Medley NE, Mangione CM, Dietrich JW. The incidence and influence of antisperm antibodies in infertile human couples on sperm-cervical mucus interactions and subsequent fertility. *Fertil Steril* 1982; **38**: 439-446 [PMID: 7117571]
- 32 **Grober ED**, Jarvi K, Lo KC, Shin EJ. Mini-incision vasectomy reversal using no-scalpel vasectomy principles: efficacy and postoperative pain compared with traditional approaches to vasectomy reversal. *Urology* 2011; **77**: 602-606 [PMID: 21185588 DOI: 10.1016/j.urology.2010.09.051]
- 33 **Werthman P**. Mini-incision microsurgical vasoepididymostomy: a new surgical approach. *Urology* 2007; **70**: 794-796 [PMID: 17991562 DOI: 10.1016/j.urology.2007.07.055]
- 34 **Smith RP**, Khanna A, Kovac JR, Badhiwala N, Coward R, Lipshultz LI. The significance of sperm heads and tails within the vasal fluid during vasectomy reversal. *Indian J Urol* 2014; **30**: 164-168 [PMID: 24744514 DOI: 10.1016/j.jpaa.2014.09.019]
- 35 **Kolettis PN**, Burns JR, Nangia AK, Sandlow JI. Outcomes for vasovasostomy performed when only sperm parts are present in the vasal fluid. *J Androl* 2006; **27**: 565-567 [PMID: 16582406 DOI: 10.2164/jandrol.05190]
- 36 **Belker AM**, Thomas AJ, Fuchs EF, Konnak JW, Sharlip ID. Results of 1,469 microsurgical vasectomy reversals by the Vasovasostomy Study Group. *J Urol* 1991; **145**: 505-511 [PMID: 1997700]
- 37 **Silber SJ**. Microscopic vasectomy reversal. *Fertil Steril* 1977; **28**: 1191-1202 [PMID: 923835]
- 38 **Hagan KF**, Coffey DS. The adverse effects of sperm during vasovasostomy. *J Urol* 1977; **118**: 269-273 [PMID: 330887]
- 39 **Schmidt SS**. Vas anastomosis: a return to simplicity. *Br J Urol* 1975; **47**: 309-314 [PMID: 1095106 DOI: 10.1111/j.1464-410X.1975.tb03972.x]
- 40 **Goldstein M**, Li PS, Matthews GJ. Microsurgical vasovasostomy: the microdot technique of precision suture placement. *J Urol* 1998; **159**: 188-190 [PMID: 9400469 DOI: 10.1016/S0022-5347(01)64053-9]
- 41 **Patel SR**, Sigman M. Comparison of outcomes of vasovasostomy performed in the convoluted and straight vas deferens. *J Urol* 2008; **179**: 256-259 [PMID: 18001786 DOI: 10.1016/j.juro.2007.08.169]
- 42 **Sandlow JI**, Kolettis PN. Vasovasostomy in the convoluted vas deferens: indications and outcomes. *J Urol* 2005; **173**: 540-542 [PMID: 15643242 DOI: 10.1097/01.ju.0000149981.89230.50]
- 43 **Lizza EF**, Marmar JL, Schmidt SS, Lanasa JA, Sharlip ID, Thomas AJ, Belker AM, Nagler HM. Transseptal crossed vasovasostomy. *J Urol* 1985; **134**: 1131-1132 [PMID: 4057402]
- 44 **Hamidinia A**. Transvasovasostomy--an alternative operation for obstructive azoospermia. *J Urol* 1988; **140**: 1545-1548 [PMID: 3143018]
- 45 **Hollingsworth MR**, Sandlow JI, Schrepferman CG, Brannigan RE, Kolettis PN. Repeat vasectomy reversal yields high success rates. *Fertil Steril* 2007; **88**: 217-219 [PMID: 17336963 DOI: 10.1016/j.fertnstert.2006.11.077]

- 46 **Paick JS**, Park JY, Park DW, Park K, Son H, Kim SW. Microsurgical vasovasostomy after failed vasovasostomy. *J Urol* 2003; **169**: 1052-1055 [PMID: 12576844 DOI: 10.1097/01.ju.0000052666.97595.f6]
- 47 **Elzanaty S**, Dohle GR. Vasovasostomy and predictors of vasal patency: a systematic review. *Scand J Urol Nephrol* 2012; **46**: 241-246 [PMID: 22452615 DOI: 10.3109/00365599.2012.669790]
- 48 **Friedrich MG**, Friedrich E, Graefen M, Heinzer H, Michl U, Huland H, Noldus J. [Success rates of two-layer, microsurgical vasovasostomy. Results from a patient questionnaire and comparison with one-layer technique]. *Aktuelle Urol* 2006; **37**: 58-63 [PMID: 16440248 DOI: 10.1055/s-2005-870944]
- 49 **Boorjian S**, Lipkin M, Goldstein M. The impact of obstructive interval and sperm granuloma on outcome of vasectomy reversal. *J Urol* 2004; **171**: 304-306 [PMID: 14665900 DOI: 10.1097/01.ju.0000098652.35575.85]
- 50 **Gerrard ER**, Sandlow JJ, Oster RA, Burns JR, Box LC, Kolettis PN. Effect of female partner age on pregnancy rates after vasectomy reversal. *Fertil Steril* 2007; **87**: 1340-1344 [PMID: 17258213 DOI: 10.1016/j.fertnstert.2006.11.038]
- 51 **Kolettis PN**, Fretz P, Burns JR, D'Amico AM, Box LC, Sandlow JJ. Secondary azoospermia after vasovasostomy. *Urology* 2005; **65**: 968-971 [PMID: 15882733 DOI: 10.1016/j.urology.2004.11.027]
- 52 **Kolettis PN**, Sabanegh ES, Nalesnik JG, D'Amico AM, Box LC, Burns JR. Pregnancy outcomes after vasectomy reversal for female partners 35 years old or older. *J Urol* 2003; **169**: 2250-2252 [PMID: 12771762 DOI: 10.1097/01.ju.0000063780.74931.d6]
- 53 **Bernie AM**, Osterberg EC, Stahl PJ, Ramasamy R, Goldstein M. Vasectomy reversal in humans. *Spermatogenesis* 2012; **2**: 273-278 [PMID: 23248768 DOI: 10.4161/spmg.22591]
- 54 **Hinz S**, Rais-Bahrami S, Kempkensteffen C, Weiske WH, Schrader M, Magheli A. Fertility rates following vasectomy reversal: importance of age of the female partner. *Urol Int* 2008; **81**: 416-420 [PMID: 19077402 DOI: 10.1159/000167839]
- 55 **Schlegel PN**, Goldstein M. Microsurgical vasoepididymostomy: refinements and results. *J Urol* 1993; **150**: 1165-1168 [PMID: 8371380]
- 56 **Chan PT**, Brandell RA, Goldstein M. Prospective analysis of outcomes after microsurgical intussusception vasoepididymostomy. *BJU Int* 2005; **96**: 598-601 [PMID: 16104917 DOI: 10.1111/j.1464-410X.2005.05691.x]
- 57 **Wagenknecht LV**, Klosterhalfen H, Schirren C. Microsurgery in andrologic urology. I. Refertilization. *J Microsurg* 1980; **1**: 370-376 [PMID: 7003052 DOI: 10.1002/micr.1920010604]
- 58 **Krylov VS**, Borovikov AM. Microsurgical method of reuniting ductus epididymis. *Fertil Steril* 1984; **41**: 418-423 [PMID: 6698235]
- 59 **Fogdestam I**, Fall M, Nilsson S. Microsurgical epididymovasostomy in the treatment of occlusive azoospermia. *Fertil Steril* 1986; **46**: 925-929 [PMID: 3781009]
- 60 **Schiff J**, Chan P, Li PS, Finkelberg S, Goldstein M. Outcome and late failures compared in 4 techniques of microsurgical vasoepididymostomy in 153 consecutive men. *J Urol* 2005; **174**: 651-665; quiz 801 [PMID: 16006931 DOI: 10.1097/01.ju.0000165573.53109.92]
- 61 **Marmar JL**. Modified vasoepididymostomy with simultaneous double needle placement, tubulotomy and tubular invagination. *J Urol* 2000; **163**: 483-486 [PMID: 10647661 DOI: 10.1016/S0022-5347(05)67907-4]
- 62 **Kumar A**, Fernandez-Capetillo O, Carrera AC. Nuclear phosphoinositide 3-kinase beta controls double-strand break DNA repair. *Proc Natl Acad Sci USA* 2010; **107**: 7491-7496 [PMID: 20368419 DOI: 10.1073/pnas.1014139107]
- 63 **Berger RE**. Triangulation end-to-side vasoepididymostomy. *J Urol* 1998; **159**: 1951-1953 [PMID: 9598495 DOI: 10.1016/S0022-5347(01)63205-1]
- 64 **Pasqualotto FF**, Agarwal A, Srivastava M, Nelson DR, Thomas AJ. Fertility outcome after repeat vasoepididymostomy. *J Urol* 1999; **162**: 1626-1628 [PMID: 10524883 DOI: 10.1097/00005392-199911000-00014]
- 65 **Kolettis PN**, Thomas AJ. Vasoepididymostomy for vasectomy reversal: a critical assessment in the era of intracytoplasmic sperm injection. *J Urol* 1997; **158**: 467-470 [PMID: 9224325 DOI: 10.1016/S0022-5347(01)64504-X]
- 66 **Kuang W**, Shin PR, Matin S, Thomas AJ. Initial evaluation of robotic technology for microsurgical vasovasostomy. *J Urol* 2004; **171**: 300-303 [PMID: 14665899 DOI: 10.1097/01.ju.0000098364.94347.02]
- 67 **Schiff J**, Li PS, Goldstein M. Robotic microsurgical vasovasostomy and vasoepididymostomy: a prospective randomized study in a rat model. *J Urol* 2004; **171**: 1720-1725 [PMID: 15017273 DOI: 10.1097/01.ju.0000115902.00988.68]
- 68 **Kuang W**, Shin PR, Oder M, Thomas AJ. Robotic-assisted vasovasostomy: a two-layer technique in an animal model. *Urology* 2005; **65**: 811-814 [PMID: 15833552 DOI: 10.1016/j.urology.2004.11.032]
- 69 **Parekattil SJ**, Atalah HN, Cohen MS. Video technique for human robot-assisted microsurgical vasovasostomy. *J Endourol* 2010; **24**: 511-514 [PMID: 19839783 DOI: 10.1089/end.2009.0235]
- 70 **Kavoussi PK**. Validation of robot-assisted vasectomy reversal. *Asian J Androl* 2015; **17**: 245-247 [PMID: 25475663]
- 71 **Barazani Y**, Kaouk J, Sabanegh ES. Robotic intra-abdominal vasectomy reversal: A new approach to a difficult problem. *Can Urol Assoc J* 2014; **8**: E439-E441 [PMID: 25024801 DOI: 10.5489/cuaj.1947]
- 72 **Trost L**, Parekattil S, Wang J, Hellstrom WJ. Intracorporeal robot-assisted microsurgical vasovasostomy for the treatment of bilateral vasal obstruction occurring following bilateral inguinal hernia repairs with mesh placement. *J Urol* 2014; **191**: 1120-1125 [PMID: 24333242 DOI: 10.1016/j.juro.2013.11.107]
- 73 **Matthews GJ**, Schlegel PN, Goldstein M. Patency following microsurgical vasoepididymostomy and vasovasostomy: temporal considerations. *J Urol* 1995; **154**: 2070-2073 [PMID: 7500460 DOI: 10.1097/00005392-199512000-00030]

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Value of preoperative MRI for prostate cancer staging and continence outcomes prior to prostatectomy: A review of the literature

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where the cohort population underwent pre-operative MRI followed by prostatectomy. Keywords used in the PubMed literature search included: MRI, prostate cancer, prostate cancer staging, multiparametric MRI and incontinence. Papers were included for review if they discussed use of MRI prior to prostatectomy and had corresponding pathologic data, staging, incontinence, and surgical outcomes. Primary information noted was MRI sensitivity, specificity and overall accuracy for detecting extracapsular extension (ECE) and seminal vesicle involvement (SVI). Secondary information derived included assessing the surgical influence of staging information, and identifying predictors of urinary incontinence recovery. Review of the literature showed that in regards to extracapsular extension the reported MRI accuracy ranged from 76%-98%, sensitivity from 20%-90% and specificity from 82%-99%. As for seminal vesicle involvement the reported MRI accuracy ranged from 76%-98%, sensitivity from 20%-90% and specificity from 82%-99%. There is a widely varying sensitivity and specificity for both ECE and SVI and the wide variability in the MRI technology used in the literature supports that use of MRI technology for prostate cancer remains investigational.

Key words: Magnetic resonance imaging; Metastasis; Urinary incontinence; Prostate cancer; Seminal vesicle invasion; Extracapsular extension

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Abstract

Pelvic imaging in newly diagnosed prostate cancer is primarily used for staging prior to definitive treatment. Over the past decade use of magnetic resonance imaging (MRI) for pre-surgical planning has increased, as well has the technology and methods for performing prostate MRI. To investigate and define the different MRI technologies available and further assess MRI technology ability to predict pathologic stage. Searching PubMed, we identified current published literature,

Core tip: Over the past decade use of magnetic resonance imaging (MRI) for pre-surgical planning has increased, as well has the technology and methods for performing prostate MRI. To investigate and define the different MRI technologies available and further assess MRI technology ability to predict pathologic stage. We evaluated the current literature to identify MRI sensitivity, specificity and overall accuracy for detecting extracapsular extension and

seminal vesicle involvement. Primary information noted was MRI sensitivity, specificity and overall accuracy for detecting extracapsular extension and seminal vesicle involvement. Secondary information derived included assessing the surgical influence of staging information, and identifying predictors of urinary incontinence recovery.

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INTRODUCTION

Pelvic imaging in newly diagnosed prostate cancer patients is used to stage biopsy-proven prostate cancer. Accurate staging may identify men with pelvic lymphadenopathy or locally extensive disease who are less likely to benefit from an attempt at definitive treatment. Accurate staging may also potentially guide intraoperative decisions about the ability to perform neurovascular bundle sparing. Historically, pelvic imaging has been performed by computerized tomography (CT) scan but, over time, the utilization of magnetic resonance imaging (MRI) imaging has increased based on expectation of improved accuracy.

With advances in MRI technology, pre-surgical MRI is gaining favor, as evidenced by a 6.2% increase in usage of MRI between 1999-2006^[1]. Endorectal MRI (ER-MRI) can be used to identify suspicious areas within the prostate that may influence therapeutic decisions as well as the operative approach to nerve sparing. The purpose of this review is to evaluate the accuracy of preoperative MRI in regard to identifying extracapsular extension (ECE), seminal vesicle involvement (SVI) and lymph node metastasis. Secondly, we assess MRI's influence on surgical outcomes (positive margins) and ability to predict biochemical recurrence.

CURRENT RECOMMENDATIONS ON PELVIC IMAGING IN PROSTATE CANCER

The majority of men with a prostate cancer diagnosis may not require pelvic imaging prior to definitive treatment. Studies have shown that the vast majority of prostate cancers are low risk, localized, stage T1-T2 tumors, with an average prostate specific antigen (PSA) of 6.7 ng/mL^[2] and thus do not meet the requirement for pelvic imaging. Due to concerns for overuse there have been quality improvement efforts to decrease the use of imaging in low risk prostate cancer patients^[3].

Several major organizations have proposed guidelines for appropriate pelvic imaging in patients with prostate cancer. The American Urological Association Best Practice

Statement recommends obtaining pelvic imaging only in high-risk patients: Gleason grade ≥ 8 on biopsy, PSA > 20 ng/mL or digital rectal examination concerning for extra prostatic extension^[4]. The European Association of Urology additionally includes patients with Gleason 7 in their recommendations for pelvic imaging^[5]. Lastly, the National Comprehensive Cancer Network guidelines (version 2.2014) recommend obtaining pelvic imaging for clinically T3, T4 or T1-2 tumors in which nomogram predicts the probability of lymph node involvement at $> 10\%$ ^[6]. All three organizations indicate either CT scan or MRI may be used for pelvic imaging.

MRI TECHNOLOGY

Various MRI technologies are currently in use. A recent evaluation of 36 academic centers reported that 83% were routinely utilizing pelvic MRI for prostate cancer^[7]. Of the 30 programs that responded to a questionnaire, 25% performed imaging using 1.5 T with an endorectal coil, 31% used 3.0T without an endorectal coil and 28% used 3.0 T with an endorectal coil. They also showed that most used diffusion-weighted imaging (95%) and dynamic contrast of enhancement (82%) while only 21% of the centers used MR spectroscopy as part of their standard protocol. The takeaway from this work is that it is important to know what MRI technology each institution has available, as well as its strengths and weaknesses for imaging the prostate.

In the remainder of this section, we will discuss the various MRI modalities and how they affect the ability to visualize the prostate. Notably, T-1 weighed images alone are not useful due to the inability to visualize prostate anatomy. Due to low contrast uptake in the prostate, T-2 weighted images are the main imaging modality used for imaging the prostate because of high spatial resolution and ability to delineate the peripheral zone from the central and transitional zone anatomy. However, T-2 prostate cancer images appear with low signal intensity^[8]. Post-biopsy hemorrhage can also appear as a low uptake region on T2 weighted images. However, T1 imaging can be used to differentiate hemorrhage from prostate cancer, as the former has increased and the latter decreased intensity on T1 imaging.

The use of T2 weight images with other techniques is known as multiparametric imaging. These include dynamic enhanced contrast imaging, diffusion weighted imaging, and MR spectroscopy.

Dynamic enhanced contrast imaging operates on the premise that increased vascularity is present in prostate cancer due to local hypoxia. The mechanism of angiogenesis is felt to be due to influence of vascular endothelial growth factor. This change can be studied by comparing the uptake and washout of gadolinium chelate contrast in normal and cancerous tissues^[9].

Diffusion weighted-proton diffusion uses the properties in water to produce image contrast. The images produced

Table 1 Clinical usefulness characteristics of magnetic resonance imaging for determining extracapsular extension

Ref.	Characteristic
Schiebler <i>et al</i> ^[14]	Asymmetry of the neurovascular bundle Obliteration of the rectoprostatic angle
Outwater <i>et al</i> ^[15]	A bulge in the prostatic contour Gross extracapsular tumor extension into the periprostatic fat

by the reflected protons are then acquired by applying motion gradients that cause phase shifts based on the direction and quality of the proton movement. Healthy prostate tissue is rich in structures that allow for extensive diffusion of water molecules in comparison to prostate cancer, which destroys glandular structure architecture resulting in different diffusion^[10].

MR spectroscopy reflects resonance frequencies unique to protons in the metabolites citrate and choline. When compared to normal prostate tissue, citrate is reduced and choline increased in prostate cancer due to increased cell turnover^[11].

In 2012 the European Society of Urogenital Radiology published guidelines recommending that multiparametric MRI be used for prostate cancer, which they defined as "a combination of high-resolution T2-weighted images (T2WI), and at least two functional MRI techniques, as these provide better characterization than T2WI with only one functional technique"^[12]. Thus, there remains lack of consensus as to the definitive use of all modalities. It is clear based on evidence from pre-biopsy imaging, however, that varying combinations improve the sensitivity for detecting prostate cancer^[13].

MRI FOR STAGING

The ability to accurately stage prostate cancer prior to prostatectomy would be beneficial in terms of optimizing the aggressiveness of neurovascular bundle sparing and the prevention of positive surgical margins. Studies assessing MRI staging accuracy have primarily focused on ECE and SVI.

STAGING FOR ECE

MRI was first proposed as a potentially useful tool for determining ECE by Schiebler *et al*^[14] in 1992 based on their identification of the characteristic findings of asymmetry of the neurovascular bundle and obliteration of the rectoprostatic angle^[14]. Two years later, Outwater *et al*^[15] added two additional characteristics: bulge in the contour of the prostate and extracapsular tumor gross extension in the periprostatic fat^[15] (Table 1). Using these as indications to determine extracapsular extension, studies were done looking into the accuracy of various MRI modalities and comparing their ability to identify ECE on prostatectomy specimens.

Several studies using the above criteria have looked at the accuracy, sensitivity, and specificity of predicting ECE. The accuracy ranged from 59%-95%, sensitivity from 14%-86% and specificity from 70%-99% (Table 2). Notably, several studies confirmed that an endorectal coil improved all three. In addition, studies using multiparametric MRI showed slight improvement. However it is difficult to compare studies due to the variability in technology used, for example: 1.5T vs 3.0T and different definitions of "multiparametric".

STAGING OF SEMINAL VESICLE INVASION

Due to prognostic and management implications, the ability to identify SVI preoperatively would be useful. Studies assessing this have reported MRI accuracy ranging from 76%-98%, sensitivity from 20%-90% and specificity from 82%-99%. The widely varying ranges observed likely stem from the significantly different MRI imaging technologies used. Thus, direct comparison of the accuracy between institutions is difficult. However, as was the case for ECE, many of the studies show that use of T2-weighted images with addition of endorectal coil was superior to T2 weighted images with pelvic phased array (Table 3).

FACTORS INFLUENCING STAGING MRI ACCURACY

Several prostate MRI studies have observed that experience of the radiologist influenced the overall accuracy of staging. For example Latchamestty *et al*^[16] compared their first 40 ER-MRI to their second 40 and noted an overall modest increase in staging accuracy. Bloch *et al*^[17] and Fütterer *et al*^[18] also commented that accuracy changed considerably with radiologist experience. With this in mind, it is important to know the experience of the radiologist at one's institution. Secondly, it has been observed that higher Gleason score on biopsy and on final pathology correlates with increased cancer detection on preoperative MRI^[19]. Thirdly, an abnormal prostate exam increased preoperative MRI accuracy^[20].

IMPACT OF PREOPERATIVE MRI ON SURGICAL TREATMENT

Information from MRI may also be utilized to guide intraoperative decision making. As stated previously, information about ECE or SVI may influence the aggressiveness of nerve sparing during the operation. Knowledge of prostate adenocarcinoma location preoperatively may additionally influence surgical technique and impact the sensitive margin rate.

Roethke *et al*^[21] evaluated the impact of preoperative MRI on nerve sparing and positive surgical margin

Table 2 Accuracy, sensitivity and specificity of predicting extracapsular extension by magnetic resonance imaging

Ref.	Imaging technology	Tesla	n	Accuracy	Sensitivity	Specificity	Comment
Bloch <i>et al</i> ^[17]	T2w imaging combined with dynamic contrast enhancement	1.5	32	95%	86%	96%	Determination of ECE increased by 25% with addition of DCE
Chandra <i>et al</i> ^[30]	T2w imaging with ER-MRI	1.5	38	76	69	82	
Fütterer <i>et al</i> ^[18]	T2w imaging with pelvic phased array and T2w imaging with endorectal coil	1.5	81	76-83 ER-PPA 61-63 PPA	47-63 ER-PPA 43-60 PPA	96 ER-PPA 70-72 PPA	Single reader with conscious readers bc/de?
Park <i>et al</i> ^[31]	3.0 T2w pelvic phase array <i>vs</i> er MRI	3.0 <i>vs</i> 1.5	108 (54 in each group)	72 3T <i>vs</i> 70 1.5T	1.5-T 71% 3.0-T 81%	1.5-T 73% 3.0-T 67%	The 3.0-T MRI had a lower incidence of MR artifacts than the 1.5-T MRI ($P < 0.05$). However, overall imaging quality at both 3.0 and 1.5 T had no significant difference
Zhang <i>et al</i> ^[32]	MRI with endorectal and pelvic multicoil array	1.5	110	91	55	99	
Tan <i>et al</i> ^[33]	T2w- with ERC	1.5	32	59	14	94	
Nepple <i>et al</i> ^[20]	ER-MRI	1.5	94	70	14	88	
Bloch <i>et al</i> ^[34]	T2w imaging with fast spin echo and DCE	3.0	108	86 (80%-91%)	75 (64%-83%)	92 (88%-95%)	NPV/PPV:79/91 Stratified by reader experience
Latchamsetty <i>et al</i> ^[16]	ER-MRI		80	53-73	31-64	71-78	First 40 and second 40. Concluded that experience increases accuracy
Beyer-sdorff <i>et al</i> ^[35]	T2w ER-MRI <i>vs</i> T2w imaging with torso-array	1.5 <i>vs</i> 3.0	22	73% (both)	1.5T; Extended continuity with capsule-100; Smooth bulging-80; Irregular bulging-80; Direct periprostatic infiltration-20; Asymmetry of NVB-20; Displacement of rectoprostatic angle-0 3-T; Extended continuity with capsule-100; Smooth bulging-60; Irregular bulging-40; Direct periprostatic infiltration-20; Asymmetry of NVB-40; Displacement of rectoprostatic angle-20	1.5T; Extended continuity with capsule-23; Smooth bulging-39; Irregular bulging-50; Direct periprostatic infiltration-83; Asymmetry of NVB-83; Displacement of rectoprostatic angle-100 3-T; Extended continuity with capsule-50; Smooth bulging-44; Irregular bulging-56; Direct periprostatic infiltration-72; Asymmetry of NVB-67; Displacement of rectoprostatic angle-89	Determined that image quality and tumor delineation was better with 1.5T2w ER-MRI
Lee <i>et al</i> ^[36]	ERC <i>vs</i> pelvic phased array	1.5	47 ERC <i>vs</i> 44 PPA	64	32 ERC <i>vs</i> 30 PPA	96 ERC <i>vs</i> 90 PPA	
Hegde <i>et al</i> ^[19]	T2w multiparametric ER-MRI-T2w, T1w, DCE and DW	3.0	118	75	28	91	Presence of a T3 lesion on final pathology was associated with T3 on MRI or higher Gleason score (8-10)
Kim <i>et al</i> ^[24]	T2w pelvic array MRI <i>vs</i> T2w imaging ER-MRI	1.5 <i>vs</i> 3.0	151 63 ER-88 pelvic phase array	61.4 PPA 63.4 ERC	31 PPA 33 ERC	98 PPA 97 ERC	
Tanaka <i>et al</i> ^[22]	T2w pelvic phase array	3.0	67	-	60	86	Specifically mention they did not use an ER-MRI
Roethke <i>et al</i> ^[21]	T2w imaging with ER-MRI	1.5	385	76	42	92	Overstaging occurred in 5.7% and under staged in 17.9% 91.8% sens/41.5%spec in predicting T2 disease dropped to 40.7%sen/92.9%spec for cT3

MRI: Magnetic resonance imaging; ER-MRI: Endorectal MRI; ECE: Extracapsular extension; DCE: Dynamic contrast enhanced; DW: Diffusion weighted; PPA: Pelvic phase array; ER-PPA: Endorectal pelvic phase array; NPV: Negative predictive value; PPV: Positive predictive value; ERC: Endorectal coil; NVB: Neurovascular bundle.

Table 3 Studies assessing magnetic resonance imaging accuracy in predicting seminal vesicle involvement

	Imaging technology	Tesla	n	Accuracy	Sensitivity	Specificity	Comment
Chandra <i>et al</i> ^[30]	T2w imaging with ER-MRI	1.5	38	76	69	82	
Fütterer <i>et al</i> ^[18]	T2w imaging with pelvic phased array and T2w imaging with endorectal coil	1.5	81	90-98 ER-PPA 76-86 PPA	40-90 ER-PPA 30-50 PPA	92-99 ER-PPA 80-94 PPA	
Latchamsetty <i>et al</i> ^[16]	ER-MRI		80	80-85	20-22	94-100	First 40 and second 40. Concluded that experience increases accuracy
Park <i>et al</i> ^[31]	PPA vs er MRI	3.0	108 (54 in each group)	3-T 98 vs 1.5-T 91%	1.5-T 75% 3.0-T 50%	1.5-T 92% 3.0-T 100%	The 3.0-T MRI had a lower incidence of MR artifacts than the 1.5-T MRI ($P < 0.05$). However, overall imaging quality at both 3.0 and 1.5 T had no significant difference
Zhang <i>et al</i> ^[32]	MRI with endorectal and pelvic multi-coil array	1.5	110	99	80	99	
Lee <i>et al</i> ^[36]	1.5 T ERC vs pelvic phased array	1.5	47 ERC vs 44 PPA	89	50 ERC vs 50 PPA	93 ERC vs 98 PPA	
Nepple <i>et al</i> ^[20]	T2w ER-MRI	1.5	94	93	38	99	
Hegde <i>et al</i> ^[19]	T2w multiparametric ER-MRI-T2w, T1w, DCE and DW	3.0	118	95	50	99	Presence of a T3 lesion on final pathology was associated with T3 on MRI or higher gleason score (8-10)
Kim <i>et al</i> ^[24]	T2w pelvic array MRI vs T2w imaging ER-MRI	1.5 vs 3.0	151 63 ER-MRI vs 88 pelvic phase array	81 PPA 83 ERC	43 PPA 46 ERC	92 PPA 93 ERC	

MRI: Magnetic resonance imaging; ER-MRI: Endorectal MRI; DCE: Dynamic contrast enhanced; DW: Diffusion weighted; PPA: Pelvic phase array; ER-PPA: Endorectal pelvic phase array.

rates. Bilateral nerve sparing was feasible in 48.4% of patients with stage clinical T2 lesions but in only 19.7% patients with clinical T3 or T4 disease on MRI. ER-MRI stage did not impact the possibility for patients to receive a unilateral nerve-sparing procedure, as they were able to accomplish this in 35.1% of patients with ER-MRI stage cT2 tumors and 35.2% of the patients with ER-MRI stage T3/T4 disease. Additionally, they found that positive margin rates were lower (10.8%) for cases noting no ECE on preoperative MRI compared to MRI diagnosed cT3 lesions (32.4%).

Tanaka and associates used 3-T MRI to make the decision on whether to perform nerve sparing vs resection based on evidence for ECE^[22]. Of the cases where preoperative MRI showed no evidence of ECE, 38.7% underwent nerve sparing with an overall positive margin rate of 7.5%. No patients who underwent nerve-sparing had a positive surgical margin identified. When ECE was identified on MRI, only 1 patient of the 28 was able to undergo a nerve sparing surgery. Despite this, the overall positive margin rate was 46.4%. Surgical specimens in the 67 patients identified were 75% pT2 and 25% pT3. From this, their conclusion was that MRI evidence of ECE can be used to guide surgical decision making.

CONTINENCE

Men who undergo a prostatectomy uniformly develop some degree of postoperative urinary incontinence, with

variable rates of recovery and an unknown expected final result. While a majority of men recover satisfactorily, some eventually require surgical correction. Several investigators have identified factors that influence this recovery and expected final continence status by analyzing different anatomical landmarks on preoperative MRI.

Paparel *et al*^[23] assessed whether recovery of urinary continence after open retropubic prostatectomy is influenced by preoperative membranous urethral length (MUL) identified on ER-MRI. Sixty-four patients were studied using pre- and postoperative MRI. Twenty-four patients had a MUL greater than 14 mm. They noted that these patients had improved rates of continence as well as time to continence and thus they concluded that longer preoperative MUL was in fact associated with superior continence rates.

Kim *et al*^[24] evaluated both RALP and RRP continence rates, defining continence as pad-free. They noted that longer preoperative MUL on MRI and younger age were independent prognostic factors for continence recovery.

Lim *et al*^[25] looked at anatomical information including MUL, thickness of the levator ani muscle and urogenital diaphragm on preoperative MRI to determine if these factors influenced continence status post retropubic prostatectomy. They further categorized patients into four groups based on the overlying pattern of the prostatic apex and the membranous urethra. They noted that membranous urethral length > 14.24

mm and the type of prostatic apex were significant predictors of continence at 12 mo.

von Bodman *et al.*^[26] studied preoperative MRI predictors of continence recovery. They found that urethral length and urethral volume were statistically significant predictors of regaining continence at both 6 mo and 12 mo.

As stated above, shorter urethral sphincter length on preoperative ER-MRI has been associated with increased risk of postoperative urinary incontinence and longer time to continence. Nguyen *et al* utilized this information to evaluate alternative anatomical reconstruction techniques done at their institution^[27]. They started in 2005 by using a previously described apical dissection and urethrovesical anastomosis in robotic radical prostatectomy. They then moved to an anterior reconstruction with preservation of the puboprostatic collar. In 2007 they started performing a total reconstruction with the addition of posterior reinforcement. This additional reinforcement technique was done by using a reinforcing stitch at the midline suturing of the right and left detrusor flaps behind the bladder neck to create a thick muscular bladder neck and a retrotrigonal flap, sutured into the posterior bladder neck. Based on these techniques, they assessed the overall impact of their techniques on continence and specifically in men with shorter urethral length. They studied 274 patients receiving a 1.5T endorectal MRI prior to robot-assisted laparoscopic prostatectomy. Urethral lengths were measured on the T2-weighted images and all sphincter lengths were measured from the prostatic apex to the penile bulb. They defined short urethral lengths as < 14 mm and continence was defined as zero pads or only a liner for security reasons. They observed that men with a short urethral length had a continence rate of only 47% compared to 80% for men with longer sphincter lengths on MRI. Their surgical modifications also increased the continence rate to 81% for their anterior reconstruction and 90% for a total reconstruction, up from 47%. Men with longer urethral length on MRI had only a 3% increase of continence if they received anterior reconstruction but a 19% increase of continence if they received a total reconstruction for the longer urethral length (up from 80%).

CHANCE OF BIOMEDICAL RECURRENCE BASED ON MRI

Hattori *et al.*^[28] reported that MRI stage T3 predicted for biochemical recurrence. However, long term prostate cancer oncologic outcomes relative to preoperative MRI are not available. While the analogous nature of breast cancer to prostate cancer is not certain, the concept of improved local control by preoperative MRI staging has been evaluated in breast cancer where a recent meta-analysis reported no improvement in local recurrence or distant recurrence in breast cancer

patients who received preoperative breast MRI^[29].

CONCLUSION

Preoperative MRI for prostate cancer has become increasingly utilized since the early 1990s. With advancement in technology and expansion of imaging modalities, prostate cancer detection and staging information can now be more readily ascertained. While the primary current use of prostate MRI is preoperative staging, widely varying sensitivity and specificity for both ECE and SVI and the wide variability in the MRI technology used in reported studies supports that use of MRI technology for prostate cancer remains investigational. While there appears to be a potential role in determining aggressiveness of neurovascular bundle sparing and for assessment of urethral length towards improvement in the prediction of continence recovery, no routine recommendation to use this technology should be made. Instead, the urologist should selectively use this technology based on the equipment and expertise present at their own institution. Future study is needed to further identify the value of preoperative MRI for guiding surgical decision making and evaluating the impact on patient outcomes.

REFERENCES

- 1 **Dinan MA**, Curtis LH, Hammill BG, Patz EF, Abernethy AP, Shea AM, Schulman KA. Changes in the use and costs of diagnostic imaging among Medicare beneficiaries with cancer, 1999-2006. *JAMA* 2010; **303**: 1625-1631 [PMID: 20424253 DOI: 10.1001/jama.2010.460]
- 2 **Shao YH**, Demissie K, Shih W, Mehta AR, Stein MN, Roberts CB, Dipaola RS, Lu-Yao GL. Contemporary risk profile of prostate cancer in the United States. *J Natl Cancer Inst* 2009; **101**: 1280-1283 [PMID: 19713548 DOI: 10.1093/jnci/djp262]
- 3 **Miller DC**, Murtagh DS, Suh RS, Knapp PM, Schuster TG, Dunn RL, Montie JE. Regional collaboration to improve radiographic staging practices among men with early stage prostate cancer. *J Urol* 2011; **186**: 844-849 [PMID: 21788043 DOI: 10.1016/j.juro.2011.04.078]
- 4 **Greene KL**, Albertsen PC, Babaian RJ, Carter HB, Gann PH, Han M, Kuban DA, Sartor AO, Stanford JL, Zietman A, Carroll P. Prostate specific antigen best practice statement: 2009 update. *J Urol* 2013; **189**: S2-S11 [PMID: 23234625 DOI: 10.1016/j.juro.2012.11.014]
- 5 **Heidenreich A**, Bellmunt J, Bolla M, Joniau S, Mason M, Matveev V, Mottet N, Schmid HP, van der Kwast T, Wiegel T, Zattoni F. EAU guidelines on prostate cancer. Part I: screening, diagnosis, and treatment of clinically localised disease. *Eur Urol* 2011; **59**: 61-71 [PMID: 21056534 DOI: 10.1016/j.eururo.2010.10.039]
- 6 **National Comprehensive Cancer Network**. NCCN Guidelines. Available from: URL: http://www.nccn.org/professionals/physician_gls/f_guidelines.asp#detection
- 7 **Leake JL**, Hardman R, Ojili V, Thompson I, Shanbhogue A, Hernandez J, Barentsz J. Prostate MRI: access to and current practice of prostate MRI in the United States. *J Am Coll Radiol* 2014; **11**: 156-160 [PMID: 24389134 DOI: 10.1016/j.jacr.2013.05.006]
- 8 **Mazaheri Y**, Shukla-Dave A, Muellner A, Hricak H. MR imaging of the prostate in clinical practice. *MAGMA* 2008; **21**: 379-392 [PMID: 18795354 DOI: 10.1007/s10334-008-0138-y]
- 9 **Alonzi R**, Padhani AR, Allen C. Dynamic contrast enhanced MRI in prostate cancer. *Eur J Radiol* 2007; **63**: 335-350 [PMID:

- 17689907 DOI: 10.1016/j.ejrad.2007.06.028]
- 10 **Somford DM**, Fütterer JJ, Hambroek T, Barentsz JO. Diffusion and perfusion MR imaging of the prostate. *Magn Reson Imaging Clin N Am* 2008; **16**: 685-695, ix [PMID: 18926431 DOI: 10.1016/j.mric.2008.07.002]
- 11 **Hoeks CM**, Barentsz JO, Hambroek T, Yakar D, Somford DM, Heijmink SW, Scheenen TW, Vos PC, Huisman H, van Oort IM, Witjes JA, Heerschap A, Fütterer JJ. Prostate cancer: multiparametric MR imaging for detection, localization, and staging. *Radiology* 2011; **261**: 46-66 [PMID: 21931141 DOI: 10.1148/radiol.11091822]
- 12 **Barentsz JO**, Richenberg J, Clements R, Choyke P, Verma S, Villeirs G, Rouviere O, Logager V, Fütterer JJ. ESUR prostate MR guidelines 2012. *Eur Radiol* 2012; **22**: 746-757 [PMID: 22322308 DOI: 10.1007/s00330-011-2377-y]
- 13 **Fütterer JJ**, Heijmink SW, Scheenen TW, Veltman J, Huisman HJ, Vos P, Hulsbergen-Van de Kaa CA, Witjes JA, Krabbe PF, Heerschap A, Barentsz JO. Prostate cancer localization with dynamic contrast-enhanced MR imaging and proton MR spectroscopic imaging. *Radiology* 2006; **241**: 449-458 [PMID: 16966484 DOI: 10.1148/radiol.2412051866]
- 14 **Schiebler ML**, Yankaskas BC, Tempny C, Spritzer CE, Rifkin MD, Pollack HM, Holtz P, Zerhouni EA. MR imaging in adenocarcinoma of the prostate: interobserver variation and efficacy for determining stage C disease. *AJR Am J Roentgenol* 1992; **158**: 559-562; discussion 563-564 [PMID: 1738994 DOI: 10.2214/ajr.158.3.1738994]
- 15 **Outwater EK**, Petersen RO, Siegelman ES, Gomella LG, Chernesky CE, Mitchell DG. Prostate carcinoma: assessment of diagnostic criteria for capsular penetration on endorectal coil MR images. *Radiology* 1994; **193**: 333-339 [PMID: 7972739 DOI: 10.1148/radiology.193.2.7972739]
- 16 **Lathamsetty KC**, Borden LS, Porter CR, Lacrampe M, Vaughan M, Lin E, Conti N, Wright JL, Corman JM. Experience improves staging accuracy of endorectal magnetic resonance imaging in prostate cancer: what is the learning curve? *Can J Urol* 2007; **14**: 3429-3434 [PMID: 17324322]
- 17 **Bloch BN**, Furman-Haran E, Helbich TH, Lenkinski RE, Degani H, Kratzik C, Susani M, Haitel A, Jaromi S, Ngo L, Rofsky NM. Prostate cancer: accurate determination of extracapsular extension with high-spatial-resolution dynamic contrast-enhanced and T2-weighted MR imaging--initial results. *Radiology* 2007; **245**: 176-185 [PMID: 17717328 DOI: 10.1148/radiol.2451061502]
- 18 **Fütterer JJ**, Engelbrecht MR, Jager GJ, Hartman RP, King BF, Hulsbergen-Van de Kaa CA, Witjes JA, Barentsz JO. Prostate cancer: comparison of local staging accuracy of pelvic phased-array coil alone versus integrated endorectal-pelvic phased-array coils. Local staging accuracy of prostate cancer using endorectal coil MR imaging. *Eur Radiol* 2007; **17**: 1055-1065 [PMID: 17024497 DOI: 10.1007/s00330-006-0418-8]
- 19 **Hegde JV**, Chen MH, Mulkern RV, Fennessy FM, D'Amico AV, Tempny CM. Preoperative 3-Tesla multiparametric endorectal magnetic resonance imaging findings and the odds of upgrading and upstaging at radical prostatectomy in men with clinically localized prostate cancer. *Int J Radiat Oncol Biol Phys* 2013; **85**: e101-e107 [PMID: 23040223 DOI: 10.1016/j.ijrobp.2012.08.032]
- 20 **Nepple KG**, Rosevear HM, Stolpen AH, Brown JA, Williams RD. Concordance of preoperative prostate endorectal MRI with subsequent prostatectomy specimen in high-risk prostate cancer patients. *Urol Oncol* 2013; **31**: 601-606 [PMID: 21665495 DOI: 10.1016/j.urolonc.2011.05.004]
- 21 **Roethke MC**, Lichy MP, Knies M, Werner MK, Claussen CD, Stenzl A, Schlemmer HP, Schilling D. Accuracy of preoperative endorectal MRI in predicting extracapsular extension and influence on neurovascular bundle sparing in radical prostatectomy. *World J Urol* 2013; **31**: 1111-1116 [PMID: 22249342 DOI: 10.1007/s00345-012-0826-0]
- 22 **Tanaka K**, Shigemura K, Muramaki M, Takahashi S, Miyake H, Fujisawa M. Efficacy of using three-tesla magnetic resonance imaging diagnosis of capsule invasion for decision-making about neurovascular bundle preservation in robotic-assisted radical prostatectomy. *Korean J Urol* 2013; **54**: 437-441 [PMID: 23878685 DOI: 10.4111/kju.2013.54.7.437]
- 23 **Paparel P**, Akin O, Sandhu JS, Otero JR, Serio AM, Scardino PT, Hricak H, Guillonneau B. Recovery of urinary continence after radical prostatectomy: association with urethral length and urethral fibrosis measured by preoperative and postoperative endorectal magnetic resonance imaging. *Eur Urol* 2009; **55**: 629-637 [PMID: 18801612 DOI: 10.1016/j.eururo.2008.08.057]
- 24 **Kim SC**, Song C, Kim W, Kang T, Park J, Jeong IG, Lee S, Cho YM, Ahn H. Factors determining functional outcomes after radical prostatectomy: robot-assisted versus retropubic. *Eur Urol* 2011; **60**: 413-419 [PMID: 21612859 DOI: 10.1016/j.eururo.2011.05.011]
- 25 **Lim TJ**, Lee JH, Lim JW, Moon SK, Jeon SH, Chang SG. Preoperative factors predictive of continence recovery after radical retropubic prostatectomy. *Korean J Urol* 2012; **53**: 524-530 [PMID: 22949995 DOI: 10.4111/kju.2012.53.8.524]
- 26 **von Bodman C**, Matsushita K, Savage C, Matikainen MP, Eastham JA, Scardino PT, Rabbani F, Akin O, Sandhu JS. Recovery of urinary function after radical prostatectomy: predictors of urinary function on preoperative prostate magnetic resonance imaging. *J Urol* 2012; **187**: 945-950 [PMID: 22264458 DOI: 10.1016/j.juro.2011.10.143]
- 27 **Nguyen L**, Jhaveri J, Tewari A. Surgical technique to overcome anatomical shortcoming: balancing post-prostatectomy continence outcomes of urethral sphincter lengths on preoperative magnetic resonance imaging. *J Urol* 2008; **179**: 1907-1911 [PMID: 18353395 DOI: 10.1016/j.juro.2008.01.036]
- 28 **Hattori S**, Kosaka T, Mizuno R, Kanao K, Miyajima A, Yasumizu Y, Yazawa S, Nagata H, Kikuchi E, Mikami S, Jinzaki M, Nakagawa K, Tanimoto A, Oya M. Prognostic value of preoperative multiparametric magnetic resonance imaging (MRI) for predicting biochemical recurrence after radical prostatectomy. *BJU Int* 2014; **113**: 741-747 [PMID: 23937660 DOI: 10.1111/bju.12329]
- 29 **Bleicher RJ**. Breast magnetic resonance imaging as it is, in contrast to how we wish it to be. *J Clin Oncol* 2014; **32**: 370-372 [PMID: 24395864 DOI: 10.1200/JCO.2013.54.0039]
- 30 **Chandra RV**, Heinze S, Dowling R, Shadbolt C, Costello A, Pedersen J. Endorectal magnetic resonance imaging staging of prostate cancer. *ANZ J Surg* 2007; **77**: 860-865 [PMID: 17803549 DOI: 10.1111/j.1445-2197.2007.04259.x]
- 31 **Park BK**, Kim B, Kim CK, Lee HM, Kwon GY. Comparison of phased-array 3.0-T and endorectal 1.5-T magnetic resonance imaging in the evaluation of local staging accuracy for prostate cancer. *J Comput Assist Tomogr* 2007; **31**: 534-538 [PMID: 17882027 DOI: 10.1097/01.rct.0000250108.85799.e1]
- 32 **Zhang JQ**, Loughlin KR, Zou KH, Haker S, Tempny CM. Role of endorectal coil magnetic resonance imaging in treatment of patients with prostate cancer and in determining radical prostatectomy surgical margin status: report of a single surgeon's practice. *Urology* 2007; **69**: 1134-1137 [PMID: 17572201 DOI: 10.1016/j.urolgy.2007.01.094]
- 33 **Tan JS**, Thng CH, Tan PH, Cheng CW, Lau WK, Tan TW, Ho JT, Ching BC. Local experience of endorectal magnetic resonance imaging of prostate with correlation to radical prostatectomy specimens. *Ann Acad Med Singapore* 2008; **37**: 40-43 [PMID: 18265896]
- 34 **Bloch BN**, Genega EM, Costa DN, Pedrosa I, Smith MP, Kressel HY, Ngo L, Sanda MG, Dewolf WC, Rofsky NM. Prediction of prostate cancer extracapsular extension with high spatial resolution dynamic contrast-enhanced 3-T MRI. *Eur Radiol* 2012; **22**: 2201-2210 [PMID: 22661019 DOI: 10.1007/s00330-012-2475-5]
- 35 **Beyersdorff D**, Taymoorian K, Knösel T, Schnorr D, Felix R, Hamm B, Bruhn H. MRI of prostate cancer at 1.5 and 3.0 T: comparison of image quality in tumor detection and staging. *AJR Am J Roentgenol* 2005; **185**: 1214-1220 [PMID: 16247137 DOI: 10.2214/AJR.04.1584]
- 36 **Lee SH**, Park KK, Choi KH, Lim BJ, Kim JH, Lee SW, Chung BH.

Is endorectal coil necessary for the staging of clinically localized prostate cancer? Comparison of non-endorectal versus endorectal

MR imaging. *World J Urol* 2010; **28**: 667-672 [PMID: 20623288
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Transurethral bipolar prostatectomy: Where do we stand now?

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its effective long term results with low incidence of complications. Far away from excellence, it associated with blood loss, and TUR syndrome particularly in patients with larger prostates. For this reasons, many minimally invasive new techniques have been implemented in recent years. Bipolar technique has recently been introduced, to minimize the complications of the standard TURP technique.

Key words: Transurethral; Endoscopic; Benign prostatic hyperplasia; Bipolar; Prostatectomy

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Core tip: This is a review article about the current status of clinical applications of bipolar technology for endoscopic treatment of bladder outlet obstruction caused by benign prostatic hyperplasia. Also contains valuable updated comparisons to the transurethral resection of the prostate procedure using monopolar technology.

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Abstract

Transurethral resection of the prostate (TURP) is considered the gold standard surgical treatment of symptomatic benign prostatic hyperplasia. TURP has gained ground in urologic centers of excellence for

INTRODUCTION

Transurethral resection of the prostate (TURP) is considered the gold standard surgical treatment of symptomatic benign prostatic hyperplasia^[1].

TURP has gained ground in urologic centers of excellence for its effective long term results with low incidence of complications^[2]. Far away from excellence, it associated with blood loss, and TUR syndrome

particularly in patients with larger prostates^[3] particularly in patients with larger prostates^[4].

For this reasons, many minimally invasive new techniques have been implemented in recent years^[5]. Bipolar technique has recently been introduced, to minimize the complications of the standard TURP technique^[6].

BASIC PRINCIPLES AND PHYSICS

In bipolar electro surgery, the same electrode contains both the active and passive poles and the energy is confined to the site of surgery. While the standard monopolar technique, the energy travel through the body toward skin pad. Also monopolar systems require more voltage to produce its effect. Advanced bipolar systems can modify the voltage delivered to the tissue according to the tissue reaction during resection^[7].

The main advantage of the bipolar technique that we can use normal saline as an irrigation fluid while in the standard monopolar technique we can use glycine, sorbitol, and mannitol as irrigation fluids. This will avoid the incidence of dilutional hyponatremia and TUR syndrome increasing the safety profile of the surgery even in large prostate^[7].

The first bipolar TURP system was developed in the 1990s using the PlasmaKinetic® (PK) technology (Gyrus-ACMI, South-borough, MA) and consisted of a vaporizing electrode (PK V electrode) using saline as an irrigating fluid. The invention of the current 4-mm loop configuration electrode improved this technique^[7].

The loop in bipolar system made of platinum iridium to withstand the electrical and thermal stresses of plasma, while in the standard monopolar technique; it is made of tungsten.

In the bipolar technique, the mechanism for coagulation starts by dissipation of the energy as heat within the vessel walls; a coagulum will be formed from the blood and the tissues to seal the bleeding vessel. This will be associated with white blanching of tissue indicating the formation of coagulum and shrinkage of the collagen. The lower voltage and temperatures minimizes charring of the tissue^[7].

In the standard TURP technique, no enough time is available to do simultaneous hemostasis during resection. The reduced voltage in bipolar technique provides time to do simultaneous hemostasis during the resection^[7].

Three technique of bipolar prostatectomy are available; the first technique is Bipolar plasma vaporization which requires a bipolar high-frequency generator with the power output set at 290W and 120W for vaporisation and coagulation modes, respectively. A continuous-flow irrigation is mandatory to improve the visibility and elimination of bubbles associated with vaporization. The technique starts at the bladder neck, then the lateral lobes followed by the anterior lobe, and, at the end, the apical part of the prostate^[8]. The second technique is Enucleation (Plasmakineticenucleation of the prostate)

which is similar to HoLEP, and it was previously designed by Hochreiter *et al*^[9]. Bladder irrigation is necessary until hematuria sufficiently resolved^[10]. The third technique is Bipolar TUR-P (TURIS) which is similar to monopolar TURP^[11].

DISCUSSION

According to the data from 10 randomized controlled trials comparing bipolar technique and the standard TURP technique which were analyzed by Ahyai *et al*^[11], the amount of resected tissue was not statistically significantly between the two techniques^[12,13]. Also, the functional outcome in terms of symptoms score, Q max, PVRU and quality of life was not statistically significantly between the two techniques. Pressure flow study showed similar results at 12 mo after the two techniques^[14].

The length of catheter time after monopolar TURP appeared slightly longer compared to the bipolar technique. Blood loss and blood transfusion was comparable in both techniques. TUR syndrome was not reported as a complication after the bipolar technique. The operation time was always more than one hour, and with the resected tissue did less than 37 g^[15]. Postoperative urinary retention, clot retention, and UTI were significantly less common in bipolar technique than in the mono polar technique^[15].

Three studies showed a higher incidence of stricture formation in the bipolar technique after one year follow up^[15-17] while two studies showed similar results between the two techniques^[13,18].

Mamoulakis *et al*^[19] in their Meta analysis 2009 concluded that bipolar TURP had higher safety profile than the mono polar technique on the short term follow up data while long term follow up data is still missing particularly the incidence of urethral stricture.

According to four randomized controlled trials done between 2003 and 2007, with follow up data available at 3 year^[20-23], the change in IPSS, QoL, and PVRU was comparable between the two techniques. The improvement of Qmax was statistically significant in favor of TURP.

The catheter time was longer after mono polar technique compared to the bipolar technique (mean: 2.8 d vs 1.3 d). Intra operative and peri operative complications were more statistically significant in the standard mono polar TURP compared to the bipolar TURP. Postoperative AUR was relatively higher in the bipolar technique compared to the mono polar technique. Fung *et al*^[12] and Dunsmuir *et al*^[20] reported AUR rates following the bipolar technique of 19% and 30%, respectively. Eleven percent incidence of clot retention has been reported in the bipolar technique^[22].

According to the study of Kaya *et al*^[23] with 3 year of follow-up, the improvement in IPSS and Qmax were significantly worse and that the need for secondary surgery was significantly more after bipolar technique (12%) compared to the monopolar technique (6.6%).

However, this study has limitations of small sized sample 15 monopolar techniques vs 25 bipolar techniques^[23].

Tefekli *et al*^[21] at a mean follow-up of one and half a year, demonstrated that postoperative severe storage symptoms, acute urinary retention, and urethral stricture formation were higher in the bipolar technique compared to the monopolar technique^[21].

A recently published randomized controlled study was published by Komura *et al*^[24] in 2014 comparing conventional monopolar TURP to TUR is in 136 patients and they concluded that urethral stricture was significantly higher with TUR is especially in patients with prostate volumes larger than 70 gm. Those findings are interesting and are contrasting with the findings of Fagerström *et al*^[25] in 2011 which show no difference in complications after both procedures.

CONCLUSION

Although the short term outcome efficacy and safety profile of bipolar TURP is promising, however the midterm clinical outcome is fair and the long term outcome need further multicentre RCTs with long-term follow up data.

REFERENCES

1. Wei JT, Calhoun E, Jacobsen SJ. Urologic diseases in America project: benign prostatic hyperplasia. *J Urol* 2005; **173**: 1256-1261 [PMID: 15758764 DOI: 10.1097/01.ju.0000155709.37840.f]
2. Thomas AW, Cannon A, Bartlett E, Ellis-Jones J, Abrams P. The natural history of lower urinary tract dysfunction in men: minimum 10-year urodynamic followup of transurethral resection of prostate for bladder outlet obstruction. *J Urol* 2005; **174**: 1887-1891 [PMID: 16217330 DOI: 10.1097/01.ju.0000176740.76061.24]
3. Rassweiler J, Teber D, Kuntz R, Hofmann R. Complications of transurethral resection of the prostate (TURP)--incidence, management, and prevention. *Eur Urol* 2006; **50**: 969-979; discussion 980 [PMID: 16469429 DOI: 10.1016/j.eururo.2005.12.042]
4. Reich O, Gratzke C, Bachmann A, Seitz M, Schlenker B, Hermanek P, Lack N, Stief CG. Morbidity, mortality and early outcome of transurethral resection of the prostate: a prospective multicenter evaluation of 10,654 patients. *J Urol* 2008; **180**: 246-249 [PMID: 18499179 DOI: 10.1016/j.juro.2008.03.058]
5. Yu X, Elliott SP, Wilt TJ, McBean AM. Practice patterns in benign prostatic hyperplasia surgical therapy: the dramatic increase in minimally invasive technologies. *J Urol* 2008; **180**: 241-245; discussion 245 [PMID: 18499180 DOI: 10.1016/j.juro.2008.03.039]
6. Alschibaja M, May F, Treiber U, Paul R, Hartung R. Recent improvements in transurethral high-frequency electrosurgery of the prostate. *BJU Int* 2006; **97**: 243-246 [PMID: 16430621 DOI: 10.1111/j.1464-410X.2006.05872.x]
7. Tubaro A. BPH treatment: a paradigm shift. *Eur Urol* 2006; **49**: 939-941 [PMID: 16647187]
8. Reich O, Schlenker B, Gratzke C, Tilki D, Riecken M, Stief C, Seitz M, Bachmann A. Plasma vaporisation of the prostate: initial clinical results. *Eur Urol* 2010; **57**: 693-697 [PMID: 19482414 DOI: 10.1016/j.eururo.2009.05.031]
9. Hochreiter WW, Thalmann GN, Burkhard FC, Studer UE. Holmium laser enucleation of the prostate combined with electrocautery resection: the mushroom technique. *J Urol* 2002; **168**: 1470-1474 [PMID: 12352420 DOI: 10.1016/S0022-5347(05)64476-X]
10. Liu C, Zheng S, Li H, Xu K. Transurethral enucleation and resection of prostate in patients with benign prostatic hyperplasia by plasma kinetics. *J Urol* 2010; **184**: 2440-2445 [PMID: 20952005 DOI: 10.1016/j.juro.2010.08.037]
11. Ahyai SA, Gilling P, Kaplan SA, Kuntz RM, Madersbacher S, Montorsi F, Speakman MJ, Stief CG. Meta-analysis of functional outcomes and complications following transurethral procedures for lower urinary tract symptoms resulting from benign prostatic enlargement. *Eur Urol* 2010; **58**: 384-397 [PMID: 20825758 DOI: 10.1016/j.eururo.2010.06.005]
12. Fung BT, Li SK, Yu CF, Lau BE, Hou SS. Prospective randomized controlled trial comparing plasmakinetic vaporessection and conventional transurethral resection of the prostate. *Asian J Surg* 2005; **28**: 24-28 [PMID: 15691793 DOI: 10.1016/S1015-9584(09)60253-0]
13. Michielsen DP, Debacker T, De Boe V, Van Lersberghe C, Kaufman L, Braeckman JG, Amy JJ, Keuppens FI. Bipolar transurethral resection in saline--an alternative surgical treatment for bladder outlet obstruction? *J Urol* 2007; **178**: 2035-2039; discussion 2039 [PMID: 17869297]
14. Iori F, Franco G, Leonardo C, Laurenti C, Tubaro A, D-Amico F, Dini D, De Nunzio C. Bipolar transurethral resection of prostate: clinical and urodynamic evaluation. *Urology* 2008; **71**: 252-255 [PMID: 18308095 DOI: 10.1016/j.urolgy.2007.09.064]
15. Seckiner I, Yesilli C, Akduman B, Altan K, Mungan NA. A prospective randomized study for comparing bipolar plasmakinetic resection of the prostate with standard TURP. *Urol Int* 2006; **76**: 139-143 [PMID: 16493215 DOI: 10.1159/000090877]
16. Nuhoglu B, Ayyildiz A, Karaguzel E, Cebeci O, Germiyanoglu C. Plasmakinetic prostate resection in the treatment of benign prostate hyperplasia: results of 1-year follow up. *Int J Urol* 2006; **13**: 21-24 [PMID: 16448427 DOI: 10.1111/j.1442-2042.2006.01218.x]
17. Ho HS, Yip SK, Lim KB, Fook S, Foo KT, Cheng CW. A prospective randomized study comparing monopolar and bipolar transurethral resection of prostate using transurethral resection in saline (TURIS) system. *Eur Urol* 2007; **52**: 517-522 [PMID: 17416453]
18. Autorino R, De Sio M, D'Armiento M. Bipolar plasmakinetic technology for the treatment of symptomatic benign prostatic hyperplasia: evidence beyond marketing hype? *BJU Int* 2007; **100**: 983-985 [PMID: 17578467]
19. Mamoulakis C, Ubbink DT, de la Rosette JJ. Bipolar versus monopolar transurethral resection of the prostate: a systematic review and meta-analysis of randomized controlled trials. *Eur Urol* 2009; **56**: 798-809 [PMID: 19595501]
20. Dunsmuir WD, McFarlane JP, Tan A, Dowling C, Downie J, Kourambas J, Donnellan S, Redgrave N, Fletcher R, Frydenberg M, Love C. Gyrus bipolar electrovaporization vs transurethral resection of the prostate: a randomized prospective single-blind trial with 1 y follow-up. *Prostate Cancer Prostatic Dis* 2003; **6**: 182-186 [PMID: 12806380 DOI: 10.1038/sj.pcan.4500631]
21. Tefekli A, Muslumanoglu AY, Baykal M, Binbay M, Tas A, Altunrende F. A hybrid technique using bipolar energy in transurethral prostate surgery: a prospective, randomized comparison. *J Urol* 2005; **174**: 1339-1343 [PMID: 16145415 DOI: 10.1097/01.ju.0000173075.62504.73]
22. Hon NH, Brathwaite D, Hussain Z, Ghiblawi S, Brace H, Hayne D, Coppinger SW. A prospective, randomized trial comparing conventional transurethral prostate resection with PlasmaKinetic vaporization of the prostate: physiological changes, early complications and long-term followup. *J Urol* 2006; **176**: 205-209 [PMID: 16753403 DOI: 10.1016/S0022-5347(06)00492-7]
23. Kaya C, Ilktac A, Gokmen E, Ozturk M, Karaman IM. The long-term results of transurethral vaporization of the prostate using plasmakinetic energy. *BJU Int* 2007; **99**: 845-848 [PMID: 17378844 DOI: 10.1111/j.1464-410X.2006.06683.x]
24. Komura K, Inamoto T, Takai T, Uchimoto T, Saito K, Tanda N, Minami K, Oide R, Uehara H, Takahara K, Hirano H, Nomi H, Kiyama S, Watsuji T, Azuma H. Higher Incidence of Urethral Stricture after Bipolar Transurethral Resection of the Prostate Using TURis? - Results from a Randomized Trial. *BJU Int* 2014 Jun 9; Epub ahead of print [PMID: 24909399 DOI: 10.1111/bju.12831]

- 25 **Fagerström T**, Nyman CR, Hahn RG. Complications and clinical outcome 18 months after bipolar and monopolar transurethral

resection of the prostate. *J Endourol* 2011; **25**: 1043-1049 [PMID: 21568691 DOI: 10.1089/end.2010.0714]

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Observational Study

Role of PCA3 test in clinical decision making for prostate cancer diagnosis

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Abstract

AIM: To assess the role of PCA3 urine test in the management of patients with suspected prostate cancer after repeat negative prostate biopsies.

METHODS: Patients with suspected prostate cancer either

due to high or rising prostate specific antigen (PSA) levels and with a history of prostate biopsy who were candidates for repeat procedure were prospectively recruited to undergo PCA3 urine test. The recommendations on further management including the decision whether to proceed or not to the biopsy were made based on the PCA3 score. Patients' adherence with the recommendations and influence of the PCA3 test on clinical decision making were assessed. The contribution of the multivariate model was measured with a decision curve analysis.

RESULTS: Three hundred and fifty-six patients were recruited to the study and underwent the PCA3 test. Twenty-six percent of 263 patients underwent prostate biopsy despite the low risk designation by PCA3 and 30% of 93 men did not proceed to biopsy despite a high risk result, rendering overall adherence of 73%. The variables that significantly correlated with adherence were positive family history of prostate cancer and PSA more than 10 ng/mL. Pre-test clinical stage, the number and the results of previous biopsies were not associated with the adherence. The decision curve analysis gave identical results for cut-off points of 25 and 35. On multivariate analysis the model that included PCA3 score, serum PSA, family history and result of the previous biopsy best performed with Area Under the Curve of 0.77.

CONCLUSION: PCA3 urine test markedly outperforms PSA in a repeat biopsy setting. Urologists and patients demonstrate substantial confidence in this analysis and tend to follow its recommendations.

Key words: Prostate cancer; Prostate biopsy; Prostate specific antigen; PCA3; Decision making

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Core tip: PCA3 is a molecular urine test, which is performed

in patients with high risk for prostate cancer. In this international prospective study we demonstrate that it has better performance than routine serum prostate specific antigen test in men with previously negative prostate biopsies. We also show that patients and physicians tend to follow the recommendations for this test.

Yutkin V, Al-Zahrani A, Williams A, Hidas G, Martinez C, Izawa J, Pode D, Chin J. Role of PCA3 test in clinical decision making for prostate cancer diagnosis. *World J Clin Urol* 2015; 4(1): 68-74 Available from: URL: <http://www.wjgnet.com/2219-2816/full/v4/i1/68.htm> DOI: <http://dx.doi.org/10.5410/wjcu.v4.i1.68>

INTRODUCTION

In recent years we have witnessed increasing debate involving the role of prostate specific antigen (PSA)-based screening in prostate cancer diagnosis, mainly following the seminal publications from the ERSPC^[1] and the PLCO^[2] trials. Following these and other publications, urologists have found themselves in urgent need for non-invasive diagnostic tools, in addition to PSA, in order to properly counsel their patients. The population which seems to be most in need of such tests are the patients with a high level of clinical suspicion for malignancy in spite of a prior negative biopsy, *i.e.*, high or rising PSA following the first biopsy, or finding of multifocal high grade prostatic intraepithelial neoplasia (HGPIN) or atypical small acinar proliferation (ASAP) on previous biopsy^[3]. It has been shown that the probability of finding cancer on repeat biopsy approaches 30% and different strategies have been proposed to increase its yield^[4]. On the other hand, the biopsy can be a very emotionally and physically disturbing event to the patient. This may be due to the discomfort during or following the procedure^[5] or risk of more serious complications including sepsis and bleeding^[6]. Therefore, much effort has been put into improving the predictive value of existing tests and into searching for a new biomarkers.

PCA3 is a non-transcribed product of the *DD3* gene detected in urine. It has shown superior sensitivity and specificity over serum PSA in predicting prostate cancer both in patients after repeat prostate biopsies^[7] and as a pre-biopsy screening tool^[8]. Consequently, the PCA3 test was approved for use in the European Union, and recently in United States by the Food and Drug Administration. Nevertheless, the place of PCA3 in the management algorithm of patients with suspected or proven prostate cancer^[9] is still under debate. The primary objective of this study was to explore the influence of PCA3 urine test on the shared decision process between the urologist and the patient and their adherence with the test's recommendations, with the aim of assisting this tandem in resolving the issue of performing repeat prostate biopsies. The

secondary objective of the study was to assess the performance of the test in a heterogeneous population of the patients at risk for prostate cancer.

MATERIALS AND METHODS

Patients and PCA3 assay

The study was performed at two sites: Western University, London, Ontario, Canada, and the Hadassah and Hebrew University Medical Center, Jerusalem, Israel. The patients were recruited prospectively between October 2007 and September 2011, after institutional ethics review boards of the respective institutions approved the study protocol independently. The urine PCA3 score test was performed in men fitting the following inclusion criteria: (1) previous benign result on prostate biopsy and PSA greater than 2.5 ng/mL or rising, compared to previous values; or (2) finding of ASAP or multifocal (two or more foci) HGPIN in the previous prostate biopsy. The first catch urine sample (20-30 mL after gentle prostate massage-3 lateral to medial strokes on each prostate lobe) of the participants was obtained. The analysis in both institutions was performed with the Gen-Probe® ProgenSA™ PCA3 assay^[10] according to the manufacturer's instructions. Subsequent management was planned by the urologist who referred the patient for the PCA3 test in concert with the patient and the decision regarding whether to perform the prostate biopsy was made. The biopsy consisted of 10 to 12-cores with trans-rectal ultrasound guidance. A PCA3 score of 35 or higher was considered as a higher probability of having a subsequent positive biopsy^[7]. The influence of the PCA3 test on clinical decision making was judged by concordance between the PCA3 score and subsequent management; *i.e.*, if the patient had a PCA3 score lower than 35 (as these were the manufacturer recommendations at that time) and underwent the prostate biopsy, the decision was judged as discordant. If the patient had a PCA3 score higher than 34 and underwent the prostate biopsy, the decision was judged as concordant.

Statistical analysis

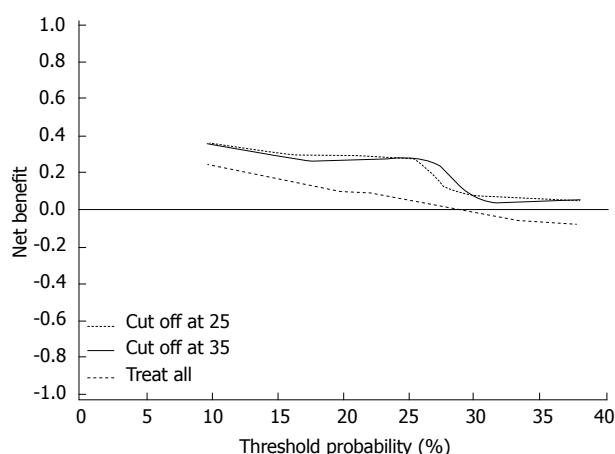
Receiver Operating Characteristic (ROC) curves were constructed to assess PCA3 as a predictive factor compared with PSA. Logistic regression was used to evaluate the association between PCA3 and patient characteristics with biopsy outcomes. A multivariable logistic regression model was used to evaluate the effect of PCA3 on biopsy outcome adjusting for significant patient outcomes. The software used was SAS version 9.3 (SAS Institute, Cary, NC, United States). A *P* value less than 0.05 was considered as significant.

A decision curve analysis (DCA) was performed^[11] to assess whether the multivariable model offers a benefit to the patient in the decision making process over PCA3 alone. The DCA was constructed by plotting the net benefit (based on the true positive and the

Table 1 Univariable and multivariable association with the adherence with the test recommendations

	Adherent		Univariable		Multivariable	
	No (<i>n</i> = 96)	Yes (<i>n</i> = 260)	OR (95%CI)	<i>P</i> value	OR (95%CI)	<i>P</i> value
Age [mean (SD)]	63.3 (6.2)	62.5 (6.8)	0.98 (0.95, 1.02)	0.29		NS
Number of previous biopsies [mean (SD)]	2.04 (1.12)	2.01 (1.08)	0.97 (0.79, 1.20)	0.794		NS
Biopsy last result-HGPIN/ASAP	24 (25.0%)	64 (24.7%)	0.99 (0.57, 1.69)	0.955		NS
Family history	4 (4.2%)	38 (14.7%)	3.96 (1.37, 11.40)	0.011	3.80 (1.31, 11.05)	0.014
Last PSA $\geq$ 10	41 (42.7%)	59 (22.8%)	0.40 (0.24, 0.65)	< 0.001	0.40 (0.24, 0.67)	< 0.001

HGPIN: High grade prostate intraepithelial neoplasia; ASAP: Atypical small acinar proliferation; PSA: Prostate specific antigen; OR: Odds ratio; NS: Not significant; SD: Standard deviation.

**Figure 1** Decision curve analysis.

false positive results of the test) of the PCA3 test against threshold probability of prostate cancer, at which the physician or patient would opt for a prostate biopsy. The optimal probability was set as the point with the maximum difference in the net benefit between treating all patients and treating the patients according to our model. The prediction model was created by adjusting the associated characteristics, allowing for entry of family history of prostate cancer, prior biopsy result and clinical stage.

RESULTS

Patient characteristics

Data on 356 patients from two centers were available for the analysis (170 from Canada and 186 from Israel). The median age was 63 (46-81) years. The majority of the men (256; 72%) had a benign histology on the biopsy prior to the PCA3 testing. An additional 100 (28%) had either multifocal HG PIN or ASAP. All patients underwent prostate biopsy before PCA3 test: 258 had 1 or 2 biopsies, 84 had 3 or 4 biopsies and 14 men had 5 or more biopsies. Forty one (11.5%) patients had a positive family history of prostate malignancy and 33 (9.3%) were currently on a 5- α reductase inhibitor for obstructive urinary symptoms.

Decision making

Two hundred and sixty-three patients (74%) had a

PCA3 score that put them in the lower risk group; despite that 68 (26%) men from this group underwent prostate biopsy following the PCA3 testing. Conversely, out of 93 men with a PCA3 score in the higher risk group for having prostate cancer, 65 (70%) underwent prostate biopsy in the subsequent follow up period of at least 6 mo. Thus, 260 (73%) patients were adherent with the PCA3 results recommendations and 96 (27%) were non-adherent. On the univariable analysis only a positive family history of prostate cancer and pre-test PSA value (both as a continuous variable and as a value greater than 10 ng/mL) demonstrated significant association with the adherence. These findings were confirmed on the multivariate model (Table 1).

We performed a decision curve analysis^[11] of the PCA3 test: for practical purposes, we assumed that the maximal threshold probability of having cancer on prostate biopsy was 40%, and the probability of finding HGPIN or ASAP on post-test biopsies was 37.1% (49/132). We found no difference in the net benefit with various threshold probabilities for the patients between two PCA3 score cut-off points: of 25 and 35. The optimal probability occurred at approximately 25% for both cut-off points (Figure 1).

PCA3 test performance

The distribution of the post-PCA3 prostate biopsy results according to the PCA3 score is shown in Table 2. Prostate cancer was found in 44 patients, 15 of them with PCA3 less than 35. We did not find any correlation of the biopsy results with presence of inflammation (either chronic or acute), prostate gland size (as per TRUS) or with the history of 5 α -reductase inhibitors intake.

The sensitivity and specificity of the PCA3 test were 63.6% (95%CI: 47.8-77.6) and 63.0% (95%CI: 52.3-72.9), respectively with a cutoff point of 35, and 77.3% (95%CI: 62.2-88.5) and 48.9% (95%CI: 38.3-59.6), respectively with a cutoff point of 25. Univariable associations of post-PCA3 test biopsy results with different PCA3 cutoff points and other variables including various PSA levels are presented in Table 3. We found that biopsy results correlated with PCA3 score, family history of PCa, clinical stage more than T1c and existence of multifocal HGPIN or ASAP on previous biopsy. The odds ratios for univariable

Table 2 Distribution of biopsy results according to PCA3 test results

	PCA3	
	< 35	≥ 35
Biopsy after PCA3 test		
Not done	195	28
Done		
Normal	45	22
HGPIN/ASAP	8	14
CAP	15	29
Total	68	65
Total	263	93

HGPIN/ASAP: High grade prostatic intraepithelial neoplasia/atypical small acinar proliferation; CAP: Carcinoma of prostate.

association of PCA3 score with biopsy result were 2.99 (95%CI: 1.42-6.30, $P = 0.004$) for a cutoff point of 35 and 3.26 (95%CI: 1.44-7.35, $P = 0.005$) for a cutoff point of 25.

The ROC analysis performed for PSA and PCA3 revealed an Area Under the Curve (AUC) of 0.50 and 0.70, respectively (Figure 2).

Multivariable analysis was performed with the aim to determine the best model that predicts a biopsy result based on the pretest data. The best performing model included PCA3-score, serum PSA value (both as a continuous variable without particular cutoff points), positive family history of prostate cancer and finding on previous biopsy of HGPIN or ASAP. This model had an AUC of 0.77.

Out of 223 patients who did not perform post-PCA3 prostate biopsy, 89 had serum PSA levels available with at least 6 mo follow-up. The mean PSA levels dropped in this population from 7.86 to 6.22 ng/dL ($P = 0.003$). There were no patients with rising PSA levels during this follow-up period and there was no significant difference in the levels in the free-to-total PSA ratio between patients who underwent biopsy and those who did not.

DISCUSSION

In this study the participants mirrored the typical patient population most practicing urologists commonly face: men with high baseline or rising PSA in whom prostate biopsies showed either normal result, HGPIN or ASAP. These patients consume significant amount of ambulatory services with frequent tests and office visits. Unfortunately, despite significant health resource expenditures, the patient's anxiety is not alleviated and their diagnosis remains equivocal. Herein, we summarized our experience with PCA3 test in an international patient cohort focusing on decision patterns of the patient-urologist tandem and on the PCA3 performance. We also searched for the best model to accurately predict the actual pathology of the prostate biopsy and analyzed it using decision curve

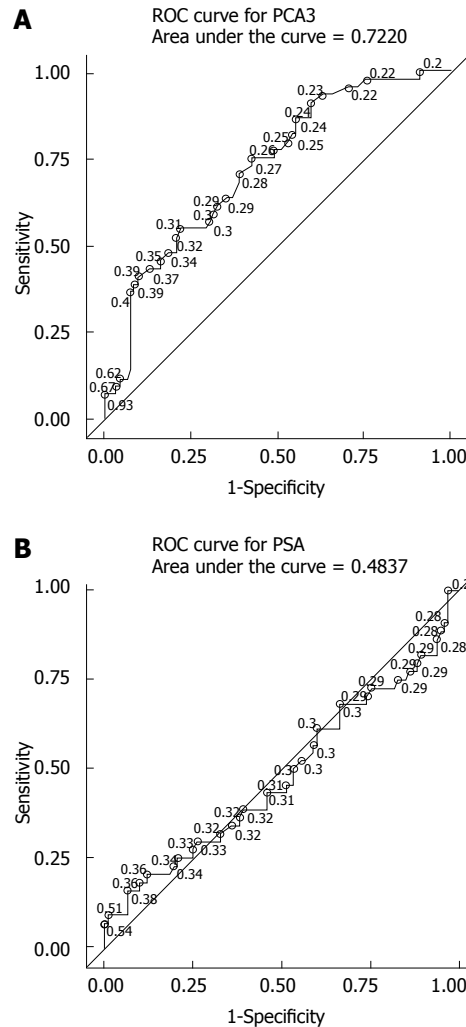


Figure 2 Receiver operating characteristic curve analysis. A: PCA3 test; B: Prostate specific antigen test. ROC: Receiver operating characteristic; PSA: Prostate specific antigen.

analysis method.

Most published experience with PCA3 testing refers to patients facing repeat prostate biopsies for various reasons^[7,12]. In an effort to eliminate the obvious selection bias, Roobol *et al*^[8] analyzed the PCA3 performance in the pre-screened patient population and found it compared favorably with PSA. In this study we employed similar approach: we included both patients after a previous normal biopsies and patients who were potential candidates for repeat biopsy based on previous finding of multifocal HG PIN or ASAP. However, unlike in previous studies, we did not aim to biopsy all participants but rather left this decision to the discretion of the treating urologist and the patient. Using this approach, only 133 (37.5%) patients proceeded towards prostate biopsy. Sixty eight (51%) of them did so despite a PCA3 score less than 35, which was considered "low risk" according to the manufacturer's recommendations at that time. With 263 men overall having a PCA3 score less than 35, it implies that 26% of men and/or their urologists

Table 3 Univariable associations with post PCA3 biopsy result

	Post PCA3 biopsy result		OR (95%CI)	P value
	Normal benign (n = 88)	CAP (n = 44)		
PCA3 [Mean (SD)]	34.8 (34.6)	73.3 (84.6)	1.02 (1.01, 1.02)	0.003
PCA3 > 15.0	57 (64.8%)	40 (90.9%)	5.44 (1.78, 16.62)	0.003
PCA3 > 20.0	52 (59.1%)	37 (84.1%)	3.66 (1.47, 9.12)	0.005
PCA3 > 25.0	46 (52.3%)	34 (77.3%)	3.10 (1.37, 7.05)	0.007
PCA3 > 35.0	35 (39.8%)	29 (65.9%)	2.93 (1.38, 6.23)	0.005
PSA [Mean (SD)]	9.3 (5.1)	11.4 (10.1)	1.04 (0.99, 1.09)	0.126
PSA > 4.0	86 (97.7%)	42 (95.5%)	0.49 (0.07, 3.59)	0.481
PSA > 7.5	48 (54.6%)	22 (50.0%)	0.83 (0.40, 1.72)	0.622
Inflammation	28 (31.8%)	16 (36.4%)	1.22 (0.57, 2.62)	0.602
Family history	4 (4.6%)	7 (15.9%)	3.97 (1.10, 14.40)	0.036
Last biopsy result-HGPIN/ASAP	24 (27.3%)	25 (56.8%)	3.51 (1.64, 7.49)	0.001
Abnormal DRE	13 (14.8%)	14 (31.8%)	2.69 (1.13, 6.40)	0.025

HGPIN/ASAP: High grade prostatic intraepithelial neoplasia/atypical small acinar proliferation; CAP: Carcinoma of prostate; DRE: Digital rectal examination; SD: Standard deviation.

decided to perform the biopsy despite the test result, rendering adherence with the recommendations with a negative test result of 74%. Conversely, 93 participants had a PCA3 score more than 34, but only 65 of them eventually underwent prostate biopsies, yielding an adherence rate with a positive test result of 70%. This is substantially lower than the figure reported by van Vugt *et al.*^[13]—these investigators had a compliance rate of 96% when the biopsy was recommended based on PSA level, digital rectal examination and trans-rectal ultrasound findings. On the other hand, the compliance with the “no biopsy” recommendation in their report was similar to ours: 64% and 74%, respectively. Our results probably reflect general reluctance of both the patients and physicians to proceed to the invasive procedures, as well as the variable confidence level in the PCA3 score results. Noteworthy, in our cohort all patients already underwent at least one prostate biopsy, thus the uncertainty and level of anxiety of being diagnosed with malignancy were lower than in the report by van Vugt *et al.*^[13], reducing even more the tendency to perform a biopsy.

Nevertheless, we found that the overall concordance of the final decision with the PCA3 score result, based on cut-off level of 35, was 73%, *i.e.*, three quarters of the men made a choice to proceed or not with a biopsy in agreement with PCA3 result (*i.e.*, PCA3 < 35: no biopsy performed, PCA3 ≥ 35: biopsy performed). In our opinion, this indicates some reliance on the test.

Results of our evaluation of the PCA3 test performance were similar to previously published data. The specificity and sensitivity using the manufacturer’s previously recommended cut-off point were 63.0% and 63.6%, respectively. Lowering the threshold to recently published FDA recommended 25 level obviously improved the sensitivity (77.3%) at the expense of specificity (48.9%). In univariable analysis, we found that the AUC for PCA3 was 0.70 as opposed to 0.50 for PSA. Obviously, the influence of selection bias has to be taken into account here, as all our patients already

had been pre-screened with PSA and prostate biopsies with no finding of invasive carcinoma. According to the multivariable analysis, the model with a PCA3 cut-off level of 25 provided a somewhat better AUC than the model with a level of 35: 0.73 and 0.71, respectively. Interestingly, the analysis of these prediction models using DCA demonstrated virtually identical net benefit of using the test with cut-off points of 25 and 35.

This inevitable trade-off between sensitivity and specificity by means of changing the threshold level has been dealt with previously and the optimal cut-off point for the PCA3 score remains moot. Hence, we considered using the PCA3 score in our multivariable models in a continuous fashion, instead of searching for the optimal cut-off value. Interestingly, similar to the finding by Klatte *et al.*^[14], we also found that using PCA3 score continuously in the multivariable model yielded the best results, predicting the prostate biopsy results with AUC of 0.77. Other variables included in this model were PSA level (likewise in a continuous fashion), family history of prostate cancer, and previous finding of HG PIN/ASAP on prostate biopsy. Previously published externally validated multivariable prediction models^[15] included, in addition to PCA3 score and PSA in their analysis (1) race, age, family history, digital rectal examination (DRE) and the result of previous prostate biopsy^[16] and (2) age, DRE, prostate volume and prior biopsy result^[17]. In the first study^[16], the PCA3 was incorporated into the Prostate Cancer Prevention Trial calculator^[18] and the prostate risk was calculated both on an internal cohort of 521 patients and externally validated on an additional 443 patients. The cut-off PCA3 value used here was 25 with a resultant AUC of 0.696. In the second trial^[17] of 1206 men, the authors examined three different PCA3 threshold scores: 17, 24 and 35 and concluded that the nomogram best performed using the PCA3 score of 17.

That being said, it should be mentioned that the recommended approach to the high-risk men with previous negative prostate biopsy is to perform a

saturation biopsy (TRUS or trans-perineal) or to use the multiparametric MRI followed by prostate biopsy according to the findings^[19]. Indeed, many of our patients did undergo MRI of the pelvis (data not shown), but the access to this test by the patients was hindered by the fact that it is not included in the health basket in both countries.

In this international prospective study we demonstrate that the urine PCA3 test has substantial influence on the pattern of decision making when considering a repeat prostate biopsy in patients suspected of having the prostate cancer. Most patients and urologists tend to follow the test results' recommendations. In addition, we confirm the superior performance of PCA3 score test in this population, relative to serum PSA alone.

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COMMENTS

Background

The currently used tumor marker for early detection of prostate cancer is a serum prostate specific antigen (PSA). Due to its relatively low specificity many men are undergoing repeat prostate biopsies, which are usually triggered by rising PSA levels or unfavorable pathology (HG PIN or ASAP). PCA3 is a urine tumor marker that reportedly has higher specificity for prediction of prostate cancer on biopsy.

Research frontiers

PCA3 is a relatively new test and many community urologists are unfamiliar with its applications. In this field the research hotspot is to clarify the value of this test in clinical practice and further explore its clinical relevance in international cohort of men.

Innovations and breakthroughs

In this study the authors demonstrate that approximately three quarters of physicians and patients follow the recommendations on the PCA3 test results. Moreover, the performance of the PCA3 test was significantly better than that of PSA serum test.

Applications

The urine PCA3 test can be used as a better predictor of a prostate malignancy in population with low PSA test performance: after previous prostate biopsies, finding of multiple HG PIN or ASAP.

Terminology

PCA3 urine test: the urine test that is specific for prostate cancer and can be used in conjunction with PSA test or as its replacement. PSA: a prostate produced protein that gains access to the blood in number of prostate benign and malignant conditions.

Peer-review

Very good article which adds doctor adherence and pt compliance to PCA3 testing.

REFERENCES

- Schröder FH, Hugosson J, Roobol MJ, Tammela TL, Ciatto S, Nelen V, Kwiatkowski M, Lujan M, Lilja H, Zappa M, Denis LJ, Recker F, Berenguer A, Mänttinen L, Bangma CH, Aus G, Villers A, Rebillard X, van der Kwast T, Blijenberg BG, Moss SM, de Koning HJ, Auvinen A. Screening and prostate-cancer mortality in a randomized European study. *N Engl J Med* 2009; **360**: 1320-1328 [PMID: 19297566 DOI: 10.1056/NEJMoa0810084]
- Andriole GL, Crawford ED, Grubb RL, Buys SS, Chia D, Church TR, Fouad MN, Gelmann EP, Kvale PA, Reding DJ, Weissfeld JL, Yokochi LA, O'Brien B, Clapp JD, Rathmell JM, Riley TL, Hayes RB, Kramer BS, Izmirlian G, Miller AB, Pinsky PF, Prorok PC, Gohagan JK, Berg CD. Mortality results from a randomized prostate-cancer screening trial. *N Engl J Med* 2009; **360**: 1310-1319 [PMID: 19297565 DOI: 10.1056/NEJMoa0810696]
- Epstein JI, Herawi M. Prostate needle biopsies containing prostatic intraepithelial neoplasia or atypical foci suspicious for carcinoma: implications for patient care. *J Urol* 2006; **175**: 820-834 [PMID: 16469560 DOI: 10.1016/S0022-5347(05)00337-X]
- Chun FK, Epstein JI, Ficarra V, Freedland SJ, Montironi R, Montorsi F, Shariat SF, Schröder FH, Scattoni V. Optimizing performance and interpretation of prostate biopsy: a critical analysis of the literature. *Eur Urol* 2010; **58**: 851-864 [PMID: 20884114 DOI: 10.1016/j.eururo.2010.08.041]
- Seymour H, Perry MJ, Lee-Elliott C, Dundas D, Patel U. Pain after transrectal ultrasonography-guided prostate biopsy: the advantages of periprostatic local anaesthesia. *BJU Int* 2001; **88**: 540-544 [PMID: 11678747 DOI: 10.1046/j.1464-410X.2001.02324.x]
- Blana A, Murat FJ, Walter B, Thuroff S, Wieland WF, Chaussy C, Gelet A. First analysis of the long-term results with transrectal HIFU in patients with localised prostate cancer. *Eur Urol* 2008; **53**: 1194-1201 [PMID: 17997026 DOI: 10.1016/j.eururo.2007.10.062]
- Marks LS, Fradet Y, Deras IL, Blase A, Mathis J, Aubin SM, Cancio AT, Desaulniers M, Ellis WJ, Rittenhouse H, Groskopf J. PCA3 molecular urine assay for prostate cancer in men undergoing repeat biopsy. *Urology* 2007; **69**: 532-535 [PMID: 17382159]
- Roobol MJ, Schröder FH, van Leeuwen P, Wolters T, van den Bergh RC, van Leenders GJ, Hessels D. Performance of the prostate cancer antigen 3 (PCA3) gene and prostate-specific antigen in prescreened men: exploring the value of PCA3 for a first-line diagnostic test. *Eur Urol* 2010; **58**: 475-481 [PMID: 20637539]
- Roobol MJ. Contemporary role of prostate cancer gene 3 in the management of prostate cancer. *Curr Opin Urol* 2011; **21**: 225-229 [PMID: 21301341 DOI: 10.1097/MOU.0b013e328344939c]
- Groskopf J, Aubin SM, Deras IL, Blase A, Bodrug S, Clark C, Brentano S, Mathis J, Pham J, Meyer T, Cass M, Hodge P, Macairan ML, Marks LS, Rittenhouse H. APTIMA PCA3 molecular urine test: development of a method to aid in the diagnosis of prostate cancer. *Clin Chem* 2006; **52**: 1089-1095 [PMID: 16627561]
- Vickers AJ, Elkin EB. Decision curve analysis: a novel method for evaluating prediction models. *Med Decis Making* 2006; **26**: 565-574 [PMID: 17099194 DOI: 10.1177/0272989X06295361]
- Wu AK, Reese AC, Cooperberg MR, Sadetsky N, Shinohara K. Utility of PCA3 in patients undergoing repeat biopsy for prostate cancer. *Prostate Cancer Prostatic Dis* 2012; **15**: 100-105 [PMID: 22042252 DOI: 10.1038/pcan.2011.52]
- van Vugt HA, Roobol MJ, Busstra M, Kil P, Oomens EH, de Jong IJ, Bangma CH, Steyerberg EW, Korfage I. Compliance with biopsy recommendations of a prostate cancer risk calculator. *BJU Int* 2012; **109**: 1480-1488 [PMID: 21933335 DOI: 10.1111/j.1464-410X.2011.10611.x]
- Klatte T, Waldert M, de Martino M, Schatzl G, Mannhalter C, Remzi M. Age-specific PCA3 score reference values for diagnosis of prostate cancer. *World J Urol* 2012; **30**: 405-410 [PMID: 21877172 DOI: 10.1007/s00345-011-0749-1]
- Perdonà S, Cavadas V, Di Lorenzo G, Damiano R, Chiappetta G, Del Prete P, Franco R, Azzarito G, Scala S, Arra C, De Sio M, Autorino R. Prostate cancer detection in the "grey area" of prostate-specific antigen below 10 ng/ml: head-to-head comparison of the updated PCPT calculator and Chun's nomogram, two risk estimators incorporating prostate cancer antigen 3. *Eur Urol* 2011; **59**: 81-87 [PMID: 20947244 DOI: 10.1016/j.eururo.2010.09.036]
- Ankerst DP, Groskopf J, Day JR, Blase A, Rittenhouse H, Pollock BH, Tangen C, Parekh D, Leach RJ, Thompson I. Predicting prostate cancer risk through incorporation of prostate cancer gene 3. *J Urol* 2008; **180**: 1303-1308; discussion 1308 [PMID: 18707724 DOI: 10.1016/j.juro.2008.06.038]
- Chun FK, de la Taille A, van Poppel H, Marberger M, Stenzl A, Mulders PF, Huland H, Abbou CC, Stillebroer AB, van Gils MP, Schalken JA, Fradet Y, Marks LS, Ellis W, Partin AW, Haese A. Prostate cancer gene 3 (PCA3): development and internal validation

of a novel biopsy nomogram. *Eur Urol* 2009; **56**: 659-667 [PMID: 19304372 DOI: 10.1016/j.eururo.2009.03.029]

- 18 **University of Texas Health Science Center San Antonio.** Individualized risk assessment of prostate cancer. Available from: URL: <http://deb.uthscsa.edu/URORiskCalc/Pages/calcs.jsp>

- 19 **National Comprehensive Cancer Network.** Prostate cancer early detection (version 1.2014). Available from: URL: http://www.nccn.org/professionals/physician_gls/pdf/prostate_detection.pdf

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Urodynamic test and female urinary stress incontinence: An open debate

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Abstract

In this editorial we discussed the pros and cons of urodynamics in the assessment of female stress urinary incontinence.

Key words: Urodynamic; Female urinary incontinence; Stress urinary incontinence

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Core tip: In the last few years, the debate on the role of urodynamic tests in the preoperative evaluation of female urinary incontinence is hot. Even in absence of strong evidence, urodynamic investigation (UDI) is used to be considered mandatory before surgery in all female patients affected by stress urinary incontinence, according to several guidelines or recommendations. Nevertheless, a clear demonstration of an improvement of outcomes or change of clinical strategy after UDI was lacking.

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In the last few years, the debate on the role of urodynamic tests in the preoperative evaluation of female urinary incontinence is hot. Even in absence of strong evidence, urodynamic investigation (UDI) is used to be considered mandatory before surgery in all female patients affected by stress urinary incontinence (SUI), according to several guidelines or recommendations^[1,2]. Nevertheless, a clear demonstration of an improvement

of outcomes or change of clinical strategy after UDI was lacking.

The scenario started to change after the publication of a relevant randomized controlled trial in 2012, aimed to compare outcomes of incontinence surgery after preoperative office evaluation (OE) and urodynamic tests or OE alone. This trial, generally known as Value of Urodynamic Evaluation (ValUE) trial^[3], showed that women with OE alone had non-inferior outcomes compared to those undergoing OE plus UDI. In 2012 and 2013, two papers from van Leijsen *et al.*^[4,5] showed that the omission of urodynamics is not inferior to the inclusion of urodynamics in the preoperative workup in women with (predominant) SUI and that the consequences of discordant findings between symptoms and urodynamics are only of limited frequency. It should be underlined, as correctly done by the Authors, that all these trials enrolled exclusively women with pure SUI or mixed incontinence with prevalent SUI, according to strict inclusion and exclusion criteria. Those patients had been classified as having an “uncomplicated” demonstrable SUI, in the ValUE trial^[3].

As a consequence, the contemporary guidelines^[6,7] are more cautious on the role of preoperative UDI stating that “there is limited evidence that performing urodynamics will alter the outcome of treatment for urinary incontinence” (European Association of Urology guidelines on incontinence^[6]); whilst, according to the International Consultation on Incontinence the grade of recommendation for urodynamics before surgery is B^[7].

A recent Cochrane systematic review by Clement *et al.*^[8] evaluated published randomized clinical trials with the aim of analyzing if pre-operative UDI could improve the clinical outcomes or alter clinical decision-making. The authors concluded that while urodynamics may change clinical decision-making, there is “some high-quality evidence that this did not result in lower urinary incontinence rates after treatment”. A systematic review and meta-analysis published recently by Rachaneni *et al.*^[9] evaluated 388 papers (including only four randomized controlled trials) and concluded that UDI do not improve outcomes “in women undergoing primary surgery for SUI or stress-predominant MUI without voiding difficulties”. These two systematic reviews included few papers and the majority of the patients analyzed came from the ValUE study^[3].

Thus, the message that could be received (at least by an inattentive reader) is that UDI before surgery for stress incontinence is simply useless in all patients (uncomplicated and complicated). This logical step is absolutely unjustified considering that uncomplicated/simple patients are the minority of the patients as it has been several times demonstrated. Agur *et al.*^[10] showed in 2009 that only 324 (5.2%) out of 6276 women with urinary incontinence, collected from an electronic database at a tertiary referral center, showed pure stress urinary incontinence, a quarter of which showed some different findings at the urodynamic evaluation. In a more recent trial, collecting data from several referral

centers in Italy, we were able to show that only 36% of more 2053 patients could have been diagnosed as having an “uncomplicated” SUI, according to ValUE trial criteria^[11]. Furthermore, preoperative UDI led to the diagnosis of different type of urinary incontinence in 74.6% of complicated vs 40% of uncomplicated SUI cases ($P = 0.0001$). Moreover, a voiding dysfunction on UDI was observed in 13.4% of the uncomplicated cases and in 22.5% of the complicated cases ($P = 0.0001$).

In our opinion, some important informations come from these studies: first of all the so-called “uncomplicated” SUI patients are a minority. Also in the ValUE trial the majority of the screened patients (more than 60%) had been excluded from the study because non fitting in inclusion/exclusion criteria^[3]. This result confirms the observation coming from our recent study^[11], in which 64% of patients were considered “complicated”, using the ValUE trial criteria. A second consideration emerging from our study is that in the majority of our “complicated” patients the urodynamic observation varies from the pre-urodynamic diagnosis much more frequently than in the “uncomplicated” patients. In a sub analysis of the ValUE trial^[12], Sirls *et al.*^[12] showed that UDI was able to add some data to the pre-urodynamic information, but that these new informations changed the following surgical management only in around 12% of patients. In our study we confirmed that UDI was able to cancel/change the surgical management in a comparable percentage of “uncomplicated” SUI patients (11%), but much more frequently in the “complicated” ones (23.8%). Thus, it is possible to suppose that UDI effectively changes the surgical management of one quarter of “complicated” patients, and possibly in a 20% of the total patients’ population.

Actually, a tailored treatment is an essential target to obtain. UDI may prevent surgical intervention in women without USI or with prevalent detrusor overactivity incontinence. Recently, Serati *et al.*^[13] demonstrated that UDI is able to show that several patients with symptoms of pure SUI present an underlying detrusor overactivity and do not require surgery, even one year after UDI. In these patients, antimuscarinic treatment appears to ensure a good rate of cure; thus, UDI could lead to the avoidance of several surgical procedures^[13]. Furthermore, some urodynamic variables could guide the choice of the operation and potentially the surgical technique (*e.g.*, trans-obturator vs retropubic mid-urethral sling). They may also identify patients at risk of failure and at risk of the development of postoperative urgency, urgency incontinence and voiding dysfunction. This accurate assessment of the risks and benefits of surgery is fundamental to facilitate a correct preoperative counseling directed towards appropriate patient expectations, as well as guide the proactive management of postoperative symptoms^[14]. In particular, the presence of a pre-existing voiding dysfunction could affect the outcomes: in a reply to a letter to the Editor on the ValUE trial^[15] published on Neurourology and Urodynamics in 2013, Nager^[16] affirmed that patients diagnosed with

a voiding dysfunction met a successful outcome in a reduced proportion in comparison to the rest of the population (62.1% vs 78.8%). This difference was not statistically significant ($P = 0.06$), but, considering the huge difference in groups number (29 vs 230 patients) and the lack of power of the study for this outcome, a voiding dysfunction could be considered a negative prognostic factor for success after surgery. This condition, according to the VALUE trial and to our study, may be diagnosed in the majority of patients only after UDI even in "uncomplicated" patients.

In conclusion, we believe that in the majority of patients (the "complicated" ones) the role of UDI has not been fully evaluated. Nevertheless, data coming from literature together with data coming from daily clinical practice show that UDI may provide valuable data to evaluate the best clinical strategy. In uncomplicated cases, pretreatment UDI is probably not mandatory but it could give important informations (voiding dysfunction in about 10% of cases) offering a valuable guide to the surgeon and to the patient. "Primum non nocere" (First, do not harm) is one of the principal precepts of bioethics. A careful patient assessment allows to avoid a negligent practice. Urodynamic investigations is a valuable tool able to help us in counseling our patients with the aim of cure their symptoms, never risking of worsening them or causing further discomfort. In summary UDI help us in trying to "Primum non nocere".

REFERENCES

- 1 **Thüroff JW**, Abrams P, Andersson KE, Artibani W, Chapple CR, Drake MJ, Hampel C, Neisius A, Schröder A, Tubaro A. EAU guidelines on urinary incontinence. *Eur Urol* 2011; **59**: 387-400 [PMID: 21130559 DOI: 10.1016/j.eururo.2010.11.021]
- 2 **Ghoniem G**, Stanford E, Kenton K, Ahtari C, Goldberg R, Mascarenhas T, Parekh M, Tamussino K, Tosson S, Lose G, Petri E. Evaluation and outcome measures in the treatment of female urinary stress incontinence: International Urogynecological Association (IUGA) guidelines for research and clinical practice. *Int Urogynecol J Pelvic Floor Dysfunct* 2008; **19**: 5-33 [PMID: 18026681 DOI: 10.1007/s00192-007-0495-5]
- 3 **Nager CW**, Brubaker L, Litman HJ, Zyczynski HM, Varner RE, Amundsen C, Sirls LT, Norton PA, Arisco AM, Chai TC, Zimmern P, Barber MD, Dandreo KJ, Menefee SA, Kenton K, Lowder J, Richter HE, Khandwala S, Nygaard I, Kraus SR, Johnson HW, Lemack GE, Mihova M, Albo ME, Mueller E, Sutkin G, Wilson TS, Hsu Y, Rozanski TA, Rickey LM, Rahn D, Tennstedt S, Kusek JW, Gormley EA. A randomized trial of urodynamic testing before stress-incontinence surgery. *N Engl J Med* 2012; **366**: 1987-1997 [PMID: 22551104 DOI: 10.1056/NEJMoa1113595]
- 4 **van Leijsen SA**, Kluivers KB, Mol BW, Broekhuis SR, Milani AL, Bongers MY, Aalders CI, Dietz V, Malmberg GG, Vierhout ME, Heesakkers JP. Can preoperative urodynamic investigation be omitted in women with stress urinary incontinence? A non-inferiority randomized controlled trial. *Neurourol Urodyn* 2012; **31**: 1118-1123 [PMID: 22488817 DOI: 10.1002/nau.22230]
- 5 **van Leijsen SA**, Kluivers KB, Mol BW, Hout J, Milani AL, Roovers JP, Boon Jd, van der Vaart CH, Langen PH, Hartog FE, Dietz V, Tiersma ES, Hovius MC, Bongers MY, Spaans W, Heesakkers JP, Vierhout ME. Value of urodynamics before stress urinary incontinence surgery: a randomized controlled trial. *Obstet Gynecol* 2013; **121**: 999-1008 [PMID: 23635736 DOI: 10.1097/AOG.0b013e31828c68e3]
- 6 **Lucas MG**, Bosch RJ, Burkhard FC, Cruz F, Madden TB, Nambiar AK, Neisius A, de Ridder DJ, Tubaro A, Turner WH, Pickard RS. EAU guidelines on surgical treatment of urinary incontinence. *Eur Urol* 2012; **62**: 1118-1129 [PMID: 23040204 DOI: 10.1016/j.eururo.2012.09.023]
- 7 **Abrams P**, Cardozo L, Khoury S, Wein A. Incontinence. Fifth International Consultation on Incontinence, ICUD. Paris Feb, 2012
- 8 **Clement KD**, Lapitan MC, Omar MI, Glazener CM. Urodynamic studies for management of urinary incontinence in children and adults: A short version Cochrane systematic review and meta-analysis. *Neurourol Urodyn* 2015; **34**: 407-412 [PMID: 24853652 DOI: 10.1002/nau.22584]
- 9 **Rachaneni S**, Latthe P. Does preoperative urodynamics improve outcomes for women undergoing surgery for stress urinary incontinence? A systematic review and meta-analysis. *BJOG* 2015; **122**: 8-16 [PMID: 25041381 DOI: 10.1111/1471-0528.12954]
- 10 **Agur W**, Housami F, Drake M, Abrams P. Could the National Institute for Health and Clinical Excellence guidelines on urodynamics in urinary incontinence put some women at risk of a bad outcome from stress incontinence surgery? *BJU Int* 2009; **103**: 635-639 [PMID: 19021606 DOI: 10.1111/j.1464-410X.2008.08121]
- 11 **Finazzi Agrò E**, Costantini E, Pietropaolo A, Palleschi G, Carbone A, Topazio L, Soligo M, Del Popolo G, Li Marzi V, Salvatore S, Serati M. Urodynamics useless before surgery for female stress urinary incontinence: Are you sure? Results from a multicenter single nation database. *European Urology Supplements*, Volume 13, Issue 1, April 2014: e386-e386a
- 12 **Sirls LT**, Richter HE, Litman HJ, Kenton K, Lemack GE, Lukacz ES, Kraus SR, Goldman HB, Weidner A, Rickey L, Norton P, Zyczynski HM, Kusek JW. The effect of urodynamic testing on clinical diagnosis, treatment plan and outcomes in women undergoing stress urinary incontinence surgery. *J Urol* 2013; **189**: 204-209 [PMID: 22982425 DOI: 10.1016/j.juro.2012.09.050]
- 13 **Serati M**, Cattoni E, Siesto G, Braga A, Sorice P, Cantaluppi S, Cromi A, Ghezzi F, Vitobello D, Bolis P, Salvatore S. Urodynamic evaluation: can it prevent the need for surgical intervention in women with apparent pure stress urinary incontinence? *BJU Int* 2013; **112**: E344-E350 [PMID: 23421421 DOI: 10.1111/bju.12007]
- 14 **Giarenis I**, Cardozo L. What is the value of urodynamic studies before stress incontinence surgery? *BJOG* 2013; **120**: 130-132 [PMID: 23240793 DOI: 10.1111/1471-0528.12102]
- 15 **Finazzi-Agrò E**, Serati M, Salvatore S, Del Popolo G. Comments on "A randomized trial of urodynamic testing before stress-incontinence surgery" (N Engl J Med. 2012 May 24; 366(21): 1987-1997) From the Italian Society of Urodynamics. *Neurourol Urodyn* 2013; **32**: 301-302 [PMID: 23023985 DOI: 10.1002/nau.22324]
- 16 **Nager CW**. Re: Comments on "A randomized trial of urodynamic testing before stress-incontinence surgery" (N Engl J Med. 2012 May 24; 366(21): 1987-1997) From the Italian Society of Urodynamics. *Neurourol Urodyn* 2013; **32**: 303-304 [PMID: 23001635 DOI: 10.1002/nau.22323]

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Infectious complications after prostate biopsy: Time to rethink our clinical practice

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Abstract

Prostate biopsy is a very common procedure performed worldwide which still represents the only way for prostate cancer diagnosis and reference point for subsequent treatments. Even if transrectal prostate biopsy is considered a safe procedure, it may be accompanied by infective complications, ranging from asymptomatic bacteriuria to symptomatic urinary tract infections and sepsis. During the recent decade we observed an increasing number of infectious complications and subsequent hospitalizations after and transrectal prostate biopsy. The most probable reason for the increasing rate of infectious complications after prostate biopsy is the increasing antimicrobial resistance, especially to the current first-line recommended fluoroquinolone antibiotics. We believe the time has come to re-think our current practice of diagnosing prostate cancer. We need to focus on the selection of patients at higher risk of infective complications, on microbiological sampling of the faecal flora prior to biopsy to identify resistance to specific agents, on the number of biopsy cores, on the biopsy route (perineal or transrectal approach) and, finally, consider alternative antibiotics with improved susceptibility to be used for prophylaxis.

Key words: Prostate cancer; Prostate biopsy; Transrectal biopsy; Rectal swab; Antibiotic prophylaxis

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Core tip: Transrectal biopsy of the prostate is generally considered a safe procedure used for obtaining tissue samples for the histological diagnosis of prostate carcinoma. However, in the last years we observed a higher rate of infective complications, ranging from asymptomatic bacteriuria to sepsis that continued

to be the principal cause of hospital admission after procedure. The higher rate of sepsis could be due to the emerging resistance to fluoroquinolones, in particular to ciprofloxacin. New strategies for antibacterial prophylaxis need to be purposed.

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INTRODUCTION

Prostate biopsy is currently an indispensable method for the diagnosis of the prostate cancer and the transrectal approach is most commonly used by European urologists^[1-3]. Even if transrectal biopsy of the prostate (TR-PB) is generally considered a secure method, it may be accompanied by several clinical complications, like bleeding due to the biopsy trauma or, more frequently, infective complications ranging from asymptomatic bacteriuria to symptomatic urinary tract infections and sepsis^[4]. Although infective complications after TR-PB are well identified and a recent systematic review showed a significant reduction in the risk of bacteriuria compared with placebo^[5], an higher rate of infective complications after transrectal biopsy of the prostate has been recently reported in several countries^[6,7]. Today, the infective complications after TR-PB represent an important challenge for the urologist and a life-threatening risk for the patient, in particular due to the increased rate of antibiotic resistant bacteria.

STATE OF ART: INTERNATIONAL GUIDELINES

The European Association of Urology (EAU) guidelines suggests using fluoroquinolones and trimethoprim/sulfamethoxazole as appropriate antibiotics for prophylaxis^[8]. Moreover, the best practice policy statement on urologic surgery antimicrobial prophylaxis, edited by American Urological Association, suggest to perform antibiotic prophylaxis in all patients by using ciprofloxacin in single dose^[9]. However a recent survey showed a total of forty-eight diverse schedules utilizing 13 different antibiotics, ranging from a single oral dose of ciprofloxacin before TR-PB, to intravenous cefuroxime and enema with metronidazole before the procedure, with subsequent doses of oral cephalixin^[4,10,11]. There are huge cost variations among the prophylactic regimens^[4]. In this sense, there is a clear lack of standardization of antibiotic prophylaxis for transrectal prostate biopsy. The favorable pharmacokinetic and pharmacodynamic characteristics of fluoroquinolones are important reasons for the recommendations given in the EAU guidelines on prostate

biopsies^[8]. Fluoroquinolones reaches high concentrations in prostate tissue and prostatic secretions^[8]. Moreover, orally administered fluoroquinolones reach high concentrations in the prostate tissue that are sufficient for the treatment of chronic bacterial prostatitis^[12].

ACTUAL SCENARIO: THE INCREASING NUMBER OF INFECTIVE COMPLICATIONS AND THE ROLE OF EMERGING RESISTANT BACTERIAL STRAINS

Despite fluoroquinolones being the most prescribed drug for TR-PB prophylaxis, in line with EAU guidelines^[8], the hospital admissions due to complications after TR-PB have significantly increased during the last 10 years^[13]. The recently published results of the Global Prevalence Study of Infections in Urology study found a high rate of symptomatic urinary tract infections (5.2%) and a significant rate of hospitalization (3.1%)^[3]. Interesting, in the same study, Wagenlehner *et al*^[3] reported that fluoroquinolones were used in 98.2% of patients, in accordance with the EAU guidelines, but the resistance rate against fluoroquinolones was seen in 60% of all isolated bacterial strains. Now is the time to ask what the clinical consequences of these data are. Several studies showed that the higher risk of infection is due to an increase in ciprofloxacin resistance in *Escherichia coli* and hence a associated reduce in the efficacy of prophylaxis with ciprofloxacin in patients undergoing TR-PB^[14]. The current increasing rate of fluoroquinolone resistant organisms has become a significant contemporary health crisis. This emergency is due both to the abuse and over-prescription of antibiotics and the limited development of new molecules with subsequent reduced number of new antibiotics in the pipelines of pharmaceutical companies^[13]. Some authors hypothesize that the observed increase prevalence of ciprofloxacin resistant *Escherichia coli* strains isolated from patients with urinary tract infections reflects changes in the strains colonizing the patients' gastrointestinal tracts^[15]. In fact, a recent study showed that 22.0% of patients who had undergone TR-PB, harbored ciprofloxacin-resistant *Escherichia coli* strains^[16]. Moreover, they found that faecal carriage of *Escherichia coli* strains resistant to fluoroquinolone was a important risk factor for infective complications after TR-PB^[16].

ALTERNATIVE STRATEGIES TO DECREASE INFECTIVE COMPLICATIONS

In order to decrease the frequency of infective complications after prostate biopsy, some strategies have been purposed and evaluated: (1) risk assessment for selecting patients at higher risk for infective complications; (2) microbiological evaluation of the faecal flora prior to biopsy to identify resistance to specific agents; (3) number of biopsy cores and the use of

targeted, image fusion guided biopsies; (4) change of biopsy route (perineal approach); and (5) alternative molecules with enhanced susceptibility.

Risk assessment to selecting patients at higher risk for infective complications

Loeb *et al.*^[17] in 17472 men who had undergone prostate biopsy and 134977 controls, showing that age, race, region, year, and Charlson comorbidity score are independent prognostic factors to use for assess the risk of hospitalization. Moreover, they highlighted other two independent prognostic factors for developing febrile complications due to urinary tract infections after TR-PB: prostate enlargement and diabetes^[17]. Moreover, it is well known that hyperglycemia-related impairment of the immune response may lead to an increase in post-biopsy infections^[14]. Assessment of comorbidity is important to identify patients at higher risk of infective complications after prostate biopsy. Finally, it is well known that the prevalence of resistant bacteria is different among countries. For this reason, travelling to countries with high prevalence of resistant bacteria was associated with colonization and may be considered a risk factor for developing infective complications after prostate biopsy. However, we have no data about it in the current literature.

Microbiological evaluation of the faecal flora prior to biopsy to identify resistance to specific agents

Based on the previous evidences, some researchers proposed doing rectal swab culture test before prostate biopsy to isolate and characterize all fluoroquinolone-resistant strains from patients' rectal flora^[18]. In line with this hypothesis, Taylor *et al.*^[18] planned a longitudinal cohort study of 457 men receiving targeted antibiotic prophylaxis based on microbiological evaluation of the rectal flora as compared with empirical antibiotic prophylaxis. They did not find any statistically significant differences between the two groups in terms of number of infective complications. On the other hand, the targeted antibiotic prophylaxis obtained a cost saving of \$4499 due to the prevention of a significant number of infectious complications after the procedure^[18]. In particular, they found a cost benefit ratio of 38:1 if compared to the indiscriminate use of fluorquinolone-based antibiotic prophylaxis^[18]. Moreover, Williamson found that a specific fluoroquinolone-resistant *Escherichia coli* strain (*E. coli* ST131) was an significant cause of sepsis after TR-PB^[19]. These reports have significant clinical relevance and should be taken into account as it has been shown that faecal fluoroquinolone resistant *Escherichia coli* can be selected even by only one dose of oral 500 mg ciprofloxacin given as prophylaxis before transrectal biopsy of the prostate^[20]. Furthermore, the use of fluoroquinolones in the 6 mo period before prostate biopsy has also been shown to be associated with a higher risk of faecal carriage of fluoroquinolone-resistant *Escherichia coli* strains^[16]. Recently, Taylor *et*

al.^[21] evaluated the prevalence of ciprofloxacin-resistant strains in patients who had undergone TR-PB and estimated the subsequent risk of infectious complications after TR-PB with peri-operative ciprofloxacin prophylaxis. They collected a pre and post biopsy rectal swab and urine culture and analyzed the susceptibility to the most commonly used antibiotics^[21]. Among 865 investigated patients, *Escherichia coli* was the most common strain (80.9%) and accounted for 90.6% of ciprofloxacin resistant specimens while the rate of ciprofloxacin-resistant coliforms in general was 19%^[21]. Infectious complications occurred in 3.6% of patients and 48% of these patients had ciprofloxacin resistant bacteria at pre-biopsy microbiological evaluation of the rectal flora. Their findings strongly indicate that the increasing prevalence of infection rate after TR-PB is due to an increasing prevalence of ciprofloxacin-resistant *E. coli* in the rectal flora^[21]. Paralleling the worldwide increase of fluoroquinolone resistance in enterobacteria faecal fluoroquinolone-resistant bacteria can indeed explain the increase of infective complications after TR-PB^[3]. But what about giving a course of a customized prophylaxis regimen prior to a transrectal prostate biopsy based of the findings of the microbiological evaluation of the rectal flora? Some aspects should be addressed. Firstly, rectal swab would represent a significant difficulty for clinical microbiology laboratories and might fail to identify ciprofloxacin-sensitive isolates with intermediate MICs. Secondly, there is a relative instability of ciprofloxacin in specific microbiological procedures, and there is no commercially accessible ciprofloxacin containing media^[14].

Number of biopsy cores and the use of targeted, image fusion guided biopsies

Recently, some authors have addressed the importance of the number of biopsy cores taken. Wagenlehner *et al.*^[3] identified the number of biopsy cores to be the only important risk factor for the development of symptomatic urinary tract infections after prostate biopsy. This finding was confirmed by Dodds *et al.*^[22] who observed an increased rate of complications after prostate biopsy in 2080 patients, highlighting the number of biopsy cores as one of the main risk factor for patients' hospitalization. On the other hand, a randomized trial of 6 vs 12 core biopsies reported no significant differences in terms of febrile complications^[23]. The authors concluded that prostate biopsy with 12-cores is generally well tolerated and can be safely performed with no significant difference in pain or morbidity compared to the procedure with 6-cores^[23]. The jury is still out regarding the importance of number of biopsies for the risk of infective complications.

Change of biopsy route (perineal approach)

Even if several authors showed that no important differences in the number of complications were found between the transperineal or transrectal approach, the transperineal approach has been considered an

alternative strategy to decrease the infective complications^[13,24,25]. Recently, Grummet *et al.*^[26], evaluating the rate of hospital admission for sepsis after transperineal biopsy of the prostate, found that the rate of hospital re-admission for infective complications was zero. Moreover, the international data suggested a negligible rate of sepsis by using transperineal biopsy^[27]. In conclusion, although transrectal prostate biopsy is handy, inexpensive and quick to perform, the transperineal road should now be considered as an alternative approach, not only to patients undergoing repeat prostate biopsy, but also to all patients in whom a high risk of infective complication has found.

Alternative molecules with enhanced susceptibility

Another important aspect to discuss is an interesting finding from the Carignan's study: among *Escherichia coli* isolated from all patients who underwent TR-PB and deemed susceptible to ciprofloxacin, the MIC increased during the latter period^[14]. As already suggested by others, an increasing fluorquinolones resistance and creeping MICs call for a reassessment of the current recommendations on antibiotic prophylaxis^[28]. However, the use of alternative antibiotic prophylaxis should still be based on the susceptibility of the most common pathogens and the pharmacokinetic diffusion of the antibiotic within the prostate tissue^[3]. The rising resistance to fluoroquinolones, in particular to ciprofloxacin, is the most likely cause of the increasing prevalence of infective complications after TR-PB and new strategies for antibacterial prophylaxis need to be purposed. As reported in several studies, *Escherichia coli* accounts for most of the positive cultures in patients who had undergone TR-PB, and displays a high levels of antimicrobial resistance^[7,28]. The authors stress that the highest rates of resistance was seen for trimethoprim sulfamethoxazole and amoxicillin, a fact suggestive of that these molecules should not be used for prophylaxis before the biopsy of the prostate^[7,28,29]. An alternative strategy is to try and obtain better treatment through the use of more extended antimicrobial prophylaxis^[13]. However, this suggestion should be met with caution, due to the risk of collateral damage and the actual need for lowering the use of broad spectrum antibiotics^[20]. Another valid option could be the use of antibiotics with low profile of resistance, such as fosfomycin trometamol. Fosfomycin is a candidate alternative agent for antibiotic prophylaxis in TR-PB having showed elevated activity against MDR Gram-negative bacteria and favorable pharmacokinetic parameters, including an elevated penetration into prostatic tissue^[30,31]. In a recent review paper Wagenlehner *et al.*^[32] argued that fosfomycin trometamol 3 g orally 3 h before and 24 h after, could be used as prophylaxis during traumatic endourological interventions and surgical procedures. For diagnostic procedures one single oral dose might be an alternative if perioperative antibiotic prophylaxis is indicated. Further studies are required in order to settle the role fosfomycin

trometamol in the antibiotic prophylaxis before prostate biopsy. New evidence calls for re-consideration of clinical practice and development of better preventive strategies against infectious complications in patients undergoing transrectal prostate biopsy.

From all these evidences it is clear that prostate biopsy policy should be totally revised in order to obtain acceptable prospective results in terms of infective complications, costs saving and patient compliance as recently suggested by Wagenlehner *et al.*^[33]. In conclusion, before prostate biopsy is decided a exhaustive history should be taken with special attention to risk factors for infectious complications (*i.e.*, diabetes) and for harboring resistant strains (*i.e.*, recent hospitalization, travel to certain geographical regions or antibiotic use)^[17,29,34,35].

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REFERENCES

- 1 **Chun FK**, Epstein JI, Ficarra V, Freedland SJ, Montironi R, Montorsi F, Shariat SF, Schröder FH, Scattoni V. Optimizing performance and interpretation of prostate biopsy: a critical analysis of the literature. *Eur Urol* 2010; **58**: 851-864 [PMID: 20884114 DOI: 10.1016/j.eururo.2010.08.041]
- 2 **Hodge KK**, McNeal JE, Terris MK, Stamey TA. Random systematic versus directed ultrasound guided transrectal core biopsies of the prostate. *J Urol* 1989; **142**: 71-74; discussion 74-75 [PMID: 2659827]
- 3 **Wagenlehner FM**, van Oostrum E, Tenke P, Tandogdu Z, Çek M, Grabe M, Wullt B, Pickard R, Naber KG, Pilatz A, Weidner W, Bjerkklund-Johansen TE. Infective complications after prostate biopsy: outcome of the Global Prevalence Study of Infections in Urology (GPIU) 2010 and 2011, a prospective multinational multicentre prostate biopsy study. *Eur Urol* 2013; **63**: 521-527 [PMID: 22704727 DOI: 10.1016/j.eururo.2012.06.003]
- 4 **Zani EL**, Clark OA, Rodrigues Netto N. Antibiotic prophylaxis for transrectal prostate biopsy. *Cochrane Database Syst Rev* 2011; **(5)**: CD006576 [PMID: 21563156 DOI: 10.1002/14651858]
- 5 **Bootsma AM**, Laguna Pes MP, Geerlings SE, Goossens A. Antibiotic prophylaxis in urologic procedures: a systematic review. *Eur Urol* 2008; **54**: 1270-1286 [PMID: 18423974 DOI: 10.1016/j.eururo.2008.03.033]
- 6 **Nam RK**, Saskin R, Lee Y, Liu Y, Law C, Klotz LH, Loblaw DA, Trachtenberg J, Stanimirovic A, Simor AE, Seth A, Urbach DR, Narod SA. Increasing hospital admission rates for urological complications after transrectal ultrasound guided prostate biopsy. *J Urol* 2010; **183**: 963-968 [PMID: 20089283 DOI: 10.1016/j.juro.2009.11.043]
- 7 **Loeb S**, van den Heuvel S, Zhu X, Bangma CH, Schröder FH, Roobol MJ. Infectious complications and hospital admissions after prostate biopsy in a European randomized trial. *Eur Urol* 2012; **61**: 1110-1114 [PMID: 22244150 DOI: 10.1016/j.eururo.2011.12.058]
- 8 **Grabe M**, Bjerkklund-Johansen TE, Botto H, Wullt B, Cek M, Naber KG, Pickard RS, Tenke P, Wagenlehner F. Guidelines on Urological Infections. European Association of Urology Guidelines, 2012: 69
- 9 **American Urological Association**. Best Practice Policy Statement on urologic surgery antimicrobial prophylaxis. Available from: URL: <https://www.auanet.org/common/pdf/education/clinical-guidance/Antimicrobial-Prophylaxis.pdf>
- 10 **Shandera KC**, Thibault GP, Deshon GE. Variability in patient preparation for prostate biopsy among American urologists.

- Urology* 1998; **52**: 644-646 [PMID: 9763086 DOI: 10.1016/S0090-4295(98)00313-6]
- 11 **Taylor HM**, Bingham JB. The use of prophylactic antibiotics in ultrasound-guided transrectal prostate biopsy. *Clin Radiol* 1997; **52**: 787-790 [PMID: 9366541 DOI: 10.1016/S0009-9260(97)80161-4]
 - 12 **Wagenlehner FM**, Weidner W, Sörgel F, Naber KG. The role of antibiotics in chronic bacterial prostatitis. *Int J Antimicrob Agents* 2005; **26**: 1-7 [PMID: 15970433 DOI: 10.1016/j.ijantimicag.2005.04.013]
 - 13 **Bartoletti R**, Cai T. Prostate biopsies should be performed according to a standard of care. *Eur Urol* 2013; **63**: 528-529 [PMID: 22795518 DOI: 10.1016/j.eururo.2012.06.050]
 - 14 **Carignan A**, Roussy JF, Lapointe V, Valiquette L, Sabbagh R, Pépin J. Increasing risk of infectious complications after transrectal ultrasound-guided prostate biopsies: time to reassess antimicrobial prophylaxis? *Eur Urol* 2012; **62**: 453-459 [PMID: 22575912 DOI: 10.1016/j.eururo.2012.04.044]
 - 15 **Pépin J**, Plamondon M, Lacroix C, Alarie I. Emergence of and risk factors for ciprofloxacin-gentamicin-resistant *Escherichia coli* urinary tract infections in a region of Quebec. *Can J Infect Dis Med Microbiol* 2009; **20**: e163-e168 [PMID: 21119795]
 - 16 **Steensels D**, Slabbaert K, De Wever L, Vermeersch P, Van Poppel H, Verhaegen J. Fluoroquinolone-resistant *E. coli* in intestinal flora of patients undergoing transrectal ultrasound-guided prostate biopsy--should we reassess our practices for antibiotic prophylaxis? *Clin Microbiol Infect* 2012; **18**: 575-581 [PMID: 21958149 DOI: 10.1111/j.1469-0691.2011.03638.x]
 - 17 **Loeb S**, Carter HB, Berndt SI, Ricker W, Schaeffer EM. Complications after prostate biopsy: data from SEER-Medicare. *J Urol* 2011; **186**: 1830-1834 [PMID: 21944136 DOI: 10.1016/j.juro.2011.06.057]
 - 18 **Taylor AK**, Zembower TR, Nadler RB, Scheetz MH, Cashy JP, Bowen D, Murphy AB, Dielubanza E, Schaeffer AJ. Targeted antimicrobial prophylaxis using rectal swab cultures in men undergoing transrectal ultrasound guided prostate biopsy is associated with reduced incidence of postoperative infectious complications and cost of care. *J Urol* 2012; **187**: 1275-1279 [PMID: 22341272 DOI: 10.1016/j.juro.2011.11.115]
 - 19 **Williamson DA**, Roberts SA, Paterson DL, Sidjabat H, Silvey A, Masters J, Rice M, Freeman JT. *Escherichia coli* bloodstream infection after transrectal ultrasound-guided prostate biopsy: implications of fluoroquinolone-resistant sequence type 131 as a major causative pathogen. *Clin Infect Dis* 2012; **54**: 1406-1412 [PMID: 22419681 DOI: 10.1093/cid/cis194]
 - 20 **Wagenlehner FM**, Bartoletti R, Cek M, Grabe M, Kahlmeter G, Pickard R, Bjerklund-Johansen TE. Antibiotic stewardship: a call for action by the urologic community. *Eur Urol* 2013; **64**: 358-360 [PMID: 23746854 DOI: 10.1016/j.eururo.2013.05.044]
 - 21 **Taylor S**, Margolick J, Abughosh Z, Goldenberg SL, Lange D, Bowie WR, Bell R, Roscoe D, Machan L, Black P. Ciprofloxacin resistance in the faecal carriage of patients undergoing transrectal ultrasound guided prostate biopsy. *BJU Int* 2013; **111**: 946-953 [PMID: 23464844 DOI: 10.1111/j.1464-410X.2012.11637.x]
 - 22 **Dodds PR**, Boucher JD, Shield DE, Bernie JE, Batter SJ, Serels SR, Dodds JH. Are complications of transrectal ultrasound-guided biopsies of the prostate gland increasing? *Conn Med* 2011; **75**: 453-457 [PMID: 21980673]
 - 23 **Naughton CK**, Ornstein DK, Smith DS, Catalona WJ. Pain and morbidity of transrectal ultrasound guided prostate biopsy: a prospective randomized trial of 6 versus 12 cores. *J Urol* 2000; **163**: 168-171 [PMID: 10604338]
 - 24 **Hara R**, Jo Y, Fujii T, Kondo N, Yokoyama T, Miyaji Y, Nagai A. Optimal approach for prostate cancer detection as initial biopsy: prospective randomized study comparing transperineal versus transrectal systematic 12-core biopsy. *Urology* 2008; **71**: 191-195 [PMID: 18308081 DOI: 10.1016/j.urology.2007.09.029]
 - 25 **Shen PF**, Zhu YC, Wei WR, Li YZ, Yang J, Li YT, Li DM, Wang J, Zeng H. The results of transperineal versus transrectal prostate biopsy: a systematic review and meta-analysis. *Asian J Androl* 2012; **14**: 310-315 [PMID: 22101942 DOI: 10.1038/aja.2011.130]
 - 26 **Grummet JP**, Weerakoon M, Huang S, Lawrentschuk N, Frydenberg M, Moon DA, O'Reilly M, Murphy D. Sepsis and 'superbugs': should we favour the transperineal over the transrectal approach for prostate biopsy? *BJU Int* 2014; **114**: 384-388 [PMID: 24612341 DOI: 10.1111/bju.12536]
 - 27 **El-Hakim A**, Moussa S. CUA guidelines on prostate biopsy methodology. *Can Urol Assoc J* 2010; **4**: 89-94 [PMID: 20368888]
 - 28 **Akduman B**, Akduman D, Tokgöz H, Erol B, Türker T, Ayoğlu F, Mungan NA. Long-term fluoroquinolone use before the prostate biopsy may increase the risk of sepsis caused by resistant microorganisms. *Urology* 2011; **78**: 250-255 [PMID: 21705048 DOI: 10.1016/j.urology.2011.02.065]
 - 29 **Mosharafa AA**, Torky MH, El Said WM, Meshref A. Rising incidence of acute prostatitis following prostate biopsy: fluoroquinolone resistance and exposure is a significant risk factor. *Urology* 2011; **78**: 511-514 [PMID: 21782225 DOI: 10.1016/j.urology.2011.04.064]
 - 30 **Falagas ME**, Kastoris AC, Kapaskelis AM, Karageorgopoulos DE. Fosfomycin for the treatment of multidrug-resistant, including extended-spectrum beta-lactamase producing, Enterobacteriaceae infections: a systematic review. *Lancet Infect Dis* 2010; **10**: 43-50 [PMID: 20129148]
 - 31 **Mazzei T**, Diaciaci S. Pharmacological aspects of the antibiotics used for urological diagnostic procedures. *J Chemother* 2014; **26** Suppl 1: S24-S34 [PMID: 25245708 DOI: 10.1179/1120009X14Z.000000000234]
 - 32 **Wagenlehner FM**, Thomas PM, Naber KG. Fosfomycin trometamol (3,000 mg) in perioperative antibiotic prophylaxis of healthcare-associated infections after endourological interventions: a narrative review. *Urol Int* 2014; **92**: 125-130 [PMID: 24051657 DOI: 10.1159/000355103]
 - 33 **Wagenlehner F**, Stöwer-Hoffmann J, Schneider-Brachert W, Naber KG, Lehn N. Influence of a prophylactic single dose of ciprofloxacin on the level of resistance of *Escherichia coli* to fluoroquinolones in urology. *Int J Antimicrob Agents* 2000; **15**: 207-211 [PMID: 10926443]
 - 34 **Bartoletti R**, Cai T. [Antibiotic prophylaxis and prostate biopsy]. *Urologia* 2014; **81**: 218-221 [PMID: 25532467 DOI: 10.5301/uro.5000100]
 - 35 **Wagenlehner FM**, Pilatz A, Waliszewski P, Weidner W, Johansen TE. Reducing infection rates after prostate biopsy. *Nat Rev Urol* 2014; **11**: 80-86 [PMID: 24418806 DOI: 10.1038/nrurol.2013.322]

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Update summarising the conclusions of the international consultation on male lower urinary tract symptoms

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Abstract

The International Consultation on Urological Disease have recently published comprehensive conclusions, based on evidence reviewed by eight committees, on aspects of male lower urinary tract symptoms (LUTS). In this review, we summarise the conclusions from four

of the committees, namely, the evidence regarding the epidemiology of male LUTS, patient assessment, nocturia and medical management. It is indisputable that with an expanding and ageing global population the prevalence of male LUTS is likely to increase. Therefore symptom prevention and preservation of quality of life (QoL) feature highly in the guidelines. There are now a number of different medical options, proven to lead to significant improvements in symptom scores, flow rate and QoL available to men with LUTS. Meta-analyses have shown the benefits for alpha blockers, antimuscarinics, 5- α reductase and phosphodiesterase-5 inhibitors. High level evidence also exists for combinations of all of the above with alpha blockers and so men with concomitant storage symptoms, prostate volume > 30 mL, PSA > 1.4 or erectile dysfunction may be considered for combination treatment of an alpha blocker with an antimuscarinic, 5- α reductase inhibitor or phosphodiesterase-5 inhibitor respectively. In an era of personalised medicine, appropriate patient selection is likely to provide the key to the most effective clinical management strategy.

Key words: International consultation; Antimuscarinic; Male lower urinary tract symptoms; Guidelines; Nocturia; Epidemiology; 5- α reductase; Phosphodiesterase-5 inhibitors; Alpha antagonist

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Core tip: Men with lower urinary tract symptoms (LUTS) should be assessed not only for symptom severity and bother but also for risk of progression. Men with a PSA > 1.4 or a prostate larger than 30 mL should be considered for therapy to reduce prostate volume. With the options for management of men with LUTS also involving antimuscarinics, B3 agonists, phosphodiesterase inhibitors and a plethora of surgical options, a personalised approach is required. This is intended will lead to greatest patient satisfaction and improvement in quality of life.

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INTRODUCTION

The International consultation on male lower urinary tract symptoms (LUTS) took place in Fukuoka, Japan between 30th September and 4th October 2012. This was under the auspices of the Societe Internationale d'Urologie. One of the authors of this review was the co-chair for the consultation, which consisted of more than 50 international experts in LUTS.

Committees reviewed the evidence for eight different aspects of male LUTS. These included; epidemiology and natural history, aetiology and patient assessment, nocturia, sexual dysfunction, surgical therapies, detrusor underactivity, chronic pelvic pain and medical treatments for male LUTS.

For each topic, specific questions were raised by the committee members, followed by analysis and grading of the literature using the recommendations from the Oxford centre for evidence based medicine. In this article we hope to summarise the conclusions of four of the committees in the consultation regarding male LUTS. More information regarding the full guidelines can be found at the following address: <http://www.icud.info/publications.html>.

EPIDEMIOLOGY AND NATURAL HISTORY

The majority of epidemiological studies assessing LUTS have reported prevalence of symptoms in a population which tend to vary due to the methodology of data acquisition. Prevalence estimates for an elevated International Prostate Symptom Score (IPSS) score above eight range from 16% to 52%^[1-4]. A pooled analysis of 126 studies has shown an increase in urinary incontinence prevalence with age from 21% to 32% for elderly men^[5]. The prevalence of daily urinary incontinence in this analysis was reported at 9%.

More recent studies have assessed the individual symptoms captured in the IPSS with a more complete analysis of storage, voiding and post micturition symptoms as defined by the International Continence Society (ICS)^[6,7]. Nocturia and terminal dribbling are the most commonly reported storage and voiding symptoms. However, LUTS more often occur in clusters than in isolation, with overactive bladder (OAB) accounting for a prevalence of 10% to 25% as a cluster of urgency, frequency with or without nocturia^[8].

The longest follow up study of the prevalence of symptoms has shown a significant increase in LUTS over an 11 year period with a mean annual incidence of 3.7% for OAB and 0.8% for incontinence^[9]. In a

systematic review, 21 population based cohort studies were identified which looked at the natural history of LUTS^[10]. Of these only five included men with LUTS with no studies looking at symptoms in men younger than 40 years. Urinary flow rates have also been shown to decrease from age 50^[11].

Moreover, the importance of these symptoms in relation to effects on quality of life QoL and treatment seeking has been reported to be 50% and 20% respectively^[12]. This suggests that not all symptoms require treatment from the individual's perspective and prevalence data may over-estimate true symptomatic burden.

The most well reported risk factor found to be associated with the development of LUTS is age^[13]. Although LUTS are often considered a part of ageing, certain modifications to the behaviour of older men have been shown to alter this risk. Physical activity has been found to be protective reducing risk by 29%, whereas a BMI > 30 raises the risk of LUTS by 41%^[14]. Associations between metabolic syndrome and LUTS have shown mixed correlations with some studies reporting no association^[15,16]. Foodstuffs associated with LUTS include, dietary sodium, high doses vitamin C and a high alcohol intake^[17,18]. A recent meta-analysis has assessed genetic polymorphisms associated with male LUTS^[19]. The rs731236 variant of the vitamin D receptor was found to have a consistent protective effect against LUTS in different populations. The genomic approach is only beginning to reveal the potential inherited risks in developing LUTS. Conclusions from this section are shown in Table 1.

AETIOLOGY AND PATIENT ASSESSMENT

In order to describe the aetiology of LUTS, the committee firstly define what normal LUTS function should include. The Dutch population based Krimpen study provides good estimates of frequency and voided volumes. A frequency of greater than eight in 24 h is considered high and an average void of 246 mL is reported for men 50-78 years^[20]. It is suggested that a cut off of eight voids/d is not utilised as this may vary depending on age, social and climacteric factors. The maximal voided volume (formerly known as functional bladder capacity) was found to be 400 mL.

Frequency with a reduced voided volume has a number of explanations, which include; detrusor overactivity (DO), significant post voiding residual volume, inflammatory bladder conditions, malignant bladder conditions, fear of incontinence or retention and sensory bladder dysfunction. If the bladder capacity is also found to be reduced under general anaesthesia then this may be due to fibrosis or inflammation or may be seen post radiotherapy or following surgery leading to a reduced capacity bladder.

Urgency is the hallmark symptom of OAB symptom syndrome and the symptom therefore has the same prevalence as OAB. Strictly, there is no gradation of the

Table 1 Conclusions for epidemiology section

UI has a prevalence of 21%-32% in elderly men
OAB symptom cluster occurs in 10%-25% of men
Age is the strongest risk factor for LUTS

LUTS: Lower urinary tract symptoms; OAB: Overactive bladder; UI: Urinary incontinence.

symptom and it is defined, at least by the ICS, as an all or nothing sensation^[21]. The ability to defer micturition from the onset of urgency and the time between symptoms will clearly affect an individual's QoL. Factors influencing the occurrence of incontinence include urethral sphincter tone, mobility and toilet access.

In two-thirds of patients with OAB, DO may be observed on urodynamic assessment. The aetiology of DO has many proposed mechanisms. The two main mechanisms are neurogenic and myogenic. With neurogenic aetiologies, the cited evidence links to the appearance of DO with spinal and suprapinal pathologies secondary to activation of C-fiber afferents^[22]. With the myogenic theory, patchy denervation of muscle is proposed to lead to increased spontaneous contractions of detrusor muscle^[23]. Another potential aetiological contributor is detrusor ischaemia. Ischaemic bladders have been shown to have increased DO in a rabbit model of iliac artery injury^[24]. Other mechanisms include the degeneration of post synaptic nerves in the detrusor muscle and excess release of neurotransmitters and reactive oxygen species from ischaemic muscle.

Similar to all national and international guidelines, the consultation recommends a relevant history and clinical examination of the male with LUTS. The clinical examination should include a digital rectal examination of the prostate. Thereafter, a useful tool in assessing LUTS is the frequency- volume chart which has been shown to have greater accuracy over questionnaires^[25]. The optimal duration of the frequency-volume recordings is still under debate with longer periods offering more data but risk non-compliance^[26]. Generally, a 3 to 7 d chart is considered acceptable.

The use of the IPSS is also recommended as it has been tested psychometrically, is responsive to change and has been used extensively. It is however, not disease specific and therefore not a diagnostic tool and only 3 of the questions deal with the bothersome storage symptoms. It also correlates poorly with urodynamic assessment^[27]. It also does not assess urgency incontinence. Other questionnaires designed specifically for male LUTS include the ICIQ questionnaires and the Dan-PSS. These have been psychometrically tested. The ICIQ-MLUTS contains 22 questions and has been shown to be responsive to change^[28]. Similarly the DAN-PSS has good test-retest validity and also is unique as it derives a score by multiplying the bother caused by symptoms with severity^[29].

The use of urinalysis in the assessment of men with LUTS has received some thought recently due to the lack

of evidence of clinical benefit. However, it is recognised as a cheap and non-invasive test which could rule out potentially life threatening causes and so remains in the guidelines.

The medical therapy of prostatic symptoms study has shown that the risk of developing renal impairment from LUTS to be < 1% and therefore it was recommended that renal function should not be assessed as routine in men with LUTS^[30]. However, a recent Korean study has reported a reduction in GFR with severity of LUTS in older men and therefore it is kept in the guidelines^[31].

Serum PSA may be measured for two reasons, to screen for prostate cancer or to guide discussions regarding progression of LUTS. To date there is no consensus on the use of PSA to screen for prostate cancer but its use in detecting men at risk of progression is recognised^[32]. Therefore it is recommended for men according to national guidelines.

Post void residual urinary volume assessment and uroflowmetry are simple non-invasive office based assessments which are recommended based on expert opinion. Neither can distinguish between detrusor underactivity and bladder outflow obstruction. However, a significantly elevated post void residue may lead to harmful sequelae.

A myriad of imaging modalities have been reported to be useful in the assessment of the male with LUTS. Ultrasound assessment of prostate size, prostatic protrusion/angle and bladder weight/thickness are discussed. Their reproducibility, standardisation, sensitivity and specificity are inferior to formal urodynamic assessment and therefore these have not been recommended in the guidelines^[33].

Urodynamic assessment should always be performed according to good urodynamic practice guidelines. Due to its invasiveness its use should be restricted to men where a diagnosis is required or where the findings will change management. In addition, it may be useful to obtain information about other aspects of LUT function and dysfunction. It is also recommended to understand reasons behind treatment failure.

The committee discuss the usefulness of diagnosing DO. It is argued that 60% of OAB dry and 84% of OAB wet men have DO^[34]. Also 15% of healthy individuals will show this sign on urodynamic assessment^[35]. The finding, if associated with bladder outflow obstruction may resolve in 50%-70% of cases after a TURP^[36]. The reproducibility of this finding is also questioned^[37]. Therefore the use of urodynamic assessment should be undertaken by a clinician with sufficient understanding and clear questions in mind.

The more definitive use of urodynamics is in the assessment of obstruction and detrusor underactivity. The ICS nomogram is recommended for distinguishing these with the bladder outflow obstruction index being the important calculated parameter. During repeat testing only 1% of men changed category from obstructed to non- obstructed. The diagnosis of detrusor underactivity is reported to be under-recognised. In a study of 2066

Table 2 Conclusions for assessment section

History and examination are mandatory
Frequency volume chart is recommended for 3-7 d
The IPSS is recommended but it is not disease specific
Urine dipstick assessment is recommended to exclude serious underlying conditions
Serum creatinine estimation is still recommended
PSA should be performed according to national guidelines
Flow rate and post void residual estimation are recommended
Prostatic protrusion/angle and bladder weight/thickness are inferior to cystometry
Cystometry should be limited to men where a finding will change management

IPSS: International Prostate Symptom Score.

neurologically normal individuals 224 were shown to have this urodynamic finding^[38]. These men were shown not to benefit from bladder outflow obstruction surgery. Conclusions from this section are reported in Table 2.

NOCTURIA

Nocturia is likely to occur consequent upon a spectrum of clinical conditions. The agreed terminology states one should wake to void with the intention of returning to sleep. Clearly, an adjustment is required for those who work night shifts or those who sleep for short intervals. Nocturia not only impacts upon sleep and QoL but has also been shown to affect morbidity and mortality. In a Japanese study, nocturia twice at night doubled the risk of fractures and mortality^[39]. Its association with daytime fatigue, reduced work productivity and reduced vitality is also recognised^[40,41].

In the assessment of men with nocturia, it is imperative to differentiate those with nocturnal polyuria (> 20% and 33% of urine output during sleep relative to the day in young and older individuals respectively)^[21]. Another important parameter is the maximum voided volume (functional bladder capacity). If nocturnal urine production is greater than functional bladder capacity then an individual will be forced to wake from sleep to void. Another classification proposed by the committee is the division into pathological and non-pathological nocturia. The latter essentially involves waking for another reason such as external noises which lead to a convenience void. Conversely, the former occurs due to medical factors affecting sleep or urine storage.

Pathological nocturia may be divided into five categories: (1) reduced bladder capacity; this may be due to bladder fibrosis, previous surgery, radiation, OAB syndrome and bladder outflow obstruction; (2) global polyuria; this is often due to an undiagnosed endocrine abnormality such as diabetes mellitus, diabetes insipidus, polydipsia, hypercalcaemia or pharmacotherapy; (3) nocturnal polyuria which may be secondary to congestive cardiac failure, autonomic neuropathy, hypoalbuminaemia and nephrotic syndrome. Other causes include disruption to the secretion of vasopressin, drugs

and obstructive sleep apnoea; (4) sleep disorders including insomnia, sleep walking and drugs; and (5) mixed disorders resulting from a combination of the above.

When assessing a patient with nocturia it is also desirable to investigate risk factors. In the Finnish Nocturia and Overactive bladder study half of men with benign prostatic enlargement had nocturia^[42]. Men with major depression have a 2-6 fold increased risk of nocturia compared to those without^[42,43]. Obesity is also linked with a 2-3 fold risk of nocturia^[44]. One in three patients with nocturia in a Finnish study also reported urgency, however of those with OAB, 50% have nocturia^[45].

Very few national and international guideline committees have developed nocturia guidelines separately to other LUTS. The Japanese clinical guideline recommends differentiating nocturia into nocturia only, nocturia with diurnal frequency without other LUTS and nocturia with diurnal frequency with other LUTS. It is only the latter category which should be referred to urologists.

Management should follow a stepwise approach. Conservative measures should include fluid and caffeine restriction in the evening, leg elevation during the day and mid-afternoon diuretics and elasticated stockings. A systematic review has shown no discernible benefit of 5- α reductase inhibitors in improving nocturia although it is accepted some elderly men may see a reduction in nocturia frequency^[46]. Alpha antagonists on the other hand have been shown to decrease nocturia frequency over placebo^[47]. However, the majority of studies reporting this included men with benign prostatic obstruction symptoms. Combinations of the above two drug classes have also shown significant benefits for patients with nocturia. Similarly, the combination of an antimuscarinic agent and an alpha antagonist has shown clinically significant improvements over placebo^[48].

Antimuscarinic agents are only useful in reducing nocturia when it is associated with OAB^[49]. In non OAB patients the benefit is not so apparent. Desmopressin has been shown in a meta-analysis to safely reduce nocturnal frequency, delay time to first void and improve sleep quality^[50]. In a 12-mo extension study the reduction in nocturia episodes was still reduced significantly in 67% of men. The guidelines do however, recommend monitoring of sodium levels due to the risk of hyponatraemia. Another pharmacotherapeutic option includes the use of a diuretic 6 h prior to sleep. This has been shown to reduce nocturia by 0.5/night over placebo^[51].

Non Steroidal Anti-inflammatory Drugs may reduce nocturnal frequency but their use beyond 3 mo is not recommended due to the harms outweighing the benefits^[52]. Two phytotherapies have been shown in randomised trials to lead to a reduction in nocturia episodes, pygeum africanum and secale cereal^[53,54]. The former was shown to lead to a 19% reduction and the latter halved the nocturia frequency. The trials included in these trails are of a short duration, with limited numbers

Table 3 Conclusions for nocturia section

Nocturia frequency more than twice increases morbidity and mortality
It is important to differentiate nocturia from nocturnal polyuria, global polyuria and sleep disorders
Drugs shown to improve nocturia include alpha antagonists, and antimuscarinics, which may be combined
No overall benefit has been shown for 5- α reductase inhibitors but these may be useful for some men
Desmopressin has been shown to be beneficial but caution should be applied in renal failure and elderly patients
Diuretics are useful in specific cases
Benzodiazepines may be used to improve sleep quality

and so the data should be used with caution. Finally, benzodiazepines may be used to promote sleep. These are thought to affect nocturia only *via* an indirect effect by improving sleep^[55].

Procedures such as TURP to de-obstruct men with bladder outflow obstruction have been shown to reduce nocturia^[56]. These procedures should not be used in men without symptoms of obstruction and men should be counselled about adverse events prior to embarking upon surgery. Conclusions from this section are reported in Table 3.

MEDICAL TREATMENTS FOR MALE LUTS

Phytotherapies for the treatment of male LUTS were reviewed by this committee. The committee acknowledged the large number of publications with phytotherapies. Unfortunately the majority suffered from a lack of scientific rigor. However, some RCT's did exist. Of the phytotherapies, *Serenoa repens* (Saw palmetto) was the most investigated. A meta-analysis which looked at 14 RCT's showed Permixon (commercially available Saw palmetto) led to a reduction in IPSS of 4.8, increase in Qmax of 1.2 mL/s without changes in prostate volume or PSA^[57]. The most recent Cochrane review has shown no significant benefit to LUTS with *Serenoa repens* and therefore it is not recommended by the committee^[50].

Pygeum Africanum has been compared to placebo in 18 RCT's. It is shown to lead to improvements in symptoms and flow rate. However, the majority of RCT's were of a low quality and the results were not reported in a manner which permitted meta-analysis^[58]. Similarly, *Secale cereale* has been reported in two RCT's of poor quality and a meta-analysis was withdrawn from the literature in 2011^[59].

Four RCT's have assessed β -sitosterol. The trials were of moderate quality and showed a weighted mean difference in IPSS of 4.9 points and improvement in Qmax of 3.9 mL/s^[60]. Mild adverse events were reported. The long term effects of β -sitosterol remain unknown and therefore the committee have given no recommendation to this pending more data. Similarly, *Urtica dioica* has been shown to have superiority over placebo in RCT's of moderate quality. Improvements in IPSS, Qmax, and post void residual volume are reported. The agent

has also been compared to tamsulosin and finasteride and has been found to be non-inferior^[61,62]. No current recommendation is made pending further data.

The use of α 1a and α 1d selective blockers are recommended due to reduced systemic side effects. The α 1a components work on the prostate and bladder neck and the α 1d on the bladder and spinal cord. Twelve meta-analyses have shown the efficacy α of blockers^[63]. Data on efficacy and adverse events exists to beyond five years. A new selective α blocker -Silodosin- has shown significant improvement over placebo in IPSS, Qmax and also led to better improvement in voiding symptoms over tamsulosin but higher incidence of retrograde ejaculation^[64]. Urodynamically α antagonists lead to reduction in PdetQmax of 10-20 cm H₂O and increase Qmax by 2-3 mL/s^[65].

In this section, it is acknowledged that the majority of patients in trials of antimuscarinics are women. Kaplan *et al*^[66] were unable to demonstrate efficacy with tolterodine in men with storage symptoms. However, Herschorn *et al*^[67] have conducted a meta-analysis of fesoterodine 4 and 8 mg and found a reduction in frequency, urgency and voided volumes. The risk of retention was not apparently increased in these studies.

Combination therapy is considered a useful treatment option in men with both storage and voiding symptoms. Seven RCT's have shown the superiority of combination treatment over single agent treatment and placebo. It is argued that the symptomatic differences are small but significant. However, a trial powered to assess perception of treatment benefit showed a significant difference suggesting this difference is still important to patients^[68]. It should also be noted that these trials have selected men with a predominance of storage symptoms which should not be generalised to all men with LUTS. In addition, the majority of exclusion criteria for these trials include men with a post void residue < 250 mL and it must be recognised that men with larger residuals have not been investigated.

Androgens are implicated in the development of BPH and it has long been known that surgical castration may relieve urinary retention due to BPO. The use of luteinizing hormone releasing hormone (LHRH) agonists has been shown to reduce prostate volume by 25%, improve the IPSS score and Qmax but requires long term continuation^[69]. This is often met with the side effects of androgen deprivation such as reduced libido, impotency and hot flashes. On the other hand, LHRH antagonists (cetorelix and ozarelix) have failed to show superiority over placebo. Degarelix has not been studied in a placebo controlled RCT in men with LUTS/BOO. Thus the recommendation of the committee is that LHRH agonists may be used in carefully selected men who are not surgical candidates and LHRH antagonists are not recommended.

Multiple large RCT's have demonstrated the efficacy and safety of finasteride^[70,71]. The studies quote a 6%-10% risk of sexual dysfunction with placebo having up to 6% risk. Long term safety up to 10 years has also

Table 4 Conclusions for medical therapies section

Phytotherapies are not recommended due to evidence from meta-analysis or poor RCT data
Alpha antagonists are recommended
Antimuscarinic agents have mostly been trialled in women, but there is evidence to show their efficacy
Men in antimuscarinic trials have a post void residual of < 250 mL
Men with a PSA > 1.5 or prostate volume > 30 mL are more likely to benefit from a 5- α reductase inhibitor
Combination treatments may be suitable for some men
Discontinuation of the 5- α reductase inhibitor is not recommended as the symptoms are likely to return
Phosphodiesterase inhibitors may be used in men with a combination of LUTS and erectile dysfunction

LUTS: Lower urinary tract symptoms; RCTs: Randomized controlled trials.

been shown^[72]. With finasteride a reduction of 3 point on the IPSS score is seen from 6 mo through to 4 years. Also an improvement in Qmax of 2 mL/s is reported. However, it has been shown that not all men benefit from finasteride. Meta-analysis has revealed men with a PSA > 1.5 or prostate volume > 30 mL are more likely to obtain benefit^[73]. The mean change in prostate volume is 20% and a 50% reduction in PSA after 6 mo. Long term studies have shown a reduction in acute urinary retention rates from 2.7% to 1.1%. The proscar long term efficacy and safety study revealed a risk reduction of requiring TURP from 10% to 5%^[30]. Clearly, the reduction of risk for acute retention and need for surgery will depend on the characteristics of the selected population and those with a poorer flow rate, larger prostate and higher PSA are at increased risk of progression and thus more likely to benefit from this therapy^[74].

Dutasteride inhibits both isoenzymes of 5- α reductase and thus a more profound reduction in intraprostatic dihydrotestosterone levels is seen (95% vs 70%)^[75]. Similarly multiple RCT's have demonstrated efficacy in symptom improvement, flow rate and QoL up to two years and is summarised in a meta-analysis^[76]. An open label study, where the placebo group were switched to dutasteride and the dutasteride group continued follow up, showed lesser improvements in the group which was switched compared to the group already taking dutasteride suggesting earlier commencement of the drug leads to greater benefit than later initiation^[30]. All men selected for the dutasteride studies had a prostate volume > 30 mL and/or a PSA > 1.5 ng/mL. This may explain differences between the findings in these trials compared to those for finasteride.

The Enlarged Prostate International Comparator Study trial has compared 12-mo outcomes in men randomised to dutasteride or finasteride^[77]. The improvements in IPSS were 5.8 and 5.5 points and in Qmax 2 and 1.7 mL/s respectively. Another important study looked at the effect of discontinuation of finasteride and dutasteride^[78]. All participants took either finasteride or dutasteride with tamsulosin for one year and then stopped the 5- α

reductase inhibitor. After one year of discontinuation prostate volume and PSA levels returned to 90%-95% of baseline. Therefore discontinuation is not recommended. The PCPT and REDUCE trials reported a relative risk reduction of 40% of developing clinical BPH with the use of finasteride over 7 years or dutasteride over 4 years respectively^[79].

The committee also reviewed the use of phosphodiesterase-5 inhibitors in men with benign prostatic obstruction. Four RCT's have assessed tadalafil, one sildenafil and one vardenafil. Improvements are shown in IPSS, Qmax and IIEF scores. Only one study has compared tadalafil to tamsulosin and shown similar improvements in IPSS and flow rate between the drugs^[80]. One open label study has shown continued improvements up to one year^[81]. Adverse events are reported in a meta-analysis and include flushing, gastro-oesophageal reflux, headache, dyspepsia, back pain and sinusitis^[82].

The combination of alpha antagonists and 5- α reductase has been reviewed in a recent systematic review^[83]. Three studies have investigated combination treatments vs placebo. The largest studies are the MTOPS and CombAT^[84]. The former assessed the risk of progression in 3047 men with moderate to severe LUTS. The use of doxazosin alone reduced this risk by 39%, finasteride by 34% and combination therapy by 66%. However, the risk of requiring invasive treatment was only seen to be delayed by doxazosin compared to finasteride which reduced the risk. The latter study randomised 4500 patients to one of placebo, tamsulosin, dutasteride or combination. The major difference between this and the MTOPS study was the inclusion of only men with prostate volumes greater than 30 mL in the CombAT study. In this study, dutasteride was superior to tamsulosin but only after 18 mo. Combination was however superior to both individual therapies and placebo.

There are five non-placebo controlled randomised studies assessing the use of alpha blockers and phosphodiesterase-5 inhibitors as combination therapy compared in a meta-analysis^[82]. Improvements in IPSS and Qmax were significantly greater than alpha blockers alone. More importantly, the combination was reported to be safe with no reported serious adverse events. Patients individual circumstances should dictate if combination therapy and if so which combination therapy is required. Conclusions from this section are reported in Table 4.

CONCLUSION

We hope to have provided you with the highlights and evidence from the international consultation on male LUTS. It is always important to recognise the limitations of guidelines in that they provide us with up to date evidence which is stratified by quality but patients in the majority of RCT's have been included on the basis of strict criteria which will not always fit with real life patients. It is always important to treat the individual

patient but knowing the evidence behind our decision making will hopefully lead to better patient care.

REFERENCES

- Haidinger G**, Waldhör T, Madersbacher S, Schatzl G, Vutuc C. Prevalence of lower urinary tract symptoms in Austrian males: update 2009. *Urol Int* 2011; **87**: 385-391 [PMID: 22041923 DOI: 10.1159/000332427]
- Tuncay Aki F**, Aygun C, Bilir N, Erkan I, Ozen H. Prevalence of lower urinary tract symptoms in a community-based survey of men in Turkey. *Int J Urol* 2003; **10**: 364-370 [PMID: 12823690 DOI: 10.1046/j.1442-2042.2003.00638.x]
- Boyle P**, Robertson C, Mazzetta C, Keech M, Hobbs FD, Fourcade R, Kiemeny L, Lee C. The prevalence of lower urinary tract symptoms in men and women in four centres. The UrEpik study. *BJU Int* 2003; **92**: 409-414 [PMID: 12930430 DOI: 10.1046/j.1464-410X.2003.04369.x]
- Seim A**, Hoyo C, Ostbye T, Vatten L. The prevalence and correlates of urinary tract symptoms in Norwegian men: the HUNT study. *BJU Int* 2005; **96**: 88-92 [PMID: 15963127 DOI: 10.1111/j.1464-410X.2005.05573]
- Shamliyan TA**, Wyman JF, Ping R, Wilt TJ, Kane RL. Male urinary incontinence: prevalence, risk factors, and preventive interventions. *Rev Urol* 2009; **11**: 145-165 [PMID: 19918340]
- Homma Y**, Yamaguchi O, Hayashi K. Epidemiologic survey of lower urinary tract symptoms in Japan. *Urology* 2006; **68**: 560-564 [PMID: 16979726 DOI: 10.1016/j.urology.2006.03.035]
- Coyne KS**, Sexton CC, Thompson CL, Milsom I, Irwin D, Kopp ZS, Chapple CR, Kaplan S, Tubaro A, Aiyer LP, Wein AJ. The prevalence of lower urinary tract symptoms (LUTS) in the USA, the UK and Sweden: results from the Epidemiology of LUTS (EpiLUTS) study. *BJU Int* 2009; **104**: 352-360 [PMID: 19281467 DOI: 10.1111/j.1464-410X.2009.08427]
- Irwin DE**, Milsom I, Kopp Z, Abrams P, Artibani W, Herschorn S. Prevalence, severity, and symptom bother of lower urinary tract symptoms among men in the EPIC study: impact of overactive bladder. *Eur Urol* 2009; **56**: 14-20 [PMID: 19278775 DOI: 10.1016/j.eururo.2009.02.026]
- Malmsten UG**, Molander U, Peecker R, Irwin DE, Milsom I. Urinary incontinence, overactive bladder, and other lower urinary tract symptoms: a longitudinal population-based survey in men aged 45-103 years. *Eur Urol* 2010; **58**: 149-156 [PMID: 20356669 DOI: 10.1016/j.eururo.2010.03.014]
- Irwin DE**, Milsom I, Chancellor MB, Kopp Z, Guan Z. Dynamic progression of overactive bladder and urinary incontinence symptoms: a systematic review. *Eur Urol* 2010; **58**: 532-543 [PMID: 20573443 DOI: 10.1016/j.eururo.2010.06.007]
- Fukuta F**, Masumori N, Mori M, Tsukamoto T. Natural history of lower urinary tract symptoms in Japanese men from a 15-year longitudinal community-based study. *BJU Int* 2012; **110**: 1023-1029 [PMID: 22233355 DOI: 10.1111/j.1464-410X.2011.10866.x]
- Irwin DE**, Milsom I, Kopp Z, Abrams P. Symptom bother and health care-seeking behavior among individuals with overactive bladder. *Eur Urol* 2008; **53**: 1029-1037 [PMID: 18243515 DOI: 10.1016/j.eururo.2008.01.027]
- Braun MH**, Sommer F, Haupt G, Mathers MJ, Reifenrath B, Engelmann UH. Lower urinary tract symptoms and erectile dysfunction: co-morbidity or typical "Aging Male" symptoms? Results of the "Cologne Male Survey". *Eur Urol* 2003; **44**: 588-594 [PMID: 14572759 DOI: 10.1016/S0302-2838(03)00358-0]
- Parsons JK**, Messer K, White M, Barrett-Connor E, Bauer DC, Marshall LM. Obesity increases and physical activity decreases lower urinary tract symptom risk in older men: the Osteoporotic Fractures in Men study. *Eur Urol* 2011; **60**: 1173-1180 [PMID: 21802828 DOI: 10.1016/j.eururo.2011.07.040]
- Martin SA**, Haren MT, Marshall VR, Lange K, Wittert GA. Prevalence and factors associated with uncomplicated storage and voiding lower urinary tract symptoms in community-dwelling Australian men. *World J Urol* 2011; **29**: 179-184 [PMID: 20963421 DOI: 10.1007/s00345-010-0605-8]
- Ohgaki K**, Hikima N, Horiuchi K, Kondo Y. Association between metabolic syndrome and male lower urinary tract symptoms in Japanese subjects using three sets of criteria for metabolic syndrome and International Prostate Symptom Score. *Urology* 2011; **77**: 1432-1438 [PMID: 21316081 DOI: 10.1016/j.urology.2010.12.024]
- Maserejian NN**, Giovannucci EL, McVary KT, McKinlay JB. Dietary, but not supplemental, intakes of carotenoids and vitamin C are associated with decreased odds of lower urinary tract symptoms in men. *J Nutr* 2011; **141**: 267-273 [PMID: 21178086 DOI: 10.3945/jn.110.132514]
- Rohrmann S**, Crespo CJ, Weber JR, Smit E, Giovannucci E, Platz EA. Association of cigarette smoking, alcohol consumption and physical activity with lower urinary tract symptoms in older American men: findings from the third National Health And Nutrition Examination Survey. *BJU Int* 2005; **96**: 77-82 [PMID: 15963125 DOI: 10.1111/j.1464-410X.2005.05571.x]
- Cartwright R**, Mangera A, Tikkinen KA, Rajan P, Pesonen J, Kirby AC, Thiagamoorthy G, Ambrose C, Gonzalez-Maffei J, Bennett PR, Palmer T, Walley A, Järvelin MR, Khullar V, Chapple C. Systematic review and meta-analysis of candidate gene association studies of lower urinary tract symptoms in men. *Eur Urol* 2014; **66**: 752-768 [PMID: 24491308 DOI: 10.1016/j.eururo.2014.01.007]
- Blanker MH**, Groeneveld FP, Bohnen AM, Bernsen RM, Prins A, Thomas S, Ruud Bosch JL. Voided volumes: normal values and relation to lower urinary tract symptoms in elderly men, a community-based study. *Urology* 2001; **57**: 1093-1098 discussion 1098-1099 [PMID: 11377315 DOI: 10.1016/S0090-4295(01)00988-8]
- Abrams P**, Cardozo L, Fall M, Griffiths D, Rosier P, Ulmsten U, van Kerrebroeck P, Victor A, Wein A. The standardisation of terminology of lower urinary tract function: report from the Standardisation Sub-committee of the International Continence Society. *Neurourol Urodyn* 2002; **21**: 167-178 [PMID: 11857671 DOI: 10.1002/nau.10052]
- Yoshimura N**. Bladder afferent pathway and spinal cord injury: possible mechanisms inducing hyperreflexia of the urinary bladder. *Prog Neurobiol* 1999; **57**: 583-606 [PMID: 10221783 DOI: 10.1016/S0301-0082(98)00070-7]
- Gillespie JI**. The autonomous bladder: a view of the origin of bladder overactivity and sensory urge. *BJU Int* 2004; **93**: 478-483 [PMID: 15008713 DOI: 10.1111/j.1464-410X.2003.04667.x]
- Azadzoi KM**, Tarcan T, Kozlowski R, Krane RJ, Siroky MB. Overactivity and structural changes in the chronically ischemic bladder. *J Urol* 1999; **162**: 1768-1778 [PMID: 10524933 DOI: 10.1016/S0022-5347(05)68236-5]
- McCormack M**, Infante-Rivard C, Schick E. Agreement between clinical methods of measurement of urinary frequency and functional bladder capacity. *Br J Urol* 1992; **69**: 17-21 [PMID: 1737246 DOI: 10.1111/j.1464-410X.1992.tb15450.x]
- Homma Y**, Ando T, Yoshida M, Kageyama S, Takei M, Kimoto K, Ishizuka O, Gotoh M, Hashimoto T. Voiding and incontinence frequencies: variability of diary data and required diary length. *Neurourol Urodyn* 2002; **21**: 204-209 [PMID: 11948713 DOI: 10.1002/nau.10016]
- Nitti VW**, Kim Y, Combs AJ. Correlation of the AUA symptom index with urodynamics in patients with suspected benign prostatic hyperplasia. *Neurourol Urodyn* 1994; **13**: 521-527; discussion 527-529 [PMID: 7530554]
- Donovan JL**, Brookes ST, de la Rosette JJ, Peters TJ, Porru D, Kondo A, Dabhoiwala N, Millard R, Bosch R, Nordling J, Matos Ferreira A, Höfner K, Mostafid H, Walter S, Nissenkorn I, Frimodt Moller C, Mendes Silva M, Chapple C, Abrams P. The responsiveness of the ICSmale questionnaire to outcome: evidence from the ICS-BPH study. *BJU Int* 1999; **83**: 243-248 [PMID: 10233487 DOI: 10.1046/j.1464-410x.1999.00930.x]
- Pannek J**, Berges RR, Haupt G, Senge T. Value of the Danish Prostate Symptom Score compared to the AUA symptom score and pressure/flow studies in the preoperative evaluation of men with symptomatic benign prostatic hyperplasia. *Neurourol Urodyn* 1998;

- 17: 9-18 [PMID: 9453687 DOI: 10.1002/(SICI)1520-6777(1998)17:1<9::AID-NAU3>3.0.CO;2-H]
- 30 **McConnell JD**, Roehrborn CG, Bautista OM, Andriole GL, Dixon CM, Kusek JW, Lepor H, McVary KT, Nyberg LM, Clarke HS, Crawford ED, Diokno A, Foley JP, Foster HE, Jacobs SC, Kaplan SA, Kreder KJ, Lieber MM, Lucia MS, Miller GJ, Menon M, Milam DF, Ramsdell JW, Schenkman NS, Slawin KM, Smith JA. The long-term effect of doxazosin, finasteride, and combination therapy on the clinical progression of benign prostatic hyperplasia. *N Engl J Med* 2003; **349**: 2387-2398 [PMID: 14681504 DOI: 10.1056/NEJMoa030656]
- 31 **Kwon YM**, Cho B, Son KY, Choi HC, Park SG, Park JH. Lower urinary tract symptoms have negative associations with glomerular filtration rate irrespective of prostate volume in Korean men. *Urology* 2012; **79**: 182-187 [PMID: 21962878 DOI: 10.1016/j.urology.2011.08.011]
- 32 **Crawford ED**, Wilson SS, McConnell JD, Slawin KM, Lieber MC, Smith JA, Meehan AG, Bautista OM, Noble WR, Kusek JW, Nyberg LM, Roehrborn CG. Baseline factors as predictors of clinical progression of benign prostatic hyperplasia in men treated with placebo. *J Urol* 2006; **175**: 1422-1426; discussion 1426-1427 [PMID: 16516013 DOI: 10.1016/S0022-5347(05)00708-1]
- 33 **Mangera A**, Osman NI, Chapple CR. Assessment of BPH/BOO. *Indian J Urol* 2014; **30**: 177-180 [PMID: 24744517 DOI: 10.4103/0970-1591.126902]
- 34 **Hashim H**, Abrams P. Is the bladder a reliable witness for predicting detrusor overactivity? *J Urol* 2006; **175**: 191-194; discussion 194-195 [PMID: 16406907 DOI: 10.1016/S0022-5347(05)00067-4]
- 35 **Wyndaele JJ**, De Wachter S. Cystometrical sensory data from a normal population: comparison of two groups of young healthy volunteers examined with 5 years interval. *Eur Urol* 2002; **42**: 34-38 [PMID: 12121727 DOI: 10.1016/S0302-2838(02)00221-X]
- 36 **Kageyama S**, Watanabe T, Kurita Y, Ushiyama T, Suzuki K, Fujita K. Can persisting detrusor hyperreflexia be predicted after transurethral prostatectomy for benign prostatic hypertrophy? *Neurourol Urodyn* 2000; **19**: 233-240 [PMID: 10797580 DOI: 10.1002/(SICI)1520-6777(2000)19:3<233>
- 37 **Homma Y**, Kondo Y, Takahashi S, Kitamura T, Kawabe K. Reproducibility of cystometry in overactive detrusor. *Eur Urol* 2000; **38**: 681-685 [PMID: 11111184 DOI: 10.1159/000020362]
- 38 **Thomas AW**, Cannon A, Bartlett E, Ellis-Jones J, Abrams P. The natural history of lower urinary tract dysfunction in men: the influence of detrusor underactivity on the outcome after transurethral resection of the prostate with a minimum 10-year urodynamic follow-up. *BJU Int* 2004; **93**: 745-750 [PMID: 15049984 DOI: 10.1111/j.1464-410X.2003.04719.x]
- 39 **Nakagawa H**, Niu K, Hozawa A, Ikeda Y, Kaiho Y, Ohmori-Matsuda K, Nakaya N, Kuriyama S, Ebihara S, Nagatomi R, Tsuji I, Arai Y. Impact of nocturia on bone fracture and mortality in older individuals: a Japanese longitudinal cohort study. *J Urol* 2010; **184**: 1413-1418 [PMID: 20727545 DOI: 10.1016/j.juro.2010.05.093]
- 40 **Tikkinen KA**, Johnson TM, Tammela TL, Sintonen H, Haukka J, Huhtala H, Auvinen A. Nocturia frequency, bother, and quality of life: how often is too often? A population-based study in Finland. *Eur Urol* 2010; **57**: 488-496 [PMID: 19361907 DOI: 10.1016/j.eururo.2009.03.080]
- 41 **Coyne KS**, Zhou Z, Bhattacharyya SK, Thompson CL, Dhawan R, Versi E. The prevalence of nocturia and its effect on health-related quality of life and sleep in a community sample in the USA. *BJU Int* 2003; **92**: 948-954 [PMID: 14632853 DOI: 10.1111/j.1464-410X.2003.04527.x]
- 42 **Tikkinen KA**, Auvinen A, Johnson TM, Weiss JP, Keränen T, Tiitinen A, Polo O, Partinen M, Tammela TL. A systematic evaluation of factors associated with nocturia—the population-based FINNO study. *Am J Epidemiol* 2009; **170**: 361-368 [PMID: 19515794 DOI: 10.1093/aje/kwp133]
- 43 **Asplund R**, Henriksson S, Johansson S, Isacson G. Nocturia and depression. *BJU Int* 2004; **93**: 1253-1256 [PMID: 15180617 DOI: 10.1111/j.1464-410X.2004.04835.x]
- 44 **Shiri R**, Hakama M, Häkkinen J, Auvinen A, Huhtala H, Tammela TL, Koskimäki J. The effects of lifestyle factors on the incidence of nocturia. *J Urol* 2008; **180**: 2059-2062 [PMID: 18804241 DOI: 10.1016/j.juro.2008.07.042]
- 45 **Tikkinen KA**, Tammela TL, Rissanen AM, Valpas A, Huhtala H, Auvinen A. Is the prevalence of overactive bladder overestimated? A population-based study in Finland. *PLoS One* 2007; **2**: e195 [PMID: 17332843 DOI: 10.1371/journal.pone.0000195]
- 46 **Tacklind J**, Fink HA, Macdonald R, Rutks I, Wilt TJ. Finasteride for benign prostatic hyperplasia. *Cochrane Database Syst Rev* 2010; **(10)**: CD006015 [PMID: 20927745 DOI: 10.1002/14651858.CD006015.pub3]
- 47 **Vallancien G**, Emberton M, Alcaraz A, Matzkin H, van Moorselaar RJ, Hartung R, Harving N, Elhilali M. Alfuzosin 10 mg once daily for treating benign prostatic hyperplasia: a 3-year experience in real-life practice. *BJU Int* 2008; **101**: 847-852 [PMID: 18321317 DOI: 10.1111/j.1464-410X.2008.07458.x]
- 48 **Kaplan SA**, Roehrborn CG, Rovner ES, Carlsson M, Bavendam T, Guan Z. Tolerodine and tamsulosin for treatment of men with lower urinary tract symptoms and overactive bladder: a randomized controlled trial. *JAMA* 2006; **296**: 2319-2328 [PMID: 17105794 DOI: 10.1001/jama.296.19.2319]
- 49 **Kaplan SA**, Roehrborn CG, Dmochowski R, Rovner ES, Wang JT, Guan Z. Tolerodine extended release improves overactive bladder symptoms in men with overactive bladder and nocturia. *Urology* 2006; **68**: 328-332 [PMID: 16904446 DOI: 10.1016/j.urology.2006.03.006]
- 50 **Zong H**, Yang C, Peng X, Zhang Y. Efficacy and safety of desmopressin for treatment of nocturia: a systematic review and meta-analysis of double-blinded trials. *Int Urol Nephrol* 2012; **44**: 377-384 [PMID: 21898039 DOI: 10.1007/s11255-011-0054-3]
- 51 **Reynard JM**, Cannon A, Yang Q, Abrams P. A novel therapy for nocturnal polyuria: a double-blind randomized trial of frusemide against placebo. *Br J Urol* 1998; **81**: 215-218 [PMID: 9488061 DOI: 10.1046/j.1464-410X.1998.00511.x]
- 52 **Shin HI**, Kim BH, Chang HS, Park CH, Kim CI. Long-term effect of loxoprofen sodium on nocturia in patients with benign prostatic hyperplasia. *Korean J Urol* 2011; **52**: 265-268 [PMID: 21556213 DOI: 10.4111/kju.2011.52.4.265]
- 53 **Wilt T**, Ishani A, Mac Donald R, Rutks I, Stark G. Pygeum africanum for benign prostatic hyperplasia. *Cochrane Database Syst Rev* 2002; **(1)**: CD001044 [PMID: 11869585 DOI: 10.1002/14651858.CD001044]
- 54 **Wilt T**, Mac Donald R, Ishani A, Rutks I, Stark G. Cernilton for benign prostatic hyperplasia. *Cochrane Database Syst Rev* 2000; **(2)**: CD001042 [PMID: 10796739 DOI: 10.1002/14651858.CD001042]
- 55 **Takami N**, Okada A. Triazolam and nitrazepam use in elderly outpatients. *Ann Pharmacother* 1993; **27**: 506-509 [PMID: 8477130]
- 56 **Van Dijk MM**, Wijkstra H, Debruyne FM, De La Rosette JJ, Michel MC. The role of nocturia in the quality of life of men with lower urinary tract symptoms. *BJU Int* 2010; **105**: 1141-1146 [PMID: 22299137 DOI: 10.1111/j.1464-410X.2009.08969.x]
- 57 **Boyle P**, Robertson C, Lowe F, Roehrborn C. Updated meta-analysis of clinical trials of Serenoa repens extract in the treatment of symptomatic benign prostatic hyperplasia. *BJU Int* 2004; **93**: 751-756 [PMID: 15049985 DOI: 10.1111/j.1464-410X.2003.04735.x]
- 58 **MacDonald R**, Tacklind JW, Rutks I, Wilt TJ. Serenoa repens monotherapy for benign prostatic hyperplasia (BPH): an updated Cochrane systematic review. *BJU Int* 2012; **109**: 1756-1761 [PMID: 22551330 DOI: 10.1111/j.1464-410X.2012.11172.x]
- 59 **Wilt TJ**, Macdonald R, Ishani A, Rutks I, Stark G. WITHDRAWN: Cernilton for benign prostatic hyperplasia. *Cochrane Database Syst Rev* 2011; **(5)**: CD001042 [PMID: 21563128 DOI: 10.1002/14651858.CD001042.pub2]
- 60 **Wilt T**, Ishani A, MacDonald R, Stark G, Mulrow C, Lau J. Beta-sitosterols for benign prostatic hyperplasia. *Cochrane Database Syst Rev* 2000; **(2)**: CD001043 [PMID: 10796740 DOI: 10.1002/14651858.CD001043]
- 61 **Sökeland J**, Albrecht J. [Combination of Sabal and Urtica extract vs. finasteride in benign prostatic hyperplasia (Aiken stages I to

- II). Comparison of therapeutic effectiveness in a one year double-blind study]. *Urologe A* 1997; **36**: 327-333 [PMID: 9340898 DOI: 10.1007/s001200050106]
- 62 **Engelmann U**, Walther C, Bondarenko B, Funk P, Schläpke S. Efficacy and safety of a combination of sabal and urtica extract in lower urinary tract symptoms. A randomized, double-blind study versus tamsulosin. *Arzneimittelforschung* 2006; **56**: 222-229 [PMID: 16618015 DOI: 10.1055/s-0031-1296714]
- 63 **Yuan J**, Liu Y, Yang Z, Qin X, Yang K, Mao C. The efficacy and safety of alpha-1 blockers for benign prostatic hyperplasia: an overview of 15 systematic reviews. *Curr Med Res Opin* 2013; **29**: 279-287 [PMID: 23323875 DOI: 10.1185/03007995.2013.766594]
- 64 **Kawabe K**, Yoshida M, Homma Y. Silodosin, a new alpha1A-adrenoceptor-selective antagonist for treating benign prostatic hyperplasia: results of a phase III randomized, placebo-controlled, double-blind study in Japanese men. *BJU Int* 2006; **98**: 1019-1024 [PMID: 16945121 DOI: 10.1111/j.1464-410X.2006.06448.x]
- 65 **Bosch JL**. Urodynamic effects of various treatment modalities for benign prostatic hyperplasia. *J Urol* 1997; **158**: 2034-2044 [PMID: 9366308 DOI: 10.1016/S0022-5347(01)68149-7]
- 66 **Kaplan SA**, Roehrborn CG, Chancellor M, Carlsson M, Bavendam T, Guan Z. Extended-release tolterodine with or without tamsulosin in men with lower urinary tract symptoms and overactive bladder: effects on urinary symptoms assessed by the International Prostate Symptom Score. *BJU Int* 2008; **102**: 1133-1139 [PMID: 18510659 DOI: 10.1111/j.1464-410X.2008.07761.x]
- 67 **Herschorn S**, Jones JS, Oelke M, MacDiarmid S, Wang JT, Guan Z. Efficacy and tolerability of fesoterodine in men with overactive bladder: a pooled analysis of 2 phase III studies. *Urology* 2010; **75**: 1149-1155 [PMID: 19914702 DOI: 10.1016/j.urology.2009.09.007]
- 68 **MacDiarmid SA**, Peters KM, Chen A, Armstrong RB, Orman C, Aquilina JW, Nitti VW. Efficacy and safety of extended-release oxybutynin in combination with tamsulosin for treatment of lower urinary tract symptoms in men: randomized, double-blind, placebo-controlled study. *Mayo Clin Proc* 2008; **83**: 1002-1010 [PMID: 18775200 DOI: 10.4065/83.9.1002]
- 69 **Oesterling JE**. Endocrine therapies for symptomatic benign prostatic hyperplasia. *Urology* 1994; **43**: 7-16 [PMID: 7509536 DOI: 10.1016/0090-4295(94)90212-7]
- 70 **Tenover JL**, Pagano GA, Morton AS, Liss CL, Byrnes CA. Efficacy and tolerability of finasteride in symptomatic benign prostatic hyperplasia: a primary care study. Primary Care Investigator Study Group. *Clin Ther* 1997; **19**: 243-258 [PMID: 9152564 DOI: 10.1016/S0149-2918(97)80113-0]
- 71 **Andersen JT**, Ekman P, Wolf H, Beisland HO, Johansson JE, Kontturi M, Lehtonen T, Tveter K. Can finasteride reverse the progress of benign prostatic hyperplasia? A two-year placebo-controlled study. The Scandinavian BPH Study Group. *Urology* 1995; **46**: 631-637 [PMID: 7495111 DOI: 10.1016/S0090-4295(99)80291-X]
- 72 **Vaughan ED**. Long-Term Experience With 5-alpha-Reductase Inhibitors. *Rev Urol* 2003; **5** Suppl 5: S22-S27 [PMID: 16985966]
- 73 **Roehrborn CG**, Boyle P, Bergner D, Gray T, Gittelman M, Shown T, Melman A, Bracken RB, deVere White R, Taylor A, Wang D, Waldstreicher J. Serum prostate-specific antigen and prostate volume predict long-term changes in symptoms and flow rate: results of a four-year, randomized trial comparing finasteride versus placebo. PLESS Study Group. *Urology* 1999; **54**: 662-669 [PMID: 10510925 DOI: 10.1016/S0090-4295(99)00232-0]
- 74 **Roehrborn CG**, McConnell JD, Lieber M, Kaplan S, Geller J, Malek GH, Castellanos R, Coffield S, Saltzman B, Resnick M, Cook TJ, Waldstreicher J. Serum prostate-specific antigen concentration is a powerful predictor of acute urinary retention and need for surgery in men with clinical benign prostatic hyperplasia. PLESS Study Group. *Urology* 1999; **53**: 473-480 [PMID: 10096369 DOI: 10.1016/S0090-4295(98)00654-2]
- 75 **Amory JK**, Wang C, Swerdloff RS, Anawalt BD, Matsumoto AM, Bremner WJ, Walker SE, Haberer LJ, Clark RV. The effect of 5alpha-reductase inhibition with dutasteride and finasteride on semen parameters and serum hormones in healthy men. *J Clin Endocrinol Metab* 2007; **92**: 1659-1665 [PMID: 17299062 DOI: 10.1210/jc.2006-2203]
- 76 **O'Leary MP**, Roehrborn C, Andriole G, Nickel C, Boyle P, Höfner K. Improvements in benign prostatic hyperplasia-specific quality of life with dutasteride, the novel dual 5alpha-reductase inhibitor. *BJU Int* 2003; **92**: 262-266 [PMID: 12887480]
- 77 **Nickel JC**, Gilling P, Tammela TL, Morrill B, Wilson TH, Rittmaster RS. Comparison of dutasteride and finasteride for treating benign prostatic hyperplasia: the Enlarged Prostate International Comparator Study (EPICS). *BJU Int* 2011; **108**: 388-394 [PMID: 21631695 DOI: 10.1111/j.1464-410X.2011.10195.x]
- 78 **Parsons JK**, Schenk JM, Arnold KB, Messer K, Till C, Thompson IM, Kristal AR. Finasteride reduces the risk of incident clinical benign prostatic hyperplasia. *Eur Urol* 2012; **62**: 234-241 [PMID: 22459892 DOI: 10.1016/j.eururo.2012.03.007]
- 79 **Toren P**, Margel D, Kulkarni G, Finelli A, Zlotta A, Fleshner N. Effect of dutasteride on clinical progression of benign prostatic hyperplasia in asymptomatic men with enlarged prostate: a post hoc analysis of the REDUCE study. *BMJ* 2013; **346**: f2109 [PMID: 23587564]
- 80 **Oelke M**, Giuliano F, Mirone V, Xu L, Cox D, Viktrup L. Monotherapy with tadalafil or tamsulosin similarly improved lower urinary tract symptoms suggestive of benign prostatic hyperplasia in an international, randomised, parallel, placebo-controlled clinical trial. *Eur Urol* 2012; **61**: 917-925 [PMID: 22297243 DOI: 10.1016/j.eururo.2012.01.013]
- 81 **Donatucci CF**, Brock GB, Goldfischer ER, Pommerville PJ, Elion-Mboussa A, Kissel JD, Viktrup L. Tadalafil administered once daily for lower urinary tract symptoms secondary to benign prostatic hyperplasia: a 1-year, open-label extension study. *BJU Int* 2011; **107**: 1110-1116 [PMID: 21244606 DOI: 10.1111/j.1464-410X.2010.09687.x]
- 82 **Gacci M**, Corona G, Salvi M, Vignozzi L, McVary KT, Kaplan SA, Roehrborn CG, Serni S, Mirone V, Carini M, Maggi M. A systematic review and meta-analysis on the use of phosphodiesterase 5 inhibitors alone or in combination with α -blockers for lower urinary tract symptoms due to benign prostatic hyperplasia. *Eur Urol* 2012; **61**: 994-1003 [PMID: 22405510 DOI: 10.1016/j.eururo.2012.02.033]
- 83 **Füllhase C**, Chapple C, Cornu JN, De Nunzio C, Gratzke C, Kaplan SA, Marberger M, Montorsi F, Novara G, Oelke M, Porst H, Roehrborn C, Stief C, McVary KT. Systematic review of combination drug therapy for non-neurogenic male lower urinary tract symptoms. *Eur Urol* 2013; **64**: 228-243 [PMID: 23375241 DOI: 10.1016/j.eururo.2013.01.018]
- 84 **Roehrborn CG**, Barkin J, Tubaro A, Emberton M, Wilson TH, Brotherton BJ, Castro R. Influence of baseline variables on changes in International Prostate Symptom Score after combined therapy with dutasteride plus tamsulosin or either monotherapy in patients with benign prostatic hyperplasia and lower urinary tract symptoms: 4-year results of the CombAT study. *BJU Int* 2014; **113**: 623-635 [PMID: 24127818 DOI: 10.1111/bju.12500]

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Retrospective Study

Barbed polyglyconate vs monocryl suture in vesico-urethral anastomosis during robot-assisted radical prostatectomy

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Data sharing statement: Technical appendix, statistical code, and dataset available from the corresponding author at docdevang@gmail.com. Consent was not obtained but the presented data are anonymized and risk of identification is low.

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Abstract

AIM: To compare outcomes using barbed polyglyconate (V-Loc 180) vs monofilament monocryl suture in forming vesico-urethral anastomosis (VUA) during robot assisted radical prostatectomy.

METHODS: Review of prospectively collected robot assisted radical prostatectomy data between July 2011 and September 2012. VUA technique: VUA was performed using 2 cm × 15 cm 2/0 V-Loc 180 continuous sutures or 3/0 monofilament monocryl sutures. Anastomotic integrity was tested intra-operatively with a water leak test. All patients had a post-operative cystogram at day 7 to 10.

RESULTS: There were 189 patients in the study with 113 in the V-Loc group and 76 in the monocryl group. Demographics were similar for both groups ($P > 0.05$). The median operative time for V-Loc group was 130 min and monocryl group was 145 min, which was statistically significant ($P < 0.001$). The median blood loss for both groups was 200 mL with no significant difference ($P = 0.260$). The pathology results of the 2 groups were similar ($P = 0.537$). Four patients in the V-Loc group and two patients in the monocryl group had radiological urinary leak. This was not statistically significant ($P = 1.00$) and all patients improved with conservative management. The continence rates were comparable for both groups.

CONCLUSION: V-Loc suture significantly reduced operative time facilitating ease of VUA formation. Overall functional outcome and urinary morbidity were not significantly different from the monofilament group.

Key words: Prostatectomy; Prostate cancer; Robotic surgery; V-loc, Monocryl; Anastomosis; Operative time; Gleason score; Prostate volume; Incontinence

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Core tip: The V-Loc suture was found to significantly reduce the operative time and facilitate ease of vesico-urethral anastomosis formation. The overall functional outcome and urinary morbidity were not significantly different from the conventional monofilament group.

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INTRODUCTION

Robot-assisted radical prostatectomy (RARP) is a common procedure for the management of localised prostate cancer. The formation of vesico-urethral anastomosis (VUA) is an aspect that remains a challenge in RARP. Commonly, a running continuous single knot VUA is implemented as described by Van Velthoven^[1]. However, this can be challenging to perform, and the monofilament suture may slip as the anastomosis is fashioned. Accordingly the surgeon must constantly check suture tension to avoid urine leaks.

The V-Loc 180 is a unidirectional barbed (40 barbs per inch), self-anchoring suture (Covidien, Mansfield, MA, United States), a polyglyconate suture composed of a 180-day absorbable copolymer of glycolic acid and trimethylene carbonate. The barbs prevent sliding of the suture from the tissue whilst providing evenly spread of tension with its barbed points.

The unidirectional barbed suture has been introduced in plastic surgery and has demonstrated good results in tissue apposition and healing^[2,3]. As such it is an appealing choice for VUA formation. Evidence suggests that this suture affords an effective anastomosis with adequate tension without ischaemia or inflammation^[4,5]. With its relative ease of use, it has also been shown to decrease the time to perform VUA in robot-assisted radical prostatectomy^[4-10].

This study aims to report the outcomes of using a barbed suture, V-Loc 180, compared with the conventional monofilament monocryl in forming the VUA in RARP performed by two surgeons in a private hospital setting in Australia.

MATERIALS AND METHODS

This was a prospective study of patients undergoing robot-assisted radical prostatectomy by two urologists at a private hospital in Brisbane, Australia. The hospital committee approved ethics for the study. Consecutive patients undergoing VUA using V-Loc 180 suture and conventional 3/0 monocryl were included from the study period between July 2011 and September 2012. Demographics [age, body mass index (BMI), prostate specific antigen (PSA)] and perioperative data (operative time, blood loss, pathology, anastomosis leak, continence, complications) were collected for analysis.

VUA technique

Following bladder neck reconstruction and the completion of a posterior rhabdosphincter reconstruction (Rocco stitch) where appropriate, vesico-urethral anastomosis was performed using 2 cm × 15 cm 2/0 V-Loc 180 continuous sutures or 3/0 monofilament monocryl sutures. Anastomotic integrity was tested intra-operatively with a water leak test. All patients had a post-operative cystogram at day 7 to 10.

Statistical analysis

Statistical analysis was carried out using mean ± SD for age, BMI, PSA, prostate volume. Median and interquartile range was used for other data. Where appropriate, student *t*-test and Mann-Whitney Wilcoxon (operative time and blood loss) tests were used. Fisher Exact test was used for anastomotic leak comparison. The categorical variables was analysed with χ^2 test. The *P* value was set as < 0.05. Analysis was performed by Devang Desai and Kevin Lah.

RESULTS

There were 189 patients who underwent robot-assisted radical prostatectomy during the study period who were included. One hundred and thirteen patients had VUA formed by V-Loc suture and 76 patients *via* monocryl suture. The age, BMI and PSA for the two groups were similar in characteristics (Table 1).

The V-Loc group had a median operative time of 130 min whereas the monocryl group had 145 min which was statistically significant (*P* < 0.001). The median blood loss for both groups was 200 mL with no significant difference (*P* = 0.260). The pathology results of the 2 groups were similar (*P* = 0.537). In the V-Loc group, 70 patients (62%) had pT2 disease with a 2.9% positive margin rate and 43 patients (38%) had pT3 disease with a 42% positive margin rate. The monocryl group had 51 patients (67%) with pT2 disease with a 0% positive margin rate and 25 patients (33%) with pT3 disease and a 36% positive margin rate. There were 4 patients in the V-Loc group with radiological urinary leak and 2 patients in the monocryl group. However this was not statistically significant (*P* = 1.00) and all patients

Table 1 Demographics

Analysis (n = 189)	V-loc (n = 113)	Monocryl (n = 76)	P value
Age (yr)	61.09 ± 6.36	61.45 ± 6.95	0.6439
BMI (kg/m ²)	27.67 ± 3.89	27.65 ± 3.09	0.9686
PSA (ng/mL)	6.98 ± 4.67	6.41 ± 2.74	0.3443
Median prostate volume (mL)	48 (38.87- 56.85)	46.7 (40-57.5)	0.97606

BMI: Body mass index; PSA: Prostate specific antigen.

Table 2 Operative data n (%)

Analysis (n = 189)	V-loc (n = 113)		Monocryl (n = 76)		Test
Study demographics	Median	IQR	Median	IQR	P value
Operative time (min)	130	100-150	145	125-180	< 0.001
Blood loss (mL)	200	100-350	200	120-400	0.26
Gleason score					
3+3	4		1		0.224
3+4	59		40		
4+3	21		22		
4+4	1		1		
4+5	26		9		
5+4	2		3		0.537
Pathology					
pT2	70 (62)		51 (67)		
+ ve margin status	2 (2.9)		0 (0)		
pT3	43 (38)		25 (33)		
+ ve margin status	18 (42)		9 (36)		1.00
Radiological leaks	4 (3.5)		2 (2.6)		
3 mo continence					
0 pads	68 (60)		50 (65)		
1 pad	31 (27)		19 (25)		
2 pads	12 (11)		5 (7)		0.726
3 or more pads	2 (2)		2 (3)		

IQR: Inter quartile range.

improved with conservative management. Two patients required catheterisation for 7 d and one patient for 12 d. There were no clinically significant leaks in both groups. At 3 mo, the continence rate was similar for the 2 groups with 68 patients (60%) in the V-Loc group being pad-free continent and 50 patients (65%) in monocryl group. Thirty-one patients (27%) in the V-Loc group required 1 pad per day and 19 patients (25%) in the monocryl group. 12 patients (11%) in the V-Loc group required 2 pads/d and 5 patients (7%) in the monocryl group. 2 patients in each V-Loc and monocryl groups required 3 or more pads, 2% and 3% respectively (Table 2).

The aim of the study was not to examine potency and that we do not have meaningful long term 12 mo potency data as we were only examining the performance of the anastomosis. However, there were no cases of urethrovesical anastomotic stenosis in this study.

A detailed cost-benefit analysis was not the focus of this study. None-the-less it is worth noting that at our institution, the cost of a single V-Loc suture is \$AU28.67 compared to that of Monocryl at \$AU10.59. However use of the V-Loc was associated with a significantly shorter operating time. Given that the running costs of an operating theatre are around \$AU22.00 per minute, this

reduction in operating time offsets the increased suture cost and indeed may translate into cost savings for the hospital through increased efficiency.

DISCUSSION

Barbed suture is commonly used in the formation of VUA in RARP. The results demonstrated in this study were comparable to that of the literature since its introduction in urology for the VUA formation in RARP [11].

Williams *et al* [12] compared the use of one of the first barbed polyglyconate suture materials in the market to the standard polyglactin 910 suture (Vicryl, Ethicon, Somerville, NJ, United States) in the formation of VUA during RARP. Although the VUA time was statistically reduced in the barbed suture group, there was no difference in the overall operative times. With their initial experience, barbed suturing was reported to be more costly and required technical modification to avoid over-tightening, delayed healing and longer catheterisation time. They found that more patients in the barbed suture group had contrast extravasation on day 8 cystogram.

Conversely, Tewari and colleagues demonstrated that the barbed suture, V-Loc, was feasible in formation of the VUA in their study by comparing 50 consecutive patients undergoing RARP with V-Loc and 50 patients with the conventional monofilament suture prior to this new technique [4]. The V-Loc group had a significantly shorter posterior reconstruction and VUA times. The median operative time was 106 min for the V-Loc group with estimated blood loss of 150 mL. Only one patient in the V-Loc group had a small urinary leak which resolved with conservative measures. The conclusion was that a barbed suture was effective in improving operative times but needed further follow-up for urinary leak rates and functional outcomes.

Similarly, Zorn *et al* [13] found this novel technique to be safe and efficient. Their case series of 30 consecutive patients showed a mean operative time of 166 min, VUA time of 11.3 min and posterior reconstruction time of 3.3 min. They implemented Lapra-Ty clips, an absorbable anchoring device at the ends of V-Loc sutures to prevent slippage. The 3 mo pad-free continence was 65%, which was comparable to our 60%. Zorn *et al* [5] later published a prospective randomised controlled trial comparing V-Loc with standard monofilament suture in RARP. Although the total operation time was similar for both groups, the VUA time was significantly less in the V-Loc group. The 3 mo pad-free continence rate was better than their previous result with 81% in the V-Loc group and 76% in the monofilament group. Their overall conclusion was that use of barbed suture, V-Loc, was more efficient and cost effective, especially in minimising nurse set-up time and avoiding the use of absorbable suture clips.

Sammon *et al* [6] similarly performed a randomised controlled trial comparing barbed vs standard monofilament sutures in RARP. In their multi-surgeon trial, 33 patients underwent V-Loc VUA and 31 patients had the

conventional monofilament VUA. Similar to the literature, the authors found the new barbed suture to be safe and efficient in reducing the VUA time. Their median operative time was 184 min and 201 min for the V-Loc and monofilament groups, respectively. Six week pad-free continence rate was 51.6% for the V-Loc group and 50% for the monofilament group.

Furthermore, Massoud and team in France demonstrated that the V-Loc suture was effective and economically sound in VUA formation during RARP, whilst showing no difference in continence rates and complications compared with the conventional monofilament suture^[10]. There have been many studies favouring the use of barbed suture in VUA during RARP^[7,8,14].

Interestingly, Manganiello *et al*^[15] found no difference in VUA time between barbed suture and standard monofilament suture in their prospective study of 35 patients in each group. The authors commented that the involvement of residents in operative cases could have contributed to the lack of difference. Other outcomes of urinary morbidity was comparable to the control group and the authors state that they prefer the use of V-Loc in VUA as it obviates the need for an assistant to follow the suture to continually reapply tension to previous throws.

Our outcomes of operative time, blood loss and urinary morbidity are comparable to that of the literature. We have found that the V-loc suture simplifies the formation of the VUA and allows the anastomosis to be fashioned with confidence. Whilst the suture can be brittle, careful handling of the needle only, while minimizing direct handling of the suture itself has minimised any issues related to the suture snapping. One could also be concerned with regard the potential for a cheese-wire effect to occur when tension is present. However, in such cases the suture has been particularly useful as it keeps the anastomosis nicely together, while monofilament sutures by comparison would slip. It is important though to ensure that the suture is drawn through at right angles to the tissue to mitigate any cheese-wire effect. Limitations of the study include its relatively small sample size and lack of randomisation. None-the-less the series demonstrates the usefulness of the V-loc suture in VUA formation in a local Australian series.

In conclusion, the V-Loc suture was found to significantly reduce the operative time and facilitate ease of VUA formation. The overall functional outcome and urinary morbidity were not significantly different from the conventional monofilament group.

COMMENTS

Background

Barbed suture is commonly used in the formation of Vesico-urethral anastomosis (VUA) in robot-assisted radical prostatectomy (RARP). The results demonstrated in this study were comparable to that of the literature since its introduction in urology for the VUA formation in RARP.

Research frontiers

Larger randomized trial is required to evaluate the efficiency of barbed suture in

performing VUA in RARP.

Innovations and breakthroughs

Their outcomes of operative time, blood loss and urinary morbidity are comparable to that of the literature. We have found that the V-loc suture simplifies the formation of the VUA and allows the anastomosis to be fashioned with confidence. Whilst the suture can be brittle, careful handling of the needle only, while minimizing direct handling of the suture itself has minimised any issues related to the suture snapping. One could also be concerned with regard the potential for a cheese-wire effect to occur when tension is present. However, in such cases the suture has been particularly useful as it keeps the anastomosis nicely together, while monofilament sutures by comparison would slip. It is important though to ensure that the suture is drawn through at right angles to the tissue to mitigate any cheese-wire effect.

Applications

VUA can be safely and effectively performed using V-loc suture during RARP.

Terminology

RARP Robot assisted radical prostatectomy; VUA: Vesicourethral anastomosis.

Peer-review

This study aimed to compare the barbed polyglyconate suture (V-Loc 180) with standard monofilament monocril suture in VUA during robot-assisted radical prostatectomy. It is simple and well written.

REFERENCES

- 1 Van Velthoven RF, Ahlering TE, Peltier A, Skarecky DW, Clayman RV. Technique for laparoscopic running urethrovesical anastomosis: the single knot method. *Urology* 2003; **61**: 699-702 [PMID: 12670546 DOI: 10.1016/S0090-4295(02)02543-8]
- 2 Paul MD. Barbed sutures for aesthetic facial plastic surgery: indications and techniques. *Clin Plast Surg* 2008; **35**: 451-461 [PMID: 18558239 DOI: 10.1016/j.cps.2008.03.005]
- 3 Moya AP. Barbed sutures in body surgery. *Aesthet Surg J* 2013; **33**: 57S-71S [PMID: 24084880 DOI: 10.1177/1090820X13499577]
- 4 Tewari AK, Srivastava A, Sooriakumaran P, Slevin A, Grover S, Waldman O, Rajan S, Herman M, Berryhill R, Leung R. Use of a novel absorbable barbed plastic surgical suture enables a "self-cinching" technique of vesicourethral anastomosis during robot-assisted prostatectomy and improves anastomotic times. *J Endourol* 2010; **24**: 1645-1650 [PMID: 20818988 DOI: 10.1089/end.2010.0316]
- 5 Zorn KC, Trinh QD, Jeldres C, Schmitges J, Widmer H, Lattouf JB, Sammon J, Liberman D, Sun M, Bianchi M, Karakiewicz PI, Denis R, Gautam G, El-Hakim A. Prospective randomized trial of barbed polyglyconate suture to facilitate vesico-urethral anastomosis during robot-assisted radical prostatectomy: time reduction and cost benefit. *BJU Int* 2012; **109**: 1526-1532 [PMID: 22221566 DOI: 10.1111/j.1464-410X.2011.10763.x]
- 6 Sammon J, Kim TK, Trinh QD, Bhandari A, Kaul S, Sukumar S, Rogers CG, Peabody JO. Anastomosis during robot-assisted radical prostatectomy: randomized controlled trial comparing barbed and standard monofilament suture. *Urology* 2011; **78**: 572-579 [PMID: 21782218 DOI: 10.1016/j.urology.2011.03.069]
- 7 Polland AR, Graverson JA, Mues AC, Badani KK. Polyglyconate unidirectional barbed suture for posterior reconstruction and anastomosis during robot-assisted prostatectomy: effect on procedure time, efficacy, and minimum 6-month follow-up. *J Endourol* 2011; **25**: 1493-1496 [PMID: 21823984 DOI: 10.1089/end.2010.0668]
- 8 Hemal AK, Agarwal MM, Babbar P. Impact of newer unidirectional and bidirectional barbed suture on vesicourethral anastomosis during robot-assisted radical prostatectomy and its comparison with polyglecaprone-25 suture: an initial experience. *Int Urol Nephrol* 2012; **44**: 125-132 [PMID: 21523325 DOI: 10.1007/s11255-011-9967-0]

- 9 **Pan D**, Sengupta S, Webb DR. Use of a barbed suture for continuous urethro-vesical anastomosis during robot-assisted laparoscopic radical prostatectomy. *J Robotic Surg* 2012; **6**: 241-242 [DOI: 10.1007/s11701-011-0299-y]
- 10 **Massoud W**, Thanigasalam R, El Hajj A, Girard F, Théveniaud PE, Chatellier G, Baumert H. Does the use of a barbed polyglyconate absorbable suture have an impact on urethral anastomosis time, urethral stenosis rates, and cost effectiveness during robot-assisted radical prostatectomy? *Urology* 2013; **82**: 90-94 [PMID: 23806395 DOI: 10.1016/j.urology.2013.02.002]
- 11 **Kaul S**, Sammon J, Bhandari A, Peabody J, Rogers CG, Menon M. A novel method of urethrovesical anastomosis during robot-assisted radical prostatectomy using a unidirectional barbed wound closure device: feasibility study and early outcomes in 51 patients. *J Endourol* 2010; **24**: 1789-1793 [PMID: 20626271 DOI: 10.1089/end.2010.0200]
- 12 **Williams SB**, Alemozaffar M, Lei Y, Hevelone N, Lipsitz SR, Plaster BA, Hu JC. Randomized controlled trial of barbed polyglyconate versus polyglactin suture for robot-assisted laparoscopic prostatectomy anastomosis: technique and outcomes. *Eur Urol* 2010; **58**: 875-881 [PMID: 20708331 DOI: 10.1016/j.eururo.2010.07.021]
- 13 **Zorn KC**, Widmer H, Lattouf JB, Liberman D, Bhojani N, Trinh QD, Sun M, Karakiewicz PI, Denis R, El-Hakim A. Novel method of knotless vesicourethral anastomosis during robot-assisted radical prostatectomy: feasibility study and early outcomes in 30 patients using the interlocked barbed unidirectional V-LOC180 suture. *Can Urol Assoc J* 2011; **5**: 188-194 [PMID: 21672482 DOI: 10.5489/cuaj.10194]
- 14 **Chapman S**, Turo R, Cross W. Vesicourethral anastomosis using V-Loc™ barbed suture during robot-assisted radical prostatectomy. *Cent European J Urol* 2011; **64**: 236 [PMID: 24578901 DOI: 10.5173/ceju.2011.04.art10]
- 15 **Manganiello M**, Kenney P, Canes D, Sorcini A, Moinzadeh A. Unidirectional barbed suture versus standard monofilament for urethrovesical anastomosis during robotic assisted laparoscopic radical prostatectomy. *Int Braz J Urol* 2012; **38**: 89-96 [PMID: 22397770 DOI: 10.1590/S1677-55382012000100013]

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Nothing like data showing significant death reduction can better support prostate cancer screening

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Abstract

At 13 years of follow-up, the European Randomized Study of Screening for Prostate Cancer shows a 21% decrease in prostate cancer deaths in the prostate-specific antigen-screened group compared to control. This difference increases to 27% when non compliance is taken into account. The benefits of screening compared to control are higher at 28% (compared to 21%) when duration of follow-up ranges between 8 and 12 years. Such data

obtained following an average rate of one screening performed once every 5.7 years in quite impressive and strongly supports the use of screening for a successful fight against a cancer which grows to an advanced and non curable stage without any specific sign or symptom.

Key words: Prostate cancer; Screening; Prostate-specific antigen; Early diagnosis; Early treatment

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Core tip: The wide use of prostate-specific antigen for screening of prostate cancer is a major issue preventing the recruitment of true unscreened controls in studies on prostate cancer screening. This is why only studies performed some time ago can meet this requirement of a small contamination of the control group. The European Randomized Study on Screening for Prostate Cancer had a contamination of 23%-40%, thus permitting to see, at 13 years of follow-up, a 21% decrease in prostate cancer deaths in the screened group compared to no screening. The earlier Quebec trial had a contamination of only 7% with a 62% decrease in death from prostate cancer at a median follow-up of 7.9 years. A contamination of 85% of the control group prevented the United States PLCO trial from providing reliable data. The data obtained in the European and Quebec trials are strong arguments for a major positive impact of early diagnosis which needs screening for a successful fight against prostate cancer.

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INTRODUCTION

The significant decrease in prostate cancer deaths

Table 1 Comparative characteristics of the randomized European Randomized Study of Screening for Prostate Cancer and Quebec studies

Study	No. in study	Date of start/end enrolment	Contamination of control group	PSA cut off (ng/mL)	Screening frequency	Median follow-up	Planned screening interval	Controlled treatment	Effect on prostate cancer deaths
ERSPC ^[4]	162388 55-69 yr	1993-2003	23%-40%	3	1/5.7 yr	13 yr	4 yr	No	21% reduction ($P = 0.001$) 27% after adjustment for non-compliance
Quebec ^[6]	46486 45-80 yr	1988-1999	7.30% (no prestudy screening)	3	1/yr	7.9 yr	1 yr	Yes	62% reduction ($P < 0.002$)

PSA: Prostate-specific antigen; ERSPC: European Randomized Study of Screening for Prostate Cancer.

during the last two decades is mostly attributed to early diagnosis and improved treatments^[1]. Prostate cancer, however, remains the second cause of cancer death with 27740 (76/d) deaths predicted to occur in the United States alone in 2015^[2]. Two facts about prostate cancer screening deserve special consideration: (1) prostate cancer progresses insidiously to the advanced or metastatic and non-curable stage without any cancer-specific symptom or sign and; and (2) consequently, without screening, almost all men would be diagnosed with prostate cancer only at the advanced stage after losing the possibility of a cure, a situation superimposable to that of 50 years ago when late diagnosis was equivalent to the prognosis of a painful death from the disease within 2 to 3 years.

FIRST SCREENING STUDIES

While the follow-up of the European Randomized Study of Screening for Prostate Cancer (ERSPC) has already shown reduction in prostate cancer mortality after 9 and 11 years of follow-up^[3], even better results have been observed at 13 years of follow-up^[4]. The ERSPC is a multicentre and randomized trial performed in eight European countries with some variations in the protocol(s) used not but somewhat similar to the earlier Quebec clinical trial^[5] (Table 1).

At a follow-up through 2010 (13 years), the rate ratio of prostate cancer mortality was 0.79 (95%CI: 0.69-0.91) (-21%) decreasing to 0.73 (-27%) (95%CI: 0.61-0.88) after adjustment for non-participation^[4]. There were 355 deaths from prostate cancer in the screened group vs 545 in the control group for a 0.79 (-21%) rate ratio ($P = 0.001$). Men, on average, were screened 2.3 times during the 13 years of follow-up for an average of one screening every 5.7 years (Table 1).

Although expected from the long-term follow-up needed to assess the development of early stage prostate cancer, it is quite interesting to see that the benefits of screening increase with the duration of follow-up with relative ratios of death of 0.88 for years 0-4 (-12%), 0.82 at years 4-8 (-18%) and a further decrease to 0.72 (95%CI: 0.59-0.88) (-28%) at years 8-12. These ERSPC benefits, despite being of some

lower magnitude, are in agreement with the previous data of the Quebec Prostate Cancer Screening (QPCS) Trial (Table 1)^[5,6]. One partial explanation for the difference could be the absence of standardized optimal treatment in the ERSPC study^[4] since an optimal/standardized treatment should offer advantages. A second difference of importance in the two trials is the screening rate observed in the "control group" (contamination) estimated at 23%-40%^[4] in the ERSPC study compared to only 7% in the QPCS trial (Table 1)^[6]. A third difference is that screening was performed once a year in the QPCS study compared to only once every 5.7 years on average in the ERSPC trial, thus delaying the diagnosis up to an average of 4.7 years in the ERSPC study.

Despite these data showing that a significant number of lives are saved^[4,6] in the screened group and the knowledge that quality-of-life adjusted life-years is significantly improved despite the reported overdiagnosis^[7], screening remains controversial despite the fact that a large number of well-informed men decide to be screened. It seems preferable for a man to know that he has early stage prostate cancer discovered at screening and be in a position to be able to decide about treatment instead of being a non-screened person who learns later that he has only 2 to 3 years to live under the very difficult/painful conditions of advanced prostate cancer. A major source of controversy about prostate-specific antigen (PSA) screening apparently comes from the United States Prostate, Lung Colorectal and Ovarian Cancer (PLCO) study where the results obtained should never have been considered since 85% of men in the control group had been screened. In other words, both groups of men were highly screened, thus making impossible to detect a statistically significant effect on prostate cancer deaths. In short, the PLCO trial did not have a true control group, thus resulting in insufficient statistical power to reach any valid conclusion (for review see Labrie 2013)^[1].

TREATMENT DECISION INVOLVING PATIENT

The main argument for those who do not support

screening or show a hesitant position^[4] despite the convincing data of well performed studies (Table 1) concerns overdiagnosis. The facts, however, are that overdiagnosis has been estimated to occur in about 40% of cases detected by screening^[8,9] while a comparable 27%-62% decrease in deaths from prostate cancer can be achieved with screening^[4,6]. It would seem that avoiding death from prostate cancer is much preferable to "overdiagnosis" which, it must be recognized, includes the strong possibility of a cure or long-term life and is most likely to avoid death from prostate cancer.

It is clear that future research should attempt to differentiate between aggressive cancers and those which could be considered "indolent". The reality, however, is that cancers are usually multifocal, thus seriously complicating any reliable prognostic attempt. In any case, until reliable prognostic tools become available, screening accompanied by a well informed decision about treatment shared between the patient and the physician(s) appears to be the best choice if one wants to have a high probability of avoiding death from prostate cancer.

REFERENCES

- 1 **Labrie F.** PSA screening for prostate cancer: why so much controversy? *Asian J Androl* 2013; **15**: 603-607 [PMID: 23770941 DOI: 10.1038/aja.2013.70]
- 2 **Siegel RL,** Miller KD, Jemal A. Cancer statistics, 2015. *CA Cancer J Clin* 2015; **65**: 5-29 [PMID: 25559415 DOI: 10.3322/caac.21254]
- 3 **Schröder FH,** Hugosson J, Roobol MJ, Tammela TL, Ciatto S, Nelen V, Kwiatkowski M, Lujan M, Lilja H, Zappa M, Denis LJ, Recker F, Páez A, Määtänen L, Bangma CH, Aus G, Carlsson S, Villers A, Rebillard X, van der Kwast T, Kujala PM, Blijenberg BG, Stenman UH, Huber A, Taari K, Hakama M, Moss SM, de Koning HJ, Auvinen A. Prostate-cancer mortality at 11 years of follow-up. *N Engl J Med* 2012; **366**: 981-990 [PMID: 22417251 DOI: 10.1056/NEJMoa1113135]
- 4 **Schröder FH,** Hugosson J, Roobol MJ, Tammela TL, Zappa M, Nelen V, Kwiatkowski M, Lujan M, Määtänen L, Lilja H, Denis LJ, Recker F, Páez A, Bangma CH, Carlsson S, Puliti D, Villers A, Rebillard X, Hakama M, Stenman UH, Kujala P, Taari K, Aus G, Huber A, van der Kwast TH, van Schaik RH, de Koning HJ, Moss SM, Auvinen A. Screening and prostate cancer mortality: results of the European Randomised Study of Screening for Prostate Cancer (ERSPC) at 13 years of follow-up. *Lancet* 2014; **384**: 2027-2035 [PMID: 25108889 DOI: 10.1016/S0140-6736(14)60525-0]
- 5 **Labrie F,** Candas B, Dupont A, Cusan L, Gomez JL, Suburu RE, Diamond P, Lévesque J, Bélanger A. Screening decreases prostate cancer death: first analysis of the 1988 Quebec prospective randomized controlled trial. *Prostate* 1999; **38**: 83-91 [PMID: 9973093 DOI: 10.1002/(SICI)1097-0045(19990201)38]
- 6 **Labrie F,** Candas B, Cusan L, Gomez JL, Bélanger A, Brousseau G, Chevrete E, Lévesque J. Screening decreases prostate cancer mortality: 11-year follow-up of the 1988 Quebec prospective randomized controlled trial. *Prostate* 2004; **59**: 311-318 [PMID: 15042607 DOI: 10.1002/pros.20017]
- 7 **Heijnsdijk EA,** Wever EM, Auvinen A, Hugosson J, Ciatto S, Nelen V, Kwiatkowski M, Villers A, Páez A, Moss SM, Zappa M, Tammela TL, Mäkinen T, Carlsson S, Korfage IJ, Essink-Bot ML, Otto SJ, Draisma G, Bangma CH, Roobol MJ, Schröder FH, de Koning HJ. Quality-of-life effects of prostate-specific antigen screening. *N Engl J Med* 2012; **367**: 595-605 [PMID: 22894572 DOI: 10.1056/NEJMoa1201637]
- 8 **Draisma G,** Boer R, Otto SJ, van der Cruisen IW, Damhuis RA, Schröder FH, de Koning HJ. Lead times and overdiagnosis due to prostate-specific antigen screening: estimates from the European Randomized Study of Screening for Prostate Cancer. *J Natl Cancer Inst* 2003; **95**: 868-878 [PMID: 12813170 DOI: 10.1093/jnci/95.12.868]
- 9 **Cooperberg MR,** Lubeck DP, Meng MV, Mehta SS, Carroll PR. The changing face of low-risk prostate cancer: trends in clinical presentation and primary management. *J Clin Oncol* 2004; **22**: 2141-2149 [PMID: 15169800 DOI: 10.1200/JCO.2004.10.062]

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Clinical perspective on renal elasticity quantification by acoustic radiation force impulse: Where we are and where we are going

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deformity) of parenchymatous organs using tissue strain imaging techniques and elastosonography. Measures of the mechanical properties of the kidneys have given conflicting results. There are various conditions that affect the variability of renal parenchymal measures, the main target of the investigations. They can be classified as intrinsic (depending upon the patient), extrinsic (depending upon the operator) and mixed (both intrinsic and extrinsic). Indeed, the mechanical properties of the kidney depend on various conditions that alter its histology, mainly the amount of fibrosis in the renal parenchymal interstitium. Anatomical factors play an important role because the kidney is a highly anisotropic organ with important differences when considering the cortex and the medulla. Physical factors include the frequency of the probe, compression and distance from source to target. Many factors can affect measurements and it is necessary to find an accurate technique in order to avoid mistakes and to obtain reproducible data. Indeed, it is imperative to define a standardized examination technique in order to get comparable results. Therefore, the utility of acoustic radiation force imaging technique to predict only renal fibrosis or progression of chronic kidney disease is of dubious value because several variables - blood perfusion and urinary pressure - can contribute to a given measure, even with a standardized method able to minimize intra- and inter-operator variability.

Key words: Elastosonography; Acoustic radiation force imaging technique; Renal elasticity; Renal fibrosis; Chronic kidney disease

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Abstract

Recent interests have focused on the exploration of the mechanical properties (elasticity, stiffness and

Core tip: Recent interests have focused on the exploration of the mechanical properties (elasticity, stiffness and deformity) of parenchymatous organs using tissue

strain imaging techniques and elastosonography. Many factors can affect measurements and an accurate technique is necessary in order to avoid mistakes and to obtain reproducible data. The use of tissue strain imaging techniques to predict only renal fibrosis or progression of chronic kidney disease is of dubious value because other variables - blood perfusion and urinary pressure - can contribute to a given measure, even with a standardized method able to minimize intra- and inter-operator variability.

Zaffanello M, Bruno C. Clinical perspective on renal elasticity quantification by acoustic radiation force impulse: Where we are and where we are going. *World J Clin Urol* 2015; 4(3): 100-103 Available from: URL: <http://www.wjgnet.com/2219-2816/full/v4/i3/100.htm> DOI: <http://dx.doi.org/10.5410/wjcu.v4.i3.100>

INTRODUCTION

Recent interests have focused on the exploration of the mechanical properties (elasticity, stiffness and deformity) of parenchymatous organs using tissue strain imaging techniques and elastosonography. They basically work in the same way: A force induces a modification in a tissue that is closely related to its elasticity^[1].

Tissue strain imaging can be divided into two categories: Quasi-static and dynamic methods^[2]. The dynamic methods are based on detection and tracking of shear waves resulting from mechanical vibration of tissue^[3]. Two main categories can be identified (external and internal methods) based on the applied stimulus^[4]. Internal methods [*i.e.*, acoustic radiation force imaging technique (ARFI) and supersonic shear waves (SSW) elastography] involve selecting a region of interest (ROI) on a gray-scale map, after which an acoustic push pulse is aimed directly at it, inducing the generation of SSW^[5].

ARFI imaging has been demonstrated in many clinical settings, using various transducers and beam sequences depending upon the application, with promising results. These include: Abdominal imaging, cardiac imaging, vascular imaging, breast imaging, nerve imaging, prostate imaging, and monitoring thermal ablation procedures^[6]. To date, the liver is the organ most frequently studied with the ARFI technique, especially to obtain a measure of fibrosis and cirrhosis^[7]. In these sceneries, no particular debates have been reported.

CONTROVERSIES AND NEW TRENDS

Measures of the mechanical properties of the kidneys have given conflicting results. For example, the levels of renal shear wave velocity (SWV) reported in an Italian paper^[8] are twice the levels obtained by a Turkish team^[9] and a Chinese team^[10] that used the same device (Acuson S2000). Moreover, Göya *et al*^[9]

reported that the more serious the renal damage, the slower the propagation of shear waves^[11], in contrast to the results reported by Bruno *et al*^[8] for older children. The explanation comes from understanding the factors which can influence ARFI measurements.

There are various conditions that affect the variability of renal parenchymal measures, the main target of the investigations. They can be classified as intrinsic (depending on the patient), extrinsic (depending on the operator) and mixed (both intrinsic and extrinsic). These variables indicate some problems related to the technical approach and to the failure of standardized procedures. They make it difficult to have comparable results among different studies.

The first intrinsic factor is the age of the patients. Normal kidneys in healthy subjects showed variations of SWV values according to age^[10]. Recently, kidney shear wave speed values assessed by ARFI elastography in "normal" patients were reportedly influenced mainly by age and gender, with lower values being obtained in older patients and in men^[12].

Moreover, as well as other parenchymatous organs, the mechanical properties of the kidney depend on various conditions that alter its histology, mainly the amount of fibrosis in the renal parenchymal interstitium. Theoretically, the more fibrosis and inflammation present in the parenchyma, the greater the ARFI measures should be.

Various degrees of fibrosis depending on the cause of damage, the time elapsed since damage, the degree of anisotropy, and the level of vascular and urinary pressure may have an impact on SWV of the renal cortex^[11]. Changes in intrarenal vascular structure and renal blood flow may have a greater influence on SWV values. Asano *et al*^[13] showed that a decrease in blood flow affects SWV values in the kidneys more than the progression of tissue fibrosis. Gennisson *et al*^[14], in pig models, showed that the intrarenal elasticity values varied with tissue anisotropy and with vascular and urinary pressure levels. In particular, parenchymal elasticity increased linearly with elevation of urinary pressure. Nephro-urological pathology is another condition that may influence results since it is responsible for changes in renal blood perfusion and urinary pressure^[8]. Studies have shown that variability of measurements in the renal parenchyma is a real issue, whichever elastography technique is used^[15,16].

Other variables, in addition to tissue conditions, such as measure setting and target of the measures (subcapsular, cortex and medulla) can affect results. Anatomical factors play an important role^[17] as well because the kidney is a highly anisotropic organ with important differences when considering the cortex and the medulla^[18]. When observing each renal segment, the collecting ducts and vasa recta are disposed perpendicularly to the capsule and constitute a pathway along which shear waves travel at different speeds.

Physical factors include frequency of the probe, compression and distance from source to target. A lower

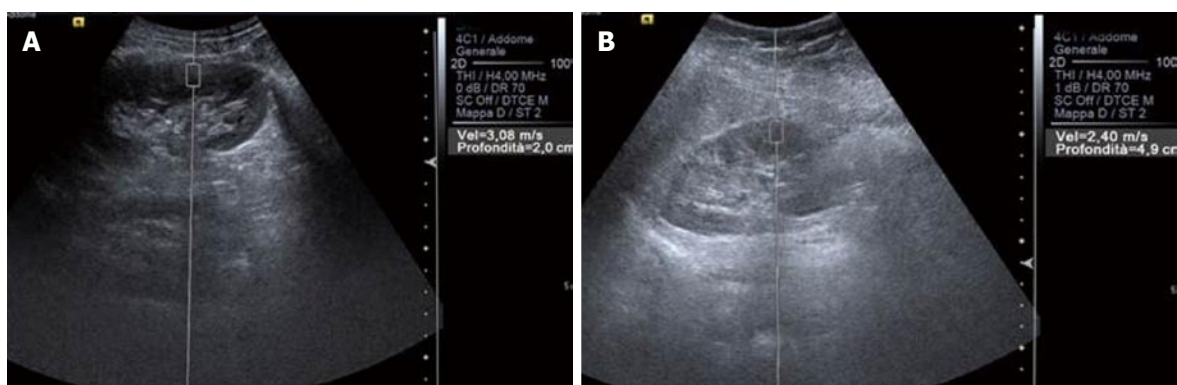


Figure 1 Effects of different source-to-target distance. A: Distance 2 cm, SWV = 3.08 m/s; B: As the distance becomes greater (4.9 cm), the SWV decreases (2.40 m/s). SWV: Shear wave velocity.

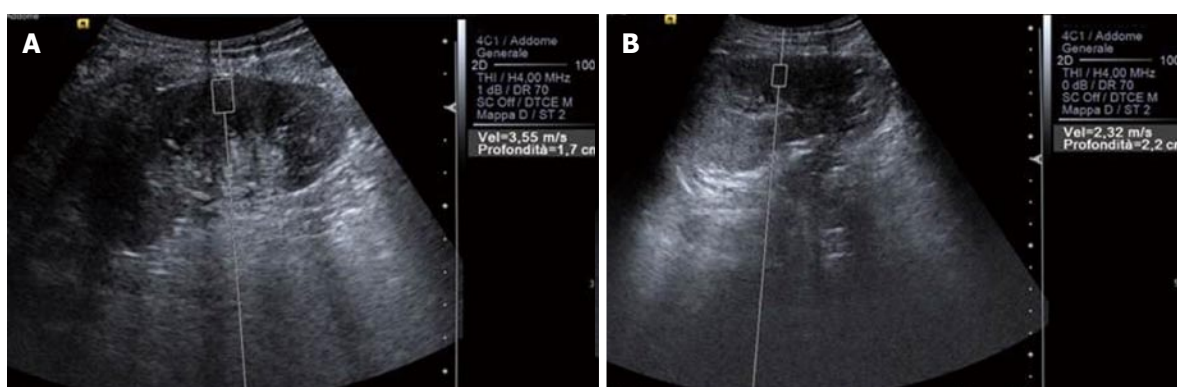


Figure 2 Effects of anisotropy. A: Distance 1.7 cm, SWV = 3.55 m/s; B: Distance 2.2 cm, SWV = 2.32 m/s. The SWV difference between the two measurements is greater than what is expected considering only the source-to-target distance. This is an effect of renal anisotropy and a consequence of an incorrect orientation of the ROI. SWV: Shear wave velocity; ROI: Region of interest.

frequency is related to lower frequency of the radiation force pulses and thus to a higher acoustic pressure with higher SWV^[19]. However, greater compression gives higher SWV values because it gives a higher elastic modulus with greater SWV^[20]. The distance from source to target is also important because for each frequency an optimal distance can be found where variability is minimum. Bota *et al*^[12] showed that measurement depth negatively influences kidney shear wave speed values: the lower the depth the higher the SWV.

Generally speaking, SWV is related to the strength of compression^[20], the source to target distance (Figure 1), the orientation of the ROI^[21] and, most important of all, anisotropy, which has great influence when dealing with kidneys. The kidney is a highly anisotropic organ^[18], and the particular decubitus when evaluating patients (for instance lying prone or supine or in lateral decubitus) is able to alter results (Figure 2).

Again, many factors can affect measurements and it is imperative to find an accurate technique in order to avoid mistakes and to obtain reproducible data. So the issue is to define a protocol for ARFI evaluation (as was done for the liver) able to minimize the differences between operators, and which includes standardization of the source to target distance, positioning of the ROI (avoiding the medulla or the dilated pyelo-caliceal

system) and, of course, the patient's decubitus. Moreover, in order to get comparable results, it is mandatory to have a standardized examination technique that clearly states that the operator should always exert the same compression on the kidney, with an ROI completely included in the cortex. The main axis of the US beam must be placed parallel to the pyramids in the segment of interest, always with the probe at the same angle, in order to minimize any effects of anisotropy^[14].

CONCLUSION

Based on the findings cited above, the utility of ARFI analysis to predict only renal fibrosis or the progression of chronic kidney disease is of dubious value because other variables - blood perfusion and urinary pressure - can contribute to a given measure, even with a standardized method that can minimize intra- and inter-operator variability (patient position, probe frequency, ROI, compression, *etc.*). Accordingly, the clinical significance of the measures obtained remains to be explored.

REFERENCES

- 1 Varghese T. Quasi-Static Ultrasound Elastography. *Ultrasound Clin*

- 2009; **4**: 323-338 [PMID: 20798841 DOI: 10.1016/j.cult.2009.10.009]
- 2 **Zaffanello M**, Piacentini G, Bruno C, Brugnara M, Fanos V. Renal elasticity quantification by acoustic radiation force impulse applied to the evaluation of kidney diseases: a review. *J Investig Med* 2015; **63**: 605-612 [PMID: 25738649 DOI: 10.1097/JIM.0000000000000186]
- 3 **Ophir J**, Garra B, Kallel F, Konofagou E, Krouskop T, Righetti R, Varghese T. Elastographic imaging. *Ultrasound Med Biol* 2000; **26** Suppl 1: S23-S29 [PMID: 10794867 DOI: 10.1016/S0301-5629(00)00156-3]
- 4 **Bharat S**, Varghese T. Radiofrequency electrode vibration-induced shear wave imaging for tissue modulus estimation: a simulation study. *J Acoust Soc Am* 2010; **128**: 1582-1585 [PMID: 20968329 DOI: 10.1121/1.3466880]
- 5 **Nightingale KR**, Palmeri ML, Nightingale RW, Trahey GE. On the feasibility of remote palpation using acoustic radiation force. *J Acoust Soc Am* 2001; **110**: 625-634 [PMID: 11508987 DOI: 10.1121/1.1378344]
- 6 **Nightingale K**. Acoustic Radiation Force Impulse (ARFI) Imaging: a Review. *Curr Med Imaging Rev* 2011; **7**: 328-339 [PMID: 22545033 DOI: 10.2174/157340511798038657]
- 7 **Sporea I**, Gilja OH, Bota S, Şirli R, Popescu A. Liver elastography - an update. *Med Ultrason* 2013; **15**: 304-314 [PMID: 24286095 DOI: 10.11152/mu.2013.2066.154.isp23]
- 8 **Bruno C**, Caliri G, Zaffanello M, Brugnara M, Zuffante M, Cecchetto M, Minniti S, Pedot A, Talamini G, Pozzi-Mucelli R. Acoustic radiation force impulse (ARFI) in the evaluation of the renal parenchymal stiffness in paediatric patients with vesicoureteral reflux: preliminary results. *Eur Radiol* 2013; **23**: 3477-3484 [PMID: 23881301 DOI: 10.1007/s00330-013-2959-y]
- 9 **Göya C**, Hamidi C, Ece A, Okur MH, Taşdemir B, Çetinçakmak MG, Hattapoğlu S, Teke M, Şahin C. Acoustic radiation force impulse (ARFI) elastography for detection of renal damage in children. *Pediatr Radiol* 2015; **45**: 55-61 [PMID: 25064187 DOI: 10.1007/s00247-014-3072-3]
- 10 **Lee MJ**, Kim MJ, Han KH, Yoon CS. Age-related changes in liver, kidney, and spleen stiffness in healthy children measured with acoustic radiation force impulse imaging. *Eur J Radiol* 2013; **82**: e290-e294 [PMID: 23433651 DOI: 10.1016/j.ejrad.2013.01.018]
- 11 **Olsen ØE**. Shear wave velocities in damaged kidneys: fast and slow. *Pediatr Radiol* 2015; **45**: 2-3 [PMID: 25064186 DOI: 10.1007/s00247-014-3070-5]
- 12 **Bota S**, Bob F, Sporea I, Şirli R, Popescu A. Factors that influence kidney shear wave speed assessed by acoustic radiation force impulse elastography in patients without kidney pathology. *Ultrasound Med Biol* 2015; **41**: 1-6 [PMID: 25438855 DOI: 10.1016/j.ultrasmedbio.2014.07.023]
- 13 **Asano K**, Ogata A, Tanaka K, Ide Y, Sankoda A, Kawakita C, Nishikawa M, Ohmori K, Kinomura M, Shimada N, Fukushima M. Acoustic radiation force impulse elastography of the kidneys: is shear wave velocity affected by tissue fibrosis or renal blood flow? *J Ultrasound Med* 2014; **33**: 793-801 [PMID: 24764334 DOI: 10.7863/ultra.33.5.793]
- 14 **Gennisson JL**, Grenier N, Combe C, Tanter M. Supersonic shear wave elastography of in vivo pig kidney: influence of blood pressure, urinary pressure and tissue anisotropy. *Ultrasound Med Biol* 2012; **38**: 1559-1567 [PMID: 22698515 DOI: 10.1016/j.ultrasmedbio.2012.04.013]
- 15 **Grenier N**, Gennisson JL, Cornelis F, Le Bras Y, Couzi L. Renal ultrasound elastography. *Diagn Interv Imaging* 2013; **94**: 545-550 [PMID: 23567180 DOI: 10.1016/j.diii.2013.02.003]
- 16 **Ozkan F**, Menzilcioglu MS, Duymus M, Yildiz S, Avcu S. Acoustic radiation force impulse elastography for evaluating renal parenchymal stiffness in children. *Pediatr Radiol* 2015; **45**: 461 [PMID: 25252829 DOI: 10.1007/s00247-014-3174-y]
- 17 **Goertz RS**, Amann K, Heide R, Bernatik T, Neurath MF, Strobel D. An abdominal and thyroid status with Acoustic Radiation Force Impulse Elastometry--a feasibility study: Acoustic Radiation Force Impulse Elastometry of human organs. *Eur J Radiol* 2011; **80**: e226-e230 [PMID: 20971591 DOI: 10.1016/j.ejrad.2010.09.025]
- 18 **Ries M**, Jones RA, Basseau F, Moonen CT, Grenier N. Diffusion tensor MRI of the human kidney. *J Magn Reson Imaging* 2001; **14**: 42-49 [PMID: 11436213 DOI: 10.1002/jmri.1149]
- 19 **Chang S**, Kim MJ, Kim J, Lee MJ. Variability of shear wave velocity using different frequencies in acoustic radiation force impulse (ARFI) elastography: a phantom and normal liver study. *Ultraschall Med* 2013; **34**: 260-265 [PMID: 23023455 DOI: 10.1055/s-0032-1313008]
- 20 **Syversveen T**, Midtvedt K, Berstad AE, Brabrand K, Strøm EH, Abildgaard A. Tissue elasticity estimated by acoustic radiation force impulse quantification depends on the applied transducer force: an experimental study in kidney transplant patients. *Eur Radiol* 2012; **22**: 2130-2137 [PMID: 22610533 DOI: 10.1007/s00330-012-2476-4]
- 21 **Fahey BJ**, Nightingale KR, Nelson RC, Palmeri ML, Trahey GE. Acoustic radiation force impulse imaging of the abdomen: demonstration of feasibility and utility. *Ultrasound Med Biol* 2005; **31**: 1185-1198 [PMID: 16176786 DOI: 10.1016/j.ultrasmedbio.2005.05.004]

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Sweet side of bladder cancer

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Abstract

The malignant transformation of cells is often accompanied by deranged expression of the sugar chains, *i.e.*, glycans, attached the cancer cell surfaces or attached to secreted proteins. The aberrant expression of specific glycans in bladder cancer has also been reported by several research groups. Similarly to other cancers, glycans such as the sialyl Tn antigens have been

suggested as diagnostic and prognostic biomarkers of bladder cancer, and associated with disease progression and patient's response to treatment. At present our understandings about the role of glycans in bladder cancer is still limited, but at the same time it is now assumed that this understanding urges and it will fuel the development of novel strategies of diagnostic and therapy.

Key words: Bladder cancer; Glycosylation; Tumor biomarker; Sialyltransferase; Immunotherapy; Bacillus Calmette-Guérin

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Core tip: The deranged expression of glycans in bladder cancer has been reported, but somehow disregarded. Glycans, such as the sialyl Tn, show a very tumor specific pattern and have been suggested as diagnostic and prognostic biomarkers of bladder cancer, and associated with disease progression and patient's response to treatment. Understandings about the role of glycans in bladder cancer is still limited, but, it is now assumed that this understanding urges and it will fuel the development of novel strategies of diagnostic and therapy.

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INTRODUCTION

Sialyl Tn in bladder cancer

Among the glycans that are known to be aberrantly expressed in bladder cancer, the sialyl Tn (STn) emerges as the most distinctive glycan due to its tumor specificity. STn is considered a pan-carcinoma antigen,

and many other epithelial cancers express it^[1]. But the most interesting feature is the fact that STn is not expressed by healthy cells, guarantying specificity in any therapy against it.

STn expression in bladder cancer was first described in the nineties by Langkilde *et al*^[2] that analysed 34 patients with initially noninvasive (Ta) transitional cell carcinomas. According to these authors, STn showed a very restricted pattern of expression in bladder cancer and it was not expressed by normal urothelium. No association with recurrence and progression was found. Much later, in 2014, the prognostic value of STn expression in bladder cancer was revised by Ferreira *et al*^[3], using higher number of cases and different patient stratification. We reported that the STn is expressed majorly in high grade lesions and in muscle invasive bladder tumors (around 70% of the cases). STn is expressed also in low grade lesions and carcinoma *in situ* but with less expression levels^[3]. STn is expressed in tissues presenting high proliferation indexes and high risk of recurrence/progression and it is related with higher invasiveness of bladder cancer cells^[3], thus being suggested as associated with malignant profile.

In contrast to other epithelial cancers there has been very little interest in studying aberrant glycosylation in bladder cancer. A possible explanation for the dormancy of research interest in the glycosylation of bladder cancers may have to do with the lack of interest in bladder cancer research itself, due to its low mortality rates. In addition, these studies require sufficient understanding on glycosylation and use methodologies that involve the collection and preservation of high quality tissue for immunodetection techniques, especially when using antibodies against glycans. Therefore with our report, we were able to bring to the spotlight the relevance of glycans and in particular of STn as bladder cancer biomarker. These findings now launch the question of the benefits of considering STn in diagnosis and bladder cancer therapy.

The STn antigen is a simple O-linked disaccharide constituted by N-acetylneuraminic acid linked to N-acetyl-galactosamine [Neu5Ac (2-6) GalNAc], bound to serine or threonine residues in proteins. The aberrant expression of STn in cancer results from the incomplete biosynthesis of mucin-type O-glycans, due to alterations of cellular glycosylation machinery, namely the increased activity of the sialyltransferase ST6GALNAC1^[4], which transfers N-acetylneuraminic acid to N-acetyl galactosamine linked to the protein carrier. The elevation of the expression of the sialyltransferase ST6GALNAC1 gene can actually be also considered as a transcriptional biomarker^[3,5].

Sialyl Tn and immune response

Nearly after, in two other reports the expression of STn in bladder cancer was associated with immunotherapy and immune responses. In the first report, in 2013, it was described that STn can be used to predict

patients response to Bacillus Calmette-Guérin (BCG) treatment^[6]. The use of STn as a predictive marker to BCG treatment response still needs to be further investigated with higher cohorts of patients. However to may be anticipated that STn identification may be useful for patient stratification and for the identification of patients that could benefit from BCG immunotherapy. Interestingly, STn expressing cancer cells internalized much better BCG and therefore experience improved BCG-induced apoptosis, when compared with STn negative cancer cells^[6]. While interesting these findings it remain to be understood which is the mechanisms that leads to better internalization of BCG into STn-expressing bladder cancer cells. It may be hypothesised that BCG express receptors, such as adhesins, that bind preferentially STn-containing glycans at cell surface of bladder cancer cells. However further investigations are needed to dissect the BCG mechanism of binding to STn.

In the second report, in 2014, we showed that STn behaves as a tolerogenic molecule inducing immunosuppression in human dendritic cells (DC). DCs are one of the most important coordinators of anti-tumor immune responses involved in the activation of multiple arms against tumor cells. However their ability to elicit anti-tumoral immune responses is critically dependent on their maturation status which in turn is highly influenced by the microenvironment. We observed that STn-expressing cancer cells dampen the maturation of DCs *in vitro*. DCs when in contact with STn-expressing cancer cells show an immature phenotype, by expressing lower levels of major histocompatibility complex class II, co-stimulatory molecules and less pro-inflammatory cytokines^[5]. Pro-inflammatory cytokines are also significantly decreased in STn positive bladder tumours^[5]. Furthermore, DCs loaded with STn⁺ cancer antigens induce T cells with regulatory properties^[5], suggesting that the adaptive immune response is compromised. It may be hypothesized that immunosuppressive receptors expressed by DCs recognize STn and mediate tolerization. In fact DCs express sialic acid-binding Ig-like lectins (Siglecs)^[7] and the macrophage galactose type lectin (MGL)^[8], which are tolerogenic receptors described to recognize STn antigens^[8]. Nevertheless, the specificity of these receptors is still debatable and validation of its capacity to recognize STn is necessary at cellular level. A better understanding of the mechanisms by which DCs are rendered tolerogenic in the presence of STn-expressing cancers is important for the development of effective immunotherapies.

The future of anti-sialyl Tn therapies in bladder cancer

Immunotherapies against STn have already been developed, in breast cancer patients^[9]. In fact, the biotech company Biomira (now Oncothyreon, Alberta, Canada) designed the Theratope™ vaccine that consists of a synthetic construct of STn disaccharide

conjugated to the Keyhole limpet hemocyanin^[10]. Breast cancer patients that were vaccinated with STn vaccine significantly improved survival. However, the benefits of Theratope were suboptimal and the clinical trials did not pass after phase III^[11]. In light of our findings showing that DCs become tolerogenic with STn, it seems that the immunosuppressive environment exerted by STn may abrogate any anti-tumor immunity against STn cancer cells, thus explaining the failure of molecular STn-based vaccines. In addition, the percentages of STn positive cases in breast cancer is less than 50% and in the Biomira trials, no patient screening has been performed, therefore the odds for successful immunization in the breast cancer patients were low. It remains to be understood the efficacy of STn vaccine in other cancers that also express STn, such as bladder cancer, where the expression of STn is much higher than breast cancer.

Interestingly, breast cancer patients receiving Theratope developed anti-STn antibodies, whose abundance was directly correlated with disease free survival^[12]. Patients receiving low-dose intravenous cyclophosphamide, an inhibitor of suppressor T cells, before vaccinations showed longer survival and generated higher antibody titers than control patients^[13]. These observations demonstrate the relevance of antibodies against STn and of strategies to break immune tolerance to maximize treatment. In agreement, we observed *in vitro* that the use of antibodies to block STn antigens expressed by bladder cancer cells was able to lower the induction of tolerance and DCs become more mature^[5]. Thus targeted therapies based on anti-STn antibodies may provide efficient means to enhance immune responses against STn-expressing tumor cells. While several antibodies have been established against STn^[14] none has actually been applied in clinics to elicit elimination of STn cancer cells. Possible limitations to its application have to do with lack of interest or low specificity and efficiency of the existing antibodies.

A better understanding of STn role in immune evasion and influence in existing immunotherapies is now deemed to boost the development of novel therapies and to better stratify patients for therapeutic regime. It has been fascinating to notice that a better understanding of the factors restricting effective immune responses launched the recent development of antibodies targeting inhibitory immune checkpoints, with an extraordinary capacity to break tumor-induced immune tolerance. In bladder cancer, the antibody MPDL3280A against the inhibitory immune checkpoints PD-L1, was already approved by Food and Drugs Administration and has shown promising results^[15]. The targeting of inhibitory immune checkpoints may be considered in the future as a therapy for cancers expressing factors, such as STn, that lead to immune tolerance. An irrefutable knowledge is arising from novel therapies that will warrant the future development of more successful treatments for bladder cancer.

REFERENCES

- 1 **Julien S**, Videira PA, Delannoy P. Sialyl-Tn in cancer: (how) did we miss the target? *Biomolecules* 2012; **2**: 435-466 [PMID: 24970145 DOI: 10.3390/biom2040435]
- 2 **Langkilde NC**, Wolf H, Clausen H, Kjeldsen T, Orntoft TF. Nuclear volume and expression of T-antigen, sialosyl-Tn-antigen, and Tn-antigen in carcinoma of the human bladder. Relation to tumor recurrence and progression. *Cancer* 1992; **69**: 219-227 [PMID: 1727666 DOI: 10.1002/1097-0142(19920101)69]
- 3 **Ferreira JA**, Videira PA, Lima L, Pereira S, Silva M, Carrascal M, Severino PF, Fernandes E, Almeida A, Costa C, Vitorino R, Amaro T, Oliveira MJ, Reis CA, Dall'Olio F, Amado F, Santos LL. Overexpression of tumour-associated carbohydrate antigen sialyl-Tn in advanced bladder tumours. *Mol Oncol* 2013; **7**: 719-731 [PMID: 23567325]
- 4 **Cazet A**, Julien S, Bobowski M, Krzewinski-Recchi MA, Harduin-Lepers A, Groux-Degroote S, Delannoy P. Consequences of the expression of sialylated antigens in breast cancer. *Carbohydr Res* 2010; **345**: 1377-1383 [PMID: 20231016 DOI: 10.1016/j.carres.2010.01.024]
- 5 **Carrascal MA**, Severino PF, Guadalupe Cabral M, Silva M, Ferreira JA, Calais F, Quinto H, Pen C, Ligeiro D, Santos LL, Dall'Olio F, Videira PA. Sialyl Tn-expressing bladder cancer cells induce a tolerogenic phenotype in innate and adaptive immune cells. *Mol Oncol* 2014; **8**: 753-765 [PMID: 24656965 DOI: 10.1016/j.molonc.2014.02.008]
- 6 **Lima L**, Severino PF, Silva M, Miranda A, Tavares A, Pereira S, Fernandes E, Cruz R, Amaro T, Reis CA, Dall'Olio F, Amado F, Videira PA, Santos L, Ferreira JA. Response of high-risk of recurrence/progression bladder tumours expressing sialyl-Tn and sialyl-6-T to BCG immunotherapy. *Br J Cancer* 2013; **109**: 2106-2114 [PMID: 24064971 DOI: 10.1038/bjc.2013.571]
- 7 **Crocker PR**, Redelinghuys P. Siglecs as positive and negative regulators of the immune system. *Biochem Soc Trans* 2008; **36**: 1467-1471 [PMID: 19021577 DOI: 10.1042/BST0361467]
- 8 **Saeland E**, van Vliet SJ, Bäckström M, van den Berg VC, Geijtenbeek TB, Meijer GA, van Kooyk Y. The C-type lectin MGL expressed by dendritic cells detects glycan changes on MUC1 in colon carcinoma. *Cancer Immunol Immunother* 2007; **56**: 1225-1236 [PMID: 17195076 DOI: 10.1007/s00262-006-0274-z]
- 9 **Adis International Ltd**. Cancer vaccine THERATOPE- Biomira. *Drugs R D* 2003; **4**: 236-240 [PMID: 12848588]
- 10 **Ragupathi G**, Howard L, Cappello S, Koganty RR, Qiu D, Longenecker BM, Reddish MA, Lloyd KO, Livingston PO. Vaccines prepared with sialyl-Tn and sialyl-Tn trimers using the 4-(4-maleimidomethyl)cyclohexane-1-carboxyl hydrazide linker group result in optimal antibody titers against ovine submaxillary mucin and sialyl-Tn-positive tumor cells. *Cancer Immunol Immunother* 1999; **48**: 1-8 [PMID: 10235483 DOI: 10.1007/s002620050542]
- 11 **Miles D**, Roché H, Martin M, Perren TJ, Cameron DA, Glaspy J, Dodwell D, Parker J, Mayordomo J, Tres A, Murray JL, Ibrahim NK. Phase III multicenter clinical trial of the sialyl-TN (STn)-keyhole limpet hemocyanin (KLH) vaccine for metastatic breast cancer. *Oncologist* 2011; **16**: 1092-1100 [PMID: 21572124 DOI: 10.1634/theoncologist.2010-0307]
- 12 **Holmberg LA**, Sandmaier BM. Vaccination with Theratope (STn-KLH) as treatment for breast cancer. *Expert Rev Vaccines* 2004; **3**: 655-663 [PMID: 15606349]
- 13 **Miles DW**, Towilson KE, Graham R, Reddish M, Longenecker BM, Taylor-Papadimitriou J, Rubens RD. A randomised phase II study of sialyl-Tn and DETOX-B adjuvant with or without cyclophosphamide pretreatment for the active specific immunotherapy of breast cancer. *Br J Cancer* 1996; **74**: 1292-1296 [PMID: 8883420 DOI: 10.1038/bjc.1996.532]
- 14 **Colcher D**, Hand PH, Nuti M, Schlom J. A spectrum of monoclonal antibodies reactive with human mammary tumor cells. *Proc Natl Acad Sci USA* 1981; **78**: 3199-3203 [PMID: 6789331]

- 15 **Powles T**, Eder JP, Fine GD, Braiteh FS, Loriot Y, Cruz C, Bellmunt J, Burris HA, Petrylak DP, Teng SL, Shen X, Boyd Z, Hegde PS, Chen DS, Vogelzang NJ. MPDL3280A (anti-PD-L1)

treatment leads to clinical activity in metastatic bladder cancer. *Nature* 2014; **515**: 558-562 [PMID: 25428503 DOI: 10.1038/nature13904]

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Is continuous bladder irrigation after prostate surgery still needed?

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Abstract

Continuous bladder irrigation (CBI) is commonly prescribed after certain prostate surgeries to help prevent the clot formation and retention that are frequently associated with these sometimes hemorrhagic surgeries. However, it remains unknown how effective CBI is in

preventing clot formation/catheter blockage because these complications still frequently occur in the presence of CBI. On the other hand, the outcome of prostate surgeries has significantly improved over the years, and these surgeries have generally become much safer and, in many hands, less hemorrhagic. Newer surgical options such as holmium laser enucleation of the prostate with associated improved hemorrhagic control have also been introduced, further creating the opportunity to eliminate CBI. Furthermore, there is a lack of review articles on CBI. Hence, this article will review the evolution and contemporary role of CBI in prostate surgeries. To eliminate CBI after prostate surgeries, it is important to achieve good hemostasis during the surgeries. Having in place a policy of non-irrigation after prostate surgeries is also important if less CBI is to be the norm. A non-irrigation policy will hopefully help reduce those cases of CBI prescribed out of long-standing surgical tradition while allowing for cases prescribed out of compelling necessity. The author's policy of a consistent non-CBI during prostate surgeries over the last 9 years will be highlighted.

Key words: Continuous bladder irrigation; Bladder irrigation; Bladder washout; Benign prostatic hyperplasia; Prostatectomy; Transurethral resection of the prostate; Holmium enucleation of the prostate

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Core tip: Continuous bladder irrigation (CBI) has been part and parcel of some prostate surgeries and might have been more relevant during the era of unpredictable hemostatic control. Hemostatic control during prostate surgeries has significantly improved, and new technologies with associated improved hemostasis have been introduced. Hence, CBI can be safely avoided in most prostate surgeries, especially when good hemostasis has been achieved and a policy to pursue the non-CBI pathway is in place.

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INTRODUCTION

Continuous bladder irrigation (CBI) can be defined as an uninterrupted and simultaneous infusion and drainage of the bladder with fluid. CBI is commonly used after some surgical procedures on the prostate [transurethral resection of the prostate (TURP), open prostatectomy] and also on the bladder [transurethral resection of bladder tumor (TURBT)]. Post-operative CBI is so commonly used that it remains a standard recommendation in urologic textbooks and journal articles^[1-9] and is also a component of practical nursing training^[10-14]. Over the years, CBI was developed and used as a valuable method of managing hemorrhage and clot formation after prostate surgeries^[15-24]. However, it remains unknown how effective CBI is in preventing clot formation/catheter blockage because these complications still frequently occur in the presence of CBI^[25]. Furthermore, there are no evidence-based guidelines for bladder irrigation strategies. On the other hand, the outcome of prostate surgeries (TURP and open prostatectomy) has significantly improved over these years, and these surgeries have generally become much safer and, in many hands, less hemorrhagic^[6,25-37]. As such, it becomes pertinent to review the contemporary role of CBI in prostate surgeries, especially in TURP and open prostatectomy where CBI is most commonly used, but also in holmium enucleation of the prostate (HoLEP), which is currently considered the endourologic equivalent of open prostatectomy. Of note, there is a lack of review articles on CBI, and it is hoped that this article will help fill that gap.

Historical background of bladder irrigation

The evolution of bladder drainage and subsequently that of bladder irrigation is closely related to the problem of hemorrhage and clot formation associated with surgeries involving the prostate and also the bladder. The concept of bladder drainage and bladder irrigation has evolved over many years and has especially been part and parcel of surgery for benign prostatic hyperplasia (BPH). Byrne^[16] found that a significant percentage of deaths that occur secondary to hemorrhage after prostatectomy can be attributed to inadequate catheter drainage of the bladder. According to Tinckler^[19], apart from general patient management, patient care following prostatectomy is mainly concerned with ensuring uninterrupted drainage of urine and blood from the lower urinary tract until normal hemostasis is attained, avoiding accumulation of blood and clot retention. The frequent and frustrating

experience of preventing catheter blockage is of much burden to both the patient and the medical staff, but most especially to the nurses who are more directly involved in monitoring the drainage function of these catheters. Lowthian P expressed this frustration in a graphic letter to the Editor of BJU^[38]. Hence, ensuring adequate catheter drainage has always been an integral component of surgical procedures on the prostate and bladder.

Postoperative drainage of the bladder has been effected through the perineum, bladder and urethra. Fuller^[39] inserted a tube through the perineum into the bladder and irrigated the bladder with hot water to aid hemostasis and wash out blood clots. Cabot^[40] described a double glass tube that was inserted suprapubically and used to irrigate and drain the bladder using water. Other suprapubic drains of interest include those of Herman *et al*^[41]. According to McEachern^[42], the introduction of the Harris prostatectomy and development of transurethral resection of the prostate helped bring to the frontline the enormity associated with the care of indwelling urethral catheters, especially the necessity of frequent bladder flushing for any questionable function or obvious signs and symptoms of blockage. The frequency of intermittent flushing of the bladder through these catheters during the first 24 h after prostatectomy could be on hourly interval^[43] if not more frequent and undoubtedly can be overwhelming for both the patients and medical personnel. Hence, exploring a method of CBI that will eliminate or reduce the frequency of intermittent flushing of the bladder could only have been a welcomed addition to the postoperative management of these patients at that point in time.

Early publications mentioning methods of CBI in the literature include those of Loughnane^[44] and Foley in Wilde *et al*^[45]. However, a more precise description of a method of continuous bladder irrigation after prostate surgery was that of Adams^[46]. Adams^[46] described a "third ureter in prostatectomy", highlighting the need of a continuous inflow of fluid into the bladder cavity, contrary to the option of intermittent washout of the bladder. This publication describes the use of a suprapubic tube connected to a reservoir of antiseptic solution for a continuous inflow of this solution into the bladder and as such, the tube serves as an additional source of fluid apart from the natural source from the kidneys through the two ureters - hence the description by the author of this additional source of fluid as a "third ureter". Further developments in the use of continuous irrigation have been numerous and variable^[16-24]. Currently, the CBI procedure is commonly performed using normal saline and a three-way Foley catheter^[1,11,12,47].

Arguments for and against CBI

Post-operative bladder irrigation has been an integral part of a number of surgical procedures on the bladder and prostate and is still widely practiced and

recommended in textbooks and journal articles^[1-14]. The reasons for advocating CBI after prostate surgery include the following: (1) prevention of clot formation and retention; (2) maintenance of the patency of the drainage catheter lumen; (3) flushing out of small clots before they become larger; and (4) bleeding control^[20]. In contrast, those who advocate not using CBI after prostate surgery^[25,37,48-52] give the following reasons: (1) less workload on the medical staff; (2) less financial cost to the patient; (3) easier calculation of urine output; (4) reduced risk of bladder rupture in the presence of a blocked urethral catheter; (5) urethral catheter blockage and clot retention still frequently occur even in the presence of CBI; (6) avoidance of confinement of the patient to the bed for CBI; and (7) avoidance of suprapubic pain/discomfort.

Efforts made to eliminate CBI from surgical practice

To eliminate CBI, varying approaches have been used by different authors. The various approaches to elimination of CBI can be divided into: (1) non-surgical; and (2) surgical.

Non-surgical: Use of diuretics: Some advocates of no irrigation effect CBI through the use of diuretics but without the use of an external irrigant. This concept of CBI that avoids external irrigants relies instead on the administration of high intravenous fluid in combination with diuretics that ultimately increases urine flow through the bladder^[48-50,52,53]. The concern with this approach is the risk of metabolic disturbance and fluid overload in these patients, who are predominantly elderly^[53].

Surgical: As mentioned in the historical background section, CBI has traditionally been intertwined with the problem of significant hemorrhage/clot formation associated with prostatic surgery. Hence, the focus of surgical modifications towards possible elimination of CBI has focused on improving hemostasis during prostate surgery.

For suprapubic prostatectomy, the approaches towards achieving better hemostasis have been variable, but in contemporary practice have commonly included packing the prostatic cavity and sutural methods of hemostasis^[41,54,55]. Generally, packing the prostatic fossa has been associated with mixed success in controlling hemorrhage with a not uncommon need to periodically re-pack a few hours following surgery due to persistent bleeding. Even in cases in which packing helped achieve control of hemostasis, periodic drainage of urine to the exterior through the drainage site and later removal of the gauze pack that can be painful and might also provoke re-bleeding due to dislodgement of the already formed clot on the prostatic fossa has decreased the appeal of this method. To avoid pain and also to be prepared for possible re-packing, many urologists remove the gauze pack in the operating room with the use of anesthesia and in doing so, subject

the involved patients to another trip to the operating room^[41]. However, some contemporary authors have reported a more successful outcome of prostatic fossa packing with lower complication rates^[56,57]. Review of some of these contemporary papers on prostatic fossa packing that reported good hemostatic control, however, showed that CBI was still routinely used^[56].

Suturing the bleeding points or areas of anatomical entrance of arterial branches supplying the hyperplastic prostatic tissues is presently the dominant method of achieving hemostasis during suprapubic prostatectomy. Lower^[58] and Harris^[59] were among the early pioneers and advocates of sutural hemostasis. There has been a persistent effort among these early surgeons to place sutures at areas of the bladder neck where it was thought they would help achieve maximum hemostasis. Harris^[59], in addition to reformation of the prostatic fossa, placed hemostatic sutures at the 5 o'clock and 7 o'clock positions of the bladder neck. In his surgical description of sutural hemostasis during suprapubic prostatectomy, Silverton^[60] prefers to place "U" shaped or mattress sutures essentially to include the areas between the 3 o'clock and 5 o'clock as well as between the 7 o'clock and 9 o'clock positions. Another very significant development in the evolution of sutural hemostasis is the concept of separating the prostatic fossa from the bladder neck. This significant modification has led to a distinct direction of sutural hemostasis with many reported good surgical outcomes. Lower^[58] and Harris^[59] were the early pioneers that described the method of separating the prostatic fossa from the bladder neck using absorbable sutures as an approach to control hemorrhage associated with suprapubic prostatectomy. Further development of the concept of separation of the prostatic fossa from the bladder neck gave rise to the use of removable purse string sutures^[61]. Malament^[62] used this approach of removable purse string sutures in separating the prostatic fossa from the bladder neck and noted a significant reduction in post suprapubic prostatectomy bleeding. Other authors using the Malament technique^[34,63,64] documented good results and hence, the Malament technique has continued to be an important option of surgical hemostasis during suprapubic prostatectomy. In a further modification of the removable purse string technique, Denis^[65] additionally placed a drain in the prostatic fossa; according to the author, placement of the drain led to retraction and tamponade of the fossa and through this combination of suturing and drain placement, improved hemostasis was achieved. Contemporary use of the removable purse string technique has led to significant improvement in hemostasis; however, some of the complications that have historically plagued the technique of separating the prostatic fossa from the bladder neck, such as bladder neck stenosis/urethral stricture, periodic need for blood transfusion, clot retention and catheter blockage, have variably persisted. With this approach, there has occasionally been the need to return to operating room to remove fragments of broken purse string suture or

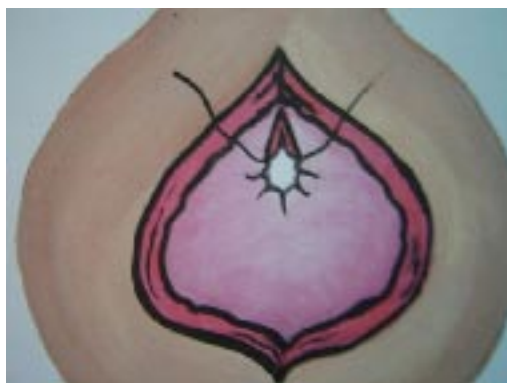


Figure 1 Running suture from the 1 o'clock position to the 11 o'clock position, suturing the bladder neck edge to the prostatic capsule^[25].



Figure 2 Bladder neck narrowed up to the diameter of the surgeon's index finger^[25].

evacuate clots, although these complications might be dependent on the surgeon or medical center^[34,66]. Most contemporary authors reporting on the removable bladder neck purse string suture technique used CBI^[65,67], whereas some others used intermittent bladder irrigation^[34,66] and a few did not irrigate^[68].

For TURP, improvements in resectoscopes, resectoscope loops, optics, energy sources, and experience of the operating surgeon have all contributed to reducing the bleeding risks historically associated with TURP^[36,69]. TURP has significantly evolved over the years to the point where some authors presently perform TURP on "day-case" basis^[32]. However, even for these day-case TURP with reported meticulous hemostasis, CBI was still routinely performed^[32].

Another important alternative to TURP and open prostatectomy with associated better hemostasis during prostate surgery is the Holmium enucleation of the prostate (HoLEP). HoLEP is currently being acclaimed as a true endourologic equivalent of open prostatectomy, especially for large prostate glands. Blood loss is significantly reduced compared to TURP and open prostatectomy, and as such, HoLEP is associated with less or no need for blood transfusion^[70-72]. This improved hemostatic control is an important factor in avoiding/minimizing CBI and can also be induced from the relatively low rate of CBI with the HoLEP technique^[70,73].

Author's modification to suprapubic prostatectomy with elimination of CBI

In contemporary practice, the most commonly recommended method of sutural hemostasis for suprapubic prostatectomy has remained the application of hemostatic stitches to the 5 and 7 o'clock positions of the bladder neck^[1,74]. This method of hemostasis can be effective in controlling hemorrhage in some of these procedures; however, in many other cases, significant hemorrhage and the need for blood transfusion has remained a persistent problem^[74] further fueling the continued search of a more effective method of hemostasis during suprapubic prostatectomy. Furthermore, CBI remains virtually a routine practice with this approach of application of hemostatic stitches to the 5

and 7 o'clock positions of the bladder neck^[1].

It would probably be an overstatement to attribute complete elimination of CBI for suprapubic prostatectomy to any single sutural hemostatic technique. In the author's opinion, elimination of CBI involves a combination of factors that includes, among other factors: appropriate patient selection, meticulous surgical technique especially during enucleation of prostatic adenomas, adequate sutural hemostasis, having in place a non-irrigation policy and proper Foley catheter selection^[25,37].

The author's modified method of surgical hemostasis during suprapubic prostatectomy^[25,37] is based on the following intent: To maximize hemostatic suturing of all arterial branches that enter into the bladder neck and proximal prostatic capsule, in contrast to the commonly practiced application of stitches to the 5 and 7 o'clock positions, and at the same time to avoid excessive narrowing of the bladder neck that could compromise the bladder neck lumen and consequently lead to prostatic fossa or bladder neck stenosis. Following a meticulous enucleation of the prostatic adenomas (probably the most important stage of the surgery in the author's opinion), the modified bladder neck repair/sutural hemostasis^[25,37] consists of a running suture from the 1 o'clock position to the 11 o'clock position, suturing the bladder neck edge to the prostatic capsule with 2-0 polyglactin suture (Figure 1) and additional interrupted sutures applied vertically starting from the 12 o'clock position downwards to narrow the bladder neck up to the diameter of the surgeon's index finger (Figure 2). With the index finger in the bladder neck, a 22 or 24 two-way urethral Foley catheter is inserted and guided into the bladder lumen. The balloon of the Foley catheter, which remains in the bladder lumen, is inflated to a minimum of 30 mL and placed on mild traction by tying a piece of gauze to the catheter and pushing it gently against the meatus for approximately two hours and additionally by taping the catheter to the thigh under moderate traction until the following morning with an adhesive strapping. In this way, the catheter balloon is gently pressed against the bladder neck, augmenting hemostasis and reducing reflux of blood from the

prostatic fossa back to the bladder. The anterior bladder wall defect and the remainder of the incisional wound layers are closed without use of suprapubic catheters or surgical drains. Post-operative bladder irrigation is not needed and is not utilized with this approach. With these modifications, none of our patients has received a blood transfusion or CBI over the last 9 years.

Is CBI still used out of necessity or out of a routine/habitual surgical tradition?

Over the years, the surgical outcomes of TURP and suprapubic prostatectomy have definitely improved^[6,25-31,33-37]. This can be attributed to a number of factors including improvements in surgical techniques and instruments. The questions then become how often is CBI used out of a long-existing surgical tradition, and in contemporary practice, how often is CBI still needed due to actual necessity? These are important questions considering the fact that authors that have reported good hemostatic control in their surgeries still continued to use CBI^[56,67,69]. Although CBI is typically performed without undue complications, significant complications do occur^[75] and moreover, the challenges that come with monitoring the CBI method can be overwhelming, especially in understaffed hospitals across developing countries. If postoperative CBI is to be avoided, then the key to success probably not only depends on a number of factors including meticulous surgical technique, very good hemostatic control, and use of good quality drainage catheters, but also on the implementation of a non-irrigation policy. Furthermore, it must be emphasized that the pursuit of good hemostasis should always be balanced with that of avoiding complications such as bladder neck stenosis, which can occur, for instance, in cases of significant narrowing of the bladder neck in suprapubic prostatectomy; however, this complication was more common in the older series of suprapubic prostatectomy than in more contemporary series^[62,76].

Since 2006, it has been possible for this author to completely avoid CBI in cases of TURP and open prostatectomy. It is important to mention that even in rare cases of significant bleeding, it has been possible to eliminate CBI by not being in a hurry to implement this irrigation. It is also important to remember that two-way catheters used for bladder drainage have a larger drainage lumen compared to three-way catheters of the same size^[52]. Hence, with adequate surgical hemostasis and with the strong aim to pursue a non-irrigation policy, it is very much feasible to avoid CBI in most cases of prostate surgery.

It can then be proposed that the key to eliminating bladder irrigation involves achieving effective surgical hemostasis and maximally reducing the presence of blood in the bladder lumen by reducing the reflux of blood from the prostatic fossa back to the bladder lumen and enhancing the immediate efflux of blood out of the bladder lumen by using good drainage catheters such as an appropriately sized two-way catheter.

However, it is very important to emphasize that changing the mindset/attitude of the surgeon towards adopting a non-irrigation policy is needed if less frequent CBI is to be achieved.

CONCLUSION

The surgical outcome of prostate surgery (TURP and open prostatectomy) has definitely improved over the years. Improved laser surgical techniques have been introduced. With these improvements, especially in the area of surgical hemostasis, it is certainly time to reconsider the routine use of CBI, which has been an integral part of prostate surgery and might have been more relevant during the evolving stages of these surgeries. This is certainly important considering the human and financial cost as well as the potential complications of CBI, among other disadvantages. Having in place a policy aimed at avoiding the routine use of CBI is also needed to achieve less frequent CBI.

REFERENCES

- 1 **Han M**, Partin AW. Retrograde and suprapubic open prostatectomy. In: Wein AJ, Kavoussi LR, Novick AC, Partin AW, Peters CA. Campbell – Walsh Urology. Philadelphia: Saunders Elsevier, 2012; 2695-2703 [DOI: 10.1016/B978-1-4160-6911-9.00094-3]
- 2 **Blandy S**, Lutman M. Hearing threshold levels and speech recognition in noise in 7-year-olds. *Int J Audiol* 2005; **44**: 435-443 [PMID: 16149238 DOI: 10.1080/149920500189203]
- 3 **Edwards LE**, Bucknall TE, Pittam MR, Richardson DR, Stanek J. Transurethral resection of the prostate and bladder neck incision: a review of 700 cases. *Br J Urol* 1985; **57**: 168-171 [PMID: 2580585 DOI: 10.1111/j.1464-410X.1985.tb06414.x]
- 4 **Varkarakis I**, Kyriakakis Z, Delis A, Protogerou V, Deliveliotis C. Long-term results of open transvesical prostatectomy from a contemporary series of patients. *Urology* 2004; **64**: 306-310 [PMID: 15302484 DOI: 10.1016/j.urology.2004.03.033]
- 5 **Helfand B**, Mouli S, Dedhia R, McVary KT. Management of lower urinary tract symptoms secondary to benign prostatic hyperplasia with open prostatectomy: results of a contemporary series. *J Urol* 2006; **176**: 2557-2561; discussion 2561 [PMID: 17085158]
- 6 **Adam C**, Hofstetter A, Deubner J, Zaak D, Weitkunat R, Seitz M, Schneede P. Retropubic transvesical prostatectomy for significant prostatic enlargement must remain a standard part of urology training. *Scand J Urol Nephrol* 2004; **38**: 472-476 [PMID: 15841780 DOI: 10.1080/00365590410015858]
- 7 **Tubaro A**, Carter S, Hind A, Vicentini C, Miano L. A prospective study of the safety and efficacy of suprapubic transvesical prostatectomy in patients with benign prostatic hyperplasia. *J Urol* 2001; **166**: 172-176 [PMID: 11435849 DOI: 10.1016/S0022-5347(05)66102-2]
- 8 **Shaheen A**, Quinlan D. Feasibility of open simple prostatectomy with early vascular control. *BJU Int* 2004; **93**: 349-352 [PMID: 14764135 DOI: 10.1111/j.1464-410X.2003.04614.x]
- 9 **Hill AG**, Njoroge P. Suprapubic transvesical prostatectomy in a rural Kenyan hospital. *East Afr Med J* 2002; **79**: 65-67 [PMID: 12380878 DOI: 10.4314/eamj.v79i2.8902]
- 10 **Elkin EB**, Weinstein MC, Winer EP, Kuntz KM, Schnitt SJ, Weeks JC. HER-2 testing and trastuzumab therapy for metastatic breast cancer: a cost-effectiveness analysis. *J Clin Oncol* 2004; **22**: 854-863 [PMID: 14990641 DOI: 10.1200/JCO.2004.04.158]
- 11 **Gilbert V**, Gobbi M. Making sense of ... bladder irrigation. *Nurs Times* 1989; **85**: 40-42 [PMID: 2726550]
- 12 **Scholtes S**. Management of clot retention following urological surgery. *Nurs Times* 2002; **98**: 48-50 [PMID: 12168380]
- 13 **Cutts B**. Developing and implementing a new bladder irrigation

- chart. *Nurs Stand* 2005; **20**: 48-52 [PMID: 16295599 DOI: 10.7748/ns2005.11.20.8.48.c3993]
- 14 **Ng C.** Assessment and intervention knowledge of nurses in managing catheter patency in continuous bladder irrigation following TURP. *Urol Nurs* 2001; **21**: 97-98, 101-107, 110-111 [PMID: 11998289]
 - 15 **Adams AW.** The range and practice of trans-urethral surgery. *Ann R Coll Surg Engl* 1951; **9**: 279-307 [PMID: 14885938]
 - 16 **Byrne JE.** Continuous bladder irrigation following prostatectomy. *Med Bull St Louis Univ* 1952; **4**: 77-79 [PMID: 12992066]
 - 17 **Kim SK.** A new device for continuous bladder irrigation. *J Urol* 1959; **81**: 330-331 [PMID: 13631829]
 - 18 **Kinder CH.** A simple irrigating catheter. *Br J Urol* 1966; **38**: 323 [PMID: 5943902 DOI: 10.1111/j.1464-410X.1966.tb09720.x]
 - 19 **Tinckler LF.** Post-prostatectomy management--a new catheter system. *Br J Urol* 1972; **44**: 165-168 [PMID: 4557439 DOI: 10.1111/j.1464-410X.1972.tb10061.x]
 - 20 **Végh A, Magasi P.** The importance of closed bladder irrigation in prostatectomy. *Acta Chir Hung* 1988; **29**: 137-141 [PMID: 3051813]
 - 21 **Miller A, Gillespie WA, Linton KB, Slade N, Mitchell JP.** Postoperative infection in urology. *Lancet* 1958; **2**: 608-612 [PMID: 13588945 DOI: 10.1016/S0140-6736(58)90335-0]
 - 22 **Clark SS, Misurec R, Kumar H, Srinivasan V.** Closed postprostatectomy irrigation-drainage system. I. Description and rationale. *Urology* 1973; **1**: 125-126 [PMID: 4771611 DOI: 10.1016/0090-4295(73)90598-0]
 - 23 **Livne PM, Servadio C, Frischer Z, Nissenkorn I.** Simple method of continuous bladder irrigation for prevention of postprostatectomy complications. *Urology* 1982; **19**: 314-315 [PMID: 7064262 DOI: 10.1016/0090-4295(82)90511-8]
 - 24 **Caro DJ.** A simpler method for continuous bladder irrigation. *Urology* 1982; **20**: 110 [PMID: 7112790 DOI: 10.1016/0090-4295(82)90559-3]
 - 25 **Okorie CO, Salia M, Liu P, Pisters LL.** Modified suprapubic prostatectomy without irrigation is safe. *Urology* 2010; **75**: 701-705 [PMID: 19914705 DOI: 10.1016/j.urology.2009.06.109]
 - 26 **Koshiba K, Egawa S, Ohori M, Uchida T, Yokoyama E, Shoji K.** Does transurethral resection of the prostate pose a risk to life? 22-year outcome. *J Urol* 1995; **153**: 1506-1509 [PMID: 7536257 DOI: 10.1016/S0022-5347(01)67447-0]
 - 27 **Ansari MZ, Costello AJ, Ackland MJ, Carson N, McDonald IG.** In-hospital mortality after transurethral resection of the prostate in Victorian public hospitals. *Aust N Z J Surg* 2000; **70**: 204-208 [PMID: 10765905 DOI: 10.1046/j.1440-1622.2000.01787.x]
 - 28 **Horninger W, Unterlechner H, Strasser H, Bartsch G.** Transurethral prostatectomy: mortality and morbidity. *Prostate* 1996; **28**: 195-200 [PMID: 8628722 DOI: 10.1002/(SICI)1097-0045(199603)28:3<195::AID-PROS6>3.0.CO;2-E]
 - 29 **Varkarakis J, Bartsch G, Horninger W.** Long-term morbidity and mortality of transurethral prostatectomy: a 10-year follow-up. *Prostate* 2004; **58**: 248-251 [PMID: 14743463 DOI: 10.1002/pros.10339]
 - 30 **Mebust WK, Holtgrewe HL, Cockett AT, Peters PC.** Transurethral prostatectomy: immediate and postoperative complications. a cooperative study of 13 participating institutions evaluating 3,885 patients. 1989. *J Urol* 2002; **167**: 999-1003; discussion 1004 [PMID: 11908420 DOI: 10.1016/S0022-5347(02)80323-8]
 - 31 **Reich O, Gratzke C, Bachmann A, Seitz M, Schlenker B, Hermanek P, Lack N, Stief CG.** Morbidity, mortality and early outcome of transurethral resection of the prostate: a prospective multicenter evaluation of 10,654 patients. *J Urol* 2008; **180**: 246-249 [PMID: 18499179 DOI: 10.1016/j.juro.2008.03.058]
 - 32 **Chander J, Vanitha V, Lal P, Ramteke VK.** Transurethral resection of the prostate as catheter-free day-care surgery. *BJU Int* 2003; **92**: 422-425 [PMID: 12930433 DOI: 10.1046/j.1464-410X.2003.04364.x]
 - 33 **Rigatti P, Cestari A, Gilling P.** The motion: large BPH should be treated by open surgery. *Eur Urol* 2007; **51**: 845-847; discussion 847-848 [PMID: 17348089 DOI: 10.1016/j.eururo.2006.12.020]
 - 34 **Meier DE, Tarpley JL, Imediogwu OO, Olaolun DA, Nkor SK, Amao EA, Hawkins TC, McConnell JD.** The outcome of suprapubic prostatectomy: a contemporary series in the developing world. *Urology* 1995; **46**: 40-44 [PMID: 7541584 DOI: 10.1016/S0090-4295(99)80156-3]
 - 35 **Servadio C.** Is open prostatectomy really obsolete? *Urology* 1992; **40**: 419-421 [PMID: 1279878 DOI: 10.1016/0090-4295(92)90454-5]
 - 36 **Berger AP, Wirtenberger W, Bektic J, Steiner H, Spranger R, Bartsch G, Horninger W.** Safer transurethral resection of the prostate: coagulating intermittent cutting reduces hemostatic complications. *J Urol* 2004; **171**: 289-291 [PMID: 14665896 DOI: 10.1097/01.ju.0000098925.76817.3a]
 - 37 **Okorie CO, Pisters LL.** Effect of modified suprapubic prostatectomy for benign prostatic hyperplasia on postoperative hemoglobin levels. *Can J Urol* 2010; **17**: 5255-5258 [PMID: 20735903]
 - 38 **Lowthian P.** Preventing clot retention after urological surgery. *BJU Int* 2003; **91**: 126 [PMID: 12614271 DOI: 10.1046/j.1464-410X.2003.t01-3-04022.x]
 - 39 **Fuller E.** Diseases of the genito-urinary system. New York: MacMillan, 1900
 - 40 **Cabot F.** Value of sight in suprapubic prostatectomy. *Tr Am Urol* 1909; **3**: 449
 - 41 **Herman JR, Castro L.** Suprapubic prostatectomy. Some early methods of hemostasis. *Urology* 1973; **1**: 612-619 [PMID: 4588823 DOI: 10.1016/0090-4295(73)90528-1]
 - 42 **McEachern AC.** The evolution of safety in prostatectomy. *Ann R Coll Surg Engl* 1958; **22**: 151-177 [PMID: 13509570]
 - 43 **Morson AC, Semple JE.** A study of the craftsmanship of the Harris technique for prostatectomy. *BJU* 1934; **6**: 207-219 [DOI: 10.1111/j.1464-410X.1934.tb11237.x]
 - 44 **Loughnane FM.** Treatment of prostatic obstruction. *Br Med J* 1937; **16**: 144-145 [DOI: 10.1136/bmj.1.3967.144-a]
 - 45 **Wilde S.** See one, do one, modify one: prostate surgery in the 1930s. *Med Hist* 2004; **48**: 351-366 [PMID: 16021930 DOI: 10.1017/S0025727300007675]
 - 46 **Adams AW.** A third ureter in prostatectomy. *Br Med J* 1949; **1**: 809 [PMID: 18120853 DOI: 10.1136/bmj.1.4609.809]
 - 47 **Attah CA.** Effect of continuous irrigation with normal saline after prostatectomy. *Int Urol Nephrol* 1993; **25**: 461-467 [PMID: 8270374]
 - 48 **Schlegel JU, Jorgensen H, Mcfadden A, Scott WW.** A physiological approach to bladder irrigation in gross hematuria. *Trans Am Assoc Genitourin Surg* 1957; **49**: 2-7 [PMID: 13496073]
 - 49 **Essenhigh DM, Eustace BR.** The use of frusemide (Lasix) in the post-operative management of prostatectomy. *Br J Urol* 1969; **41**: 579-585 [PMID: 5383556 DOI: 10.1111/j.1464-410X.1969.tb09965.x]
 - 50 **Esho JO, Kuwong MP, Gbadamosi WB.** Suprapubic prostatectomy without suprapubic tube and without bladder irrigation. *Eur Urol* 1989; **16**: 15-17 [PMID: 2469584]
 - 51 **Britton JP, Fletcher MS, Harrison NW, Royle MG.** Irrigation or no irrigation after transurethral prostatectomy? *Br J Urol* 1992; **70**: 526-528 [PMID: 1467860]
 - 52 **Mobb GE, Farrar DJ.** Is planned continuous irrigation indicated for haemorrhage following transurethral resection of the prostate? *Br J Urol* 1993; **71**: 707-710 [PMID: 8343899 DOI: 10.1111/j.1464-410X.1993.tb16070.x]
 - 53 **Malone PR, Davies JH, Standfield NJ, Bush RA, Gosling JV, Shearer RJ.** Metabolic consequences of forced diuresis following prostatectomy. *Br J Urol* 1986; **58**: 406-411 [PMID: 3756410 DOI: 10.1111/j.1464-410X.1986.tb09094.x]
 - 54 **Jasiński Z, Wolski Z.** A new technique of haemostasis following transvesical prostatectomy. *Int Urol Nephrol* 1985; **17**: 165-169 [PMID: 2417976 DOI: 10.1007/BF02082489]
 - 55 **Okorie CO, Pisters LL.** Suprapubic prostatectomy for benign prostatic hyperplasia: aspects of evolution of hemostatic methods to present time. In: Alvelos HM, Izidoro YG. Prostatectomies: procedures, benefits and potential complications. New York: Nova publishers, 2012: 31-47
 - 56 **Mireku-Boateng AO, Jackson AG.** Prostate fossa packing: a simple, quick and effective method of achieving hemostasis in suprapubic prostatectomy. *Urol Int* 2005; **74**: 180-182 [PMID: 15756072 DOI: 10.1159/000083291]
 - 57 **Bapat RD, Relekar RG, Pandit SR, Dandekar NP.** Comparative

- study between modified Freyer's prostatectomy, classical Freyer's prostatectomy and Millin's prostatectomy. *J Postgrad Med* 1991; **37**: 144-147 [PMID: 1723756]
- 58 **Lower WE**. Complete closure of the bladder following prostatectomy. *JAMA* 1927; **89**: 749-751 [DOI: 10.1001/jama.1927.02690100011004]
- 59 **Harris S**. Prostatectomy with closure: Five years' experience. *BJS* 1934; **21**: 434 [DOI: 10.1002/bjs.1800218309]
- 60 **Silverton RJ**. Sutural haemostasis in suprapubic prostatectomy. *ANZ J Surg* 1934; **3**: 276-283 [DOI: 10.1111/j.1445-2197.1934.tb02640.x]
- 61 **De la pena A**, Alcina E. Suprapubic prostatectomy: a new technique to prevent bleeding. *J Urol* 1962; **88**: 86-90 [PMID: 13884275]
- 62 **Malament M**. Maximal hemostasis in suprapubic prostatectomy. *Surg Gynecol Obstet* 1965; **120**: 1307-1312 [PMID: 14289622]
- 63 **Cohen SP**, Kopilnick MD, Robbins MA. Removable purse-string suture of the vesical neck during suprapubic prostatectomy. *J Urol* 1969; **102**: 720-722 [PMID: 4906206]
- 64 **Nicoll GA**, Riffle GN, Andersen FO. Suprapubic prostatectomy. The removable purse string: a continuing comparative analysis of 300 consecutive cases. *J Urol* 1978; **120**: 702-704 [PMID: 731809]
- 65 **Denis R**. Prostatectomy under depression. *J Urol Nephrol* (Paris) 1970; **76**: 663-672 [PMID: 5475533]
- 66 **Condie JD**, Cuthrell L, Mian A. Suprapubic prostatectomy for benign prostatic hyperplasia in rural Asia: 200 consecutive cases. *Urology* 1999; **54**: 1012-1016 [PMID: 10604700 DOI: 10.1016/S0090-4295(99)00307-6]
- 67 **Lezrek M**, Ameer A, Renteria JM, El Alj HA, Beddouch A. Modified Denis technique: a simple solution for maximal hemostasis in suprapubic prostatectomy. *Urology* 2003; **61**: 951-955 [PMID: 12736014 DOI: 10.1016/S0090-4295(02)02513-X]
- 68 **Nthumba PM**, Bird PA. Suprapubic prostatectomy with and without continuous bladder irrigation in a community with limited resources. *ECA J Surg* 2006; **12**: 53-58
- 69 **Kavanagh LE**, Jack GS, Lawrentschuk N. Prevention and management of TURP-related hemorrhage. *Nat Rev Urol* 2011; **8**: 504-514 [PMID: 21844906 DOI: 10.1038/nrurol.2011.106]
- 70 **Gilling PJ**, Kennett K, Das AK, Thompson D, Fraundorfer MR. Holmium laser enucleation of the prostate (HoLEP) combined with transurethral tissue morcellation: an update on the early clinical experience. *J Endourol* 1998; **12**: 457-459 [PMID: 9847070 DOI: 10.1089/end.1998.12.457]
- 71 **Moody JA**, Lingeman JE. Holmium laser enucleation of the prostate with tissue morcellation: initial United States experience. *J Endourol* 2000; **14**: 219-223 [PMID: 10772518 DOI: 10.1089/end.2000.14.219]
- 72 **Kuntz RM**. Current role of lasers in the treatment of benign prostatic hyperplasia (BPH). *Eur Urol* 2006; **49**: 961-969 [PMID: 16632179 DOI: 10.1016/j.eururo.2006.03.028]
- 73 **Elzayat EA**, Elhilali MM. Holmium laser enucleation of the prostate (HoLEP): the endourologic alternative to open prostatectomy. *Eur Urol* 2006; **49**: 87-91 [PMID: 16314033 DOI: 10.1016/j.eururo.2005.08.015]
- 74 **Stutzman RE**. Urologic Surgery. 4th ed. Lippincott: Philadelphia, 1991: 585-602
- 75 **Manley BJ**, Gericke RK, Brockman JA, Robles J, Raup VT, Bhayani SB. The pitfalls of electronic health orders: development of an enhanced institutional protocol after a preventable patient death. *Patient Saf Surg* 2014; **8**: 39 [PMID: 25309624]
- 76 **Hahne B**, van der Linden W. Vesical neck closure versus balloon catheter in suprapubic prostatectomy: a controlled clinical trial. *J Urol* 1978; **120**: 699-701 [PMID: 731808]

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