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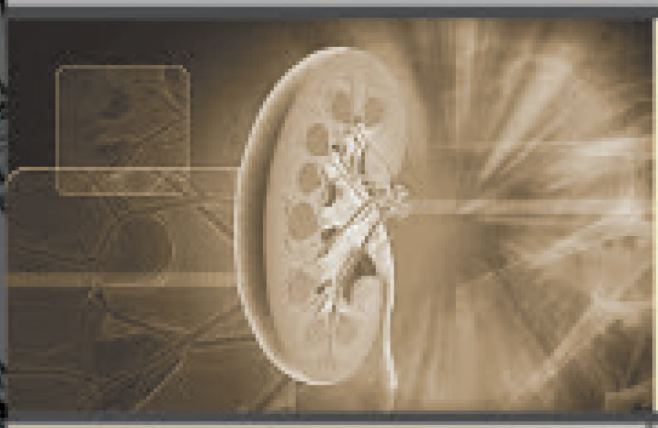

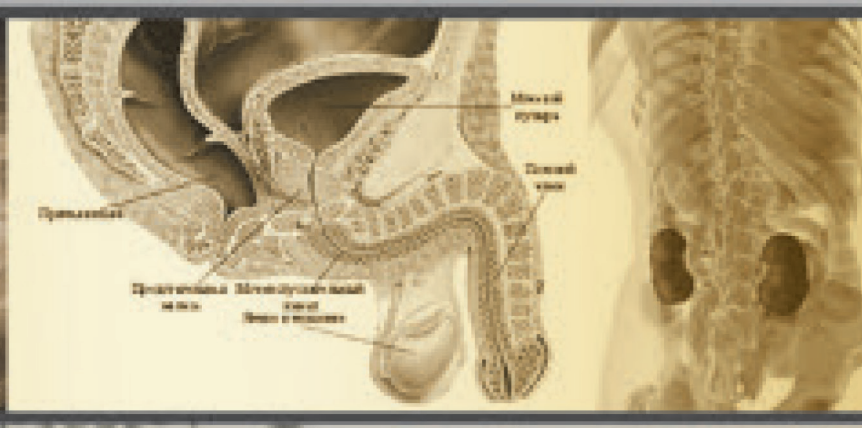

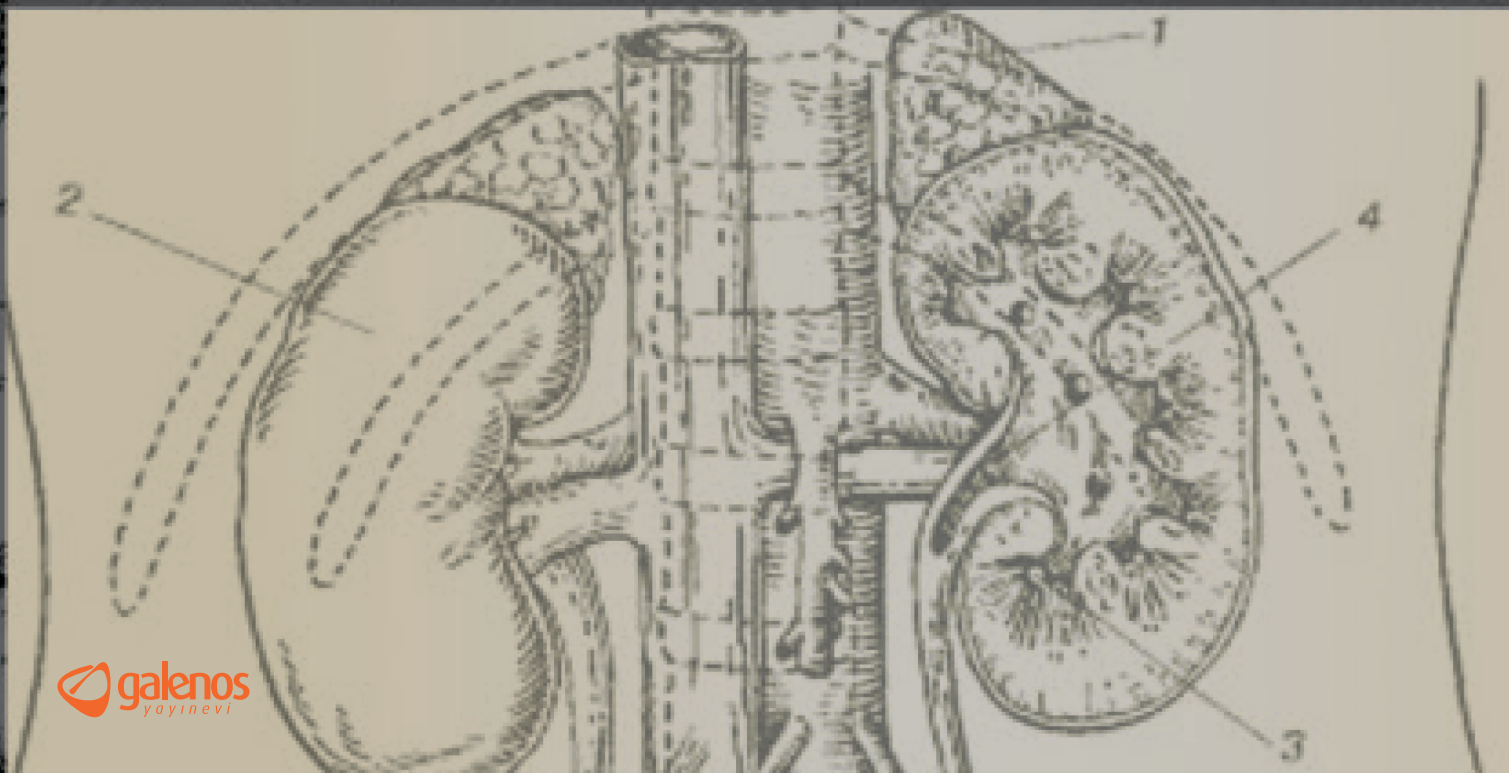

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2. Organization as Author

Yaycioglu O, Eskicorapci S, Karabulut E, Soyupak B, Gogus C, Divrik T, Turkeri L, Yazici S, Ozen H; Society of Urooncology Study Group for Kidney Cancer Prognosis. A preoperative prognostic model predicting recurrence-free survival for patients with kidney cancer. Jpn J Clin Oncol 2013;43:63-68.

3. Complete Book

Wein AJ, Kavoussi LR, Novick AC, Partin AW, Peters CA. Campbell-Walsh Urology, 10th ed. Philadelphia, Elsevier&Saunders, 2012.

4. Chapter in Book

Pearle MS, Lotan Y Urinary lithiasis: etiology, epidemiology, and pathogenesis. In: Wein AJ, Kavoussi LR, Novick AC, Partin AW, Peters CA. Campbell-Walsh Urology, 10th ed. Philadelphia, Elsevier&Saunders, 201, pp 1257-1323.

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5. Abstract

Nguyen CT, Fu AZ, Gilligan TD, Kattan MW, Wells BJ, Klein EA. Decision analysis model for clinical stage I nonseminomatous germ cell testicular cancer. J Urol 2008;179:495a (abstract).

6. Letter to the Editor

Lingeman JE. Holmium laser enucleation of the prostate-If not now, when? J Urol 2011;186:1762-1763.

7. Supplement

Fine MS, Smith KM, Shrivastava D, Cook ME, Shukla AR. Posterior Urethral Valve Treatments and Outcomes in Children Receiving Kidney Transplants. J Urol 2011;185(Suppl):2491-2496.

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REVIEW
Andrology

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Transgender Surgery: A Review Article

Kahraman Berkhan Yılmaz[1], Kamil Fehmi Narter[2]

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What's known on the subject? and What does the study add?

Transgender surgeries are complex and multidisciplinary procedures. This review aimed to summarize these operations for our colleagues according to the current literature.

Abstract

Transgender surgeries are required to correct some congenital genital defects, reconstruct genital trauma, amputate, treat cancer (e.g., penile cancer), or within a wide perspective to treat gender dysphoria. Literature about gender-affirming surgery is limited; however, surgeries for transgender patients have been done almost for a century. Evidence concerning both male-to-female and female-to-male surgeries has limitations such as insufficient controlled studies, validated assessment measures, and properly controlled groups. Transgender surgeries are mostly required to treat gender dysphoria. The community modernization and more acceptance of transgender citizens in societies have increased the demand for these surgeries within recent years. Increased numbers of patients and advanced surgical options that are available for gender reassignment surgery have made this subject an important consideration for research. Modern surgical techniques with the support of other auxiliary therapy modalities (e.g., hormonal therapy) create satisfactory results for patients; however, these therapies cause many complications as well. In the future, more transgender patients are expected, thus we have to master the subject to treat their problems, most of which probably will be related to surgery complications. This review aimed to summarize transgender surgery, especially genital reconstructive techniques for related specialties to better understand its recent update according to actual literature.
Keywords: Transgender, gender dysphoria, gender-affirming

Introduction

Gender dysphoria term was introduced in the Diagnostic and Statistical Manual of Mental Disorders-5 in 2013. It is estimated that 0.5-1.3% of the population in the United States of America has gender dysphoria (1). Although it may seem a very new concept, transgender surgery has been done for almost over a century. Surgical treatment of transgender patients is a series of consecutive operations supported with various treatment modalities. The content of these surgical techniques covers multiple complex and challenging operations. Before surgical treatment starts, a long period is necessary for physiological and endocrinological preoperative preparations. Therefore, many specialists perform these surgeries in universities or fully equipped complex utilities, which have all needed specialists. These kinds of surgeries are of interest to many specialties, such as plastic and reconstructive surgery, urology, obstetrics and gynecology, psychiatry, forensic medicine, genetic, and endocrinology. Many countries have authorized the decision to perform these operations in medical centers and committees that include several specialists. In the childhood period, congenital genital abnormalities can be reconstructed but in adulthood, other etiological problems, such as gender dysphoria or trauma, can be treated by these operations. Transgender operations contain two main groups: Male-to-female (MTF) and female-to-male (FTM) surgeries. According to literature, MTF transsexuals are four times more frequent than FTM (2,3). Transsexualism was described by Harry Benjamin in 1966 (4).

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Pediatric endocrinologist C. Migeon and psychologist J. Money were focused on intersexed children with ambiguous genitalia in 1966 and the first Gender Identity Clinic was described at Johns Hopkins University on the same date. Currently, the World Professional Association for Transgender Health is the pioneer institution that declared the standards of care, which is regularly updated (2). The etiological factors of transsexualism can be classified as biological (genetic and neuroanatomic) and psychological (environmental and internal).

Transgender surgeries are required mostly to treat gender dysphoria. Before the surgical operations, psychosocial evaluation is very important in the decision-making process (5). In most countries, including our country, candidate patients for this interchange treatment should have hormone replacement treatment under the supervision of a psychiatrist and an endocrinologist for at least 2 years. Patients are expected to live and work in the new gender role to obtain real-life experience of the opposite sex. Evaluation of a patient's body image, goals, and expectations is very crucial. After the completion of the preparation stage, the surgical treatment must be planned. In surgical treatment, efforts are made to achieve mental health, aesthetics, and functionality together. The general plastic and reconstructive surgery principles should always be considered in these operations because these operations have a considerable amount of complication rates.

Hormone-sensitive cancers (breast and prostate) and human immunodeficiency virus infection rates of transgender patients are higher than the normal population. Thus, the postoperative follow-up period is so crucial. Not only surgical but also physical and mental follow-up must be considered by the medical staff. Nowadays, linguistics/voice therapy, mental health, fertility, and sexuality topics are more researched for these patients.

This review aimed to summarize transgender surgical techniques especially genital surgeries for related specialties according to the actual literature (Table 1).

MTF Surgery

MTF surgery contains non-genital surgeries, such as breast augmentation, vocal cord, and throat surgery (tracheal cartilage shave), facial feminization surgery, and genital surgeries, such as orchidectomy, penectomy, labioplasty, clitoroplasty, and vaginoplasty (Figure 1).

Genital Surgery

1. Vaginoplasty and Orchiectomy

The Hirschfeld Institute for sexual science performed the first transgender vaginoplasty in 1931. The main purpose of vaginoplasty is to create a functional cavity in the pelvis or perineum that also allows proper urination. This neovaginal cavity is created between the prostate and rectum. Vaginoplasty and orchiectomy are made together to take the advance of having more tissue to use for genital reconstruction. For the new vagina, the penile skin flap is ideal due to its properties like being smooth, hairless, elastic, and thin. Ideal dimensions of neovagina are 10 cm in depth and 30 mm in length and without introital stenosis (6). After the removal of the corpus spongiosum and testicles, a vaginal cavity is created, and the penile (with scrotal) skin flaps are used to cover the inner lining of this neovagina. The disadvantage of the penile flap is its insufficient size, especially for small penis sizes. This flap has fewer tendencies to contract than skin grafts. Postoperative neovaginal dilation is advised for at least 1 year to prevent introital stenosis and neovaginal shrinkage. If the size of the penile flap is insufficient to cover the neovaginal cavity, skin grafts are used. In this context, flaps can be obtained from the thigh (i.e., gracilis flap) or bowel for vaginal reconstruction. For a vaginoplasty with bowel, the sigmoid is mostly the first choice. Intestinal vaginoplasty can be preferable especially for secondary vaginoplasties. The advantages of using a rectosigmoid part are its length and texture, which are very similar to the vaginal lining. One major disadvantage of intestinal vaginoplasty is

Table 1. Overview of surgical procedures

Male-to-female surgery	Female-to-male surgery
Facial feminization surgery	Facial masculinization surgery
Voice surgery and chondrolaryngoplasty	-
Breast augmentation	Subcutaneous mastectomy
Orchiectomy	Testicular prostheses
Vaginoplasty	Phalloplasty: Free radial forearm flap, pedicled anterolateral thigh flap, myocutaneous gracilis flap, fibula flap, metoidioplasty, external prosthesis

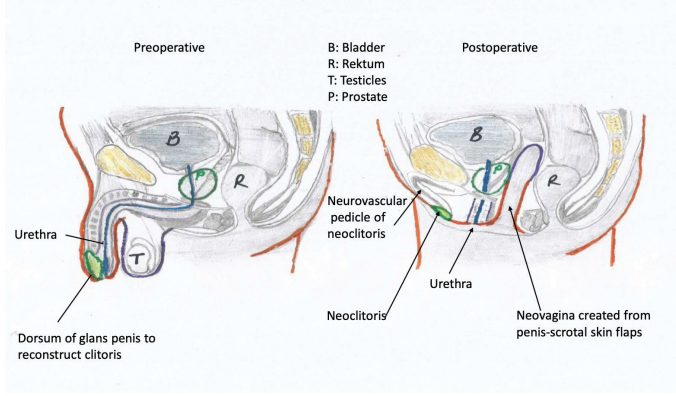

Figure 1. Schematic drawing of MTF surgery

MTF: Male-to-female

excessive discharge, which may be a social problem. In addition to this, the need for laparotomy and bowel anastomosis, which increase the risk of postoperative ileus.

As a summary, the most preferred MTF genital reconstruction sequence has 5 major steps as penile disassembly and bilateral orchiectomy, neovaginal cavity construction, labia majora creation, and female urethral meatus and clitoris reconstruction (7,8).

2. Clitoroplasty

Clitoroplasty, especially from the glans penis, was described by Rubin (9). The neurovascular bundle must be protected for postoperative well sexual satisfaction. The dorsal section of the glans is reduced by excising the central ventral tissue, leaving the sides of the glans intact. Sides are sutured together to obtain the conical shape of the neoclitoris, which is placed in front of the neourethra.

3. Labioplasty

Labioplasty is a technique that creates labia majora and minora from tissue remnants after vaginoplasty. Labia majora is mostly reconstructed from the remnants of scrotal skin flaps after orchiectomy is done. Scrotal flaps are reshaped around the newly reconstructed vagina to simulate labia majora. Labia minora is mostly reconstructed from the prepuce. When the penile inversion technique is used for vaginal reconstruction, the tissue may be inadequate to reconstruct the labia minora. However, if vaginoplasty is done with bowel flaps, there is plenty of tissue to reconstruct the labia minora and clitoral prepuce.

4. Urethroplasty

Urethrostomy is the reopening technique of shortened urethra to skin. The urethra is divided at the proximal bulb level and the urothelium is sutured to the anterior skin flap. This operation has some early complications, such as urethral meatal stenosis, the unsatisfactory direction of micturition, and residual erectile tissue due to corpus spongiosum remnants.

The most frequent early complications of all MTF operations are bleeding from operation sites, rectal fistula into the neovagina, and neovaginal prolapse or graft/flap loss due to hematoma. Late complications of these operations are meatal stenosis due to scar contracture and incontinence due to retention of urine. In addition, vaginal stenosis and hair growth within the neovagina can be seen as late postoperative complications due to the lack of regular follow-up.

A rectal-neovaginal fistula can occur due to traction or injury during the operation. Rectovaginal fistula incidence was reported at 0.8% by van der Sluis et al. (10). One other complication of these operations is the urethroneovaginal fistula. Its incidence was reported at 0.8-3.9% (11-14). After the vaginoplasty operation, one of the most serious complications is urethral stenosis, especially at the meatal level (incidence range 1-40%) (13-16). Neovaginal stenosis may occur in 7% (1-12%) of patients (17,18). Other complications were reported, such as urethral bulb bulge and cosmetic abnormality of the clitoral or labial outlook.

Before the vaginoplasty, bowel preparation and permanent hair removal are recommended. Estrogen treatment should be stopped 2 weeks before the surgery and preoperative anticoagulation should be started. Neourethral catheterization and pressure dressing are necessary for the postoperative period. Vaginal dilatation and lubrication are important procedures to protect against stenosis (3,19). After the MTF surgery, it should be kept in mind that patients are still at risk for benign prostatic hyperplasia and prostate cancer due to remnant *in situ* prostate (20). Another important risk of the neovagina is the development of squamous cell carcinoma due to penile skin (21). Therefore, patients should be followed up regularly for a long time.

Venous thromboembolic disease (VTE) is another complication of MTF surgery. Cross-sex hormone replacement therapy allows individuals to develop secondary sex characteristics to feel their new identity. But this treatment, especially estrogen use, has a major complication that includes VTE, as well as coronary artery disease, stroke, and cancer formation. If anytime during the follow-up period, a VTE is diagnosed, the hormone replacement therapy is immediately stopped, and anticoagulant therapy must be started (22).

Non-genital Surgery:

1. Facial Feminization Surgery

- Chin surgery
- Eyelid surgery
- Rhinoplasty
- Forehead reshaping
- Hair restoration

2. Chondrolaryngoplasty and Voice Surgery

3. Breast Augmentation (breast reconstruction)

- Silicone implants
- Fat grafts.

As non-genital surgeries listed here are out of the scope of a urological journal, they will be written here only as names.

FTM Surgery

FTM procedures can also be grouped as non-genital and genital operations. Non-genital procedures include mastectomy, nipple reconstruction, and facial masculinization, whereas

genital procedures include hysterectomy, oophorectomy, vaginectomy or colpectomy, and penis reconstruction. Besides, at the preoperative period, some of the masculine traits can be obtained by testosterone replacement treatment (over 1 year), such as voice, facial and body hair growth, muscle growth, and clitoral hypertrophy. Most often, after the hormonal treatment period, genital surgical operations of these patients are required (Figure 2).

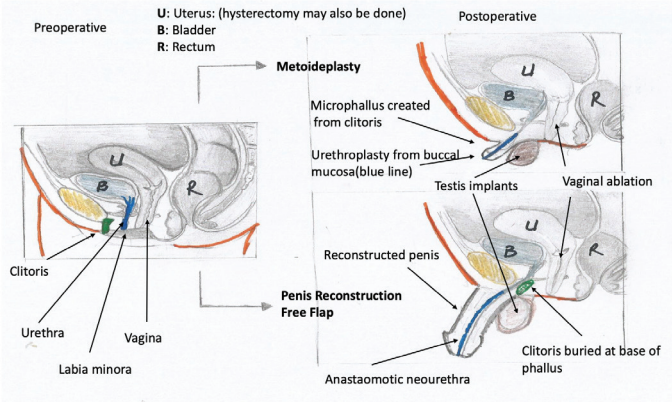

Figure 2. Schematic drawing of FTM surgery

FTM: Female-to-male

Genital Surgery

Metoidioplasty, phalloplasty, penile prosthesis implantation, and scrotal reconstruction are done for male genital and perineal reconstruction. These operations aimed to include micturation in a standing position, well cosmetic appearance, and adequate sexual performance.

1. Penile Reconstruction

Metoidioplasty is a procedure that uses the clitoris that is overdeveloped by hormonal treatment (testosterone replacement) to construct a new small phallus. This technique was first introduced by Lebovic and Laub (23). The small size of the new phallus is the main problem (5-7 cm) of this procedure. Contrarily, advantages of this technique are well tactile and erogenous sensation, erectile tissue without prostheses, and limited scar formation. Metoidioplasty contains chordee release, neurovascular pedicle reposition, and ventral phallus skin closure. In this operation, the labia minora flaps are preserved and used as additional coverage over the native urethra to ring flap anastomosis. Additionally, full metoidioplasty includes a vaginectomy, urethroplasty (urethral reconstruction), scrotoplasty, and perineal reconstruction. According to a meta-analysis reported, the metoidioplasty-associated urethral complication rate is approximately 25% (24). In addition, urethral strictures and fistulas are common and the incidence rate is approximately 50% (25,26). Neophallus has to be checked often with Doppler ultrasonography at the postoperative period for blood supply.

Phalloplasty is another option for cosmesis, which brings the adequate size of new phallus (pedicle flap phalloplasty or free flap phalloplasty). The neourethra, which also has to be reconstructed, opens to the tip of the neophallus. Vaginal epithelium and skin can be used to create a neourethra within chosen flaps. Many flap options are available to give shape to the penis; tubed pedicle flaps can be obtained from the abdomen (suprapubic phalloplasty) or free flaps can be prepared from the radial forearm free flap (RFFF), anterolateral thigh (ALT), fibula, and musculocutaneous latissimus dorsi free flap, tibial free flap, and abdominal or groin pedicle flap. Phalloplasty was done in 1936 by Nikolaj Bogoraz (27). Bogoraz reconstructed the first functional transgender neophallus using a tubed abdominal flap and autologous rib cartilage. H. Gilles described a new technique with the construction of the neourethra by a roller tube from the abdominal wall in 1946 (28). Kaplan (29) described another procedure with neourethra formed from the scrotal raphe and well sensitive neophallus innervated from the genitofemoral branches. Orticochea described a musculocutaneous gracilis flap with the cutaneous branch of the obturator nerve for phalloplasty (30). Groin flap was used by McGregor and Jackson (31). Hester et al. (32) demonstrated a single-stage total penile reconstruction with bilateral gracilis muscle flaps, and urethral reconstruction was utilized from a full-thickness skin graft in 1978. In 1982, Song developed the first successful RFFF (33). However, his technique was two-staged procedure, which includes phalloplasty and urethroplasty, separately. In 1984, Chang and Hwang (34) described one staged RFFF technique with good functional and cosmetic results using microsurgical techniques. This method was named "tube-within-a-tube" by the authors. Ten years later, Hage and De Graaf (35) changed the ideal technique definition as one-stage procedure, which created a neourethra compatible with standing micturition and suitable for prosthetic insertion. All techniques are summarized in Table 2. Many other free flap phalloplasty procedures have been described afterward like lateral arm, radial forearm osteocutaneous, free osteofasciocutaneous fibula, island tensor fasciae latae, scapular skin, ALT, superficial circumflex iliac artery perforator, musculocutaneous latissimus dorsi free, and single pedicled ALT flaps. Today, the forearm (radial) free flaps are preferable for phalloplasty in one staged or two-staged fashion. In this technique, the radial artery and the cutaneous antebrachial nerves are crucial. The radial vessels are anastomosed to the femoral artery and the long saphenous vein and cutaneous nerves are sutured to the dorsal nerve of the clitoris and the ileoinguinal nerve under a microscope view (36). Neophallus has two parts as pars pendulas (distal urethra) and pars fixa (proximal urethra). Pars fixa is created from the labia minora and vaginal epithelium, around the urethral

Table 2. Overview of penile reconstruction	
Technique	**Materials and Methods**
Metoidioplasty (G.S.Lebovic and D.R.Laub, 1999)	Clitoris and hormonal treatment (testosterone replacement therapy)
Phalloplasty	
Phalloplasty (N.Bogoraz, 1936)	Tubed abdominal flap and autologous rib cartilage
Phalloplasty with neourethra (H.Gilles, 1946)	The construction of the neourethra by a roller tube from abdominal wall
Phalloplasty with neourethra (I.Kaplan, 1971)	The neourethra formed from scrotal raphe and well sensitive neophallus innervated from genitofemoral branches
Phalloplasty with neourethra (M.Orticochea, 1972)	Musculocutaneous gracilis flap with cutaneous branch of obturator nerve
Phalloplasty with neourethra (I.A.McGregor and I.T.Jackson, 1972)	Groin flap for phalloplasty
Single stage total penile reconstruction (T.R.Hester, 1978)	Bilateral gracilis muscle flaps and urethral reconstruction was utilized from a full thickness skin graft
Free flap phalloplasty, two stages (R.Song, 1982)	Radial forearm free flap (RFFF) for phalloplasty, two stages (phalloplasty and urethraplasty)
Free flap phalloplasty with microsurgery, one stage (T.S.Chang and W.Y.Hwang, 1984)	One staged RFFF technique (tube-within-a-tube method)
Free flap phalloplasty with microsurgery, one stage (J.Hage and F.H.De Graaf, 1993)	One stage RFFF technique, neourethra compatible to standing micturition, suitable for prosthetic insertion

catheter, and this urethral part is joined to the inner tube in the neophallus. The clitoris is usually left in place at the base of the neophallus for sexual sensation and orgasm. Moreover, the Norfolk technique and its modifications can be used (rolled up skin flaps and skin grafts) for almost normal appearing glans and coronal sulcus (glansplasty and coronaplasty) (37,38).

The ideal flap reconstruction technique has to contain a good cosmetic shape and must be suitable for prosthesis insertion and functional in voiding and sexual activities. In addition, a good sensation that is enough for orgasm must be obtained and with a low morbidity rate for the donor site (donor scar). Preferably, single staged techniques which have constant vascular and neural anatomy have to be chosen. If a skin flap is to be selected, care should be taken not to disturb the blood supply of the vascular pedicle.

These operations have a high risk of having urethral stenosis, urethral fistula, and postmicturition dribble. The complication rate of FTM surgery is higher than MTF surgery (40% vs. 25%). A suggested body mass index cutoff is 35 kg/m^2 for patients desiring RFFF phalloplasty (39).

A penile prosthesis has to be placed to provide an adequate erection. After placing the prosthesis, it has to be anchored to the pelvic bone. Modern techniques prefer to use either a semi-rigid or inflatable prosthesis for implantation. It is recommended to implant a penile prosthesis into a sensate neophallus, as insensate coverage significantly increases the risk for implant erosion. Thus, waiting for the protective tactile sensation of the neophallus is very important. This process usually takes approximately 9 months. It will be better to wait for 1 year before considering implantation (40). Bilateral perineal incisions are ideal for implant insertion instead of making an incision on the reconstructed penis. If an inflatable device is chosen, the reservoir is placed in the space of Retzius with a separate abdominal incision to avoid injury to the flap vasculature.

2. Scrotoplasty

Scrotoplasty is the reconstruction of a new scrotum for testicle prosthesis. A new scrotum can be created from the labia majora tissue. Additionally, monsplasty and dermatolipectomy can be required.

Complications of FTM surgery are common, such as open wounds, urinary tract or skin infections, vascular thrombosis, hematomas, penile implant erosion, and infections. If urethral strictures or fistulas happen, these patients will require surgical repair 3-6 months after the phalloplasty. The highest risk for a urethral fistula or stricture formation is at PF-PP urethral anastomosis site and meatal level. Fistulas that are small and persist beyond 3-4 months postoperatively can be repaired primarily. Larger fistulas (>5 mm) can be treated with skin grafts or mucosal grafts that are similar to the urethral epithelium.

Penile transplantation (penis allotransplantation) is not currently used for transgender surgery. Few cases of penile transplantation were reported after traumatic amputation and oncological resection. The first successful human penis transplantation was performed in 2015 in South Africa to reconstruct the penis of a biological man who developed a complication from circumcision for which penile amputation was necessary (41). But there are still many unsolved ethico-legal issues and problems due to immunosuppression. The high cost of operation and the risks of lifelong usage of immunosuppression are still argument subjects for a non-life-saving procedure.

Non-genital Surgery:

1. Facial masculinization surgery

2. Subcutaneous mastectomy

3. Nipple-areola reconstruction (reduction).

As non-genital surgeries listed here are out of the scope of a urological journal, they will be written here only as names.

Conclusion

Gender dysphoria is no more a social problem in developed countries and patients more and more feel confident to seek gender reassignment surgery. However, transgender surgeries continue to be the most challenging and complex surgical procedures. In addition, these surgeries have very high complication rates. Assessment of the quality of life, long-term surgical follow-ups, and satisfactory outcomes are necessary for rational progress. The increasing interest in transgender surgery and advancement in medical technologies are contributing to this topic. Expert centers with multidisciplinary clinics are needed for successful outcomes. Every specialist involved in these subjects has to be more informed on these topics. Moreover, better-designed and larger-scale cohort studies are needed.

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Authorship Contributions

Surgical and Medical Practices: K.B.Y., Concept: K.B.Y., F.N., Design: F.N., Literature Search: K.B.Y., F.N., Writing: K.B.Y., F.N.

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REVIEW
Andrology

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Recent Advances in Elongated and Round Spermatid Injection

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What's known on the subject? and What does the study add?

Azoospermia is a condition that is characterized by absence of spermatozoa in the ejaculate, occurs in 15% of infertile men. Classified as obstructive azoospermia and non-obstructive azoospermia. Prior to microdissection testicular sperm extraction (microTESE) and in vitro fertilization/microinjection defined, donor insemination was the only option for non-obstructive azoospermia patients. However, the success rate of microTESE is reported up to 60% for all cases and this results forced the clinicians consider another possibilities such as the injection of early spermatids; elongated spermatids and round spermatids into oocytes. Although most of the studies are animal experiments, it has been shown that round spermatid administration can also cause fertility in humans. However, the round spermatid injection had lower success rate compared to elongated spermatid injection. This review demonstrated that the success rates of round spermatid injections are not as high as elongated spermatid injections. The he most critical factor affecting the success is correct cell selection and proper transfer. Thus, round spermatid injection success rates can approach elongated spermatid injection when carried out absolutely correctly. Although congenital anomalies are rarely reported after spermatid injection, the risk is known to be higher than in natural conception.

Abstract

Azoospermia is commonly identified in patients with infertility. Non-obstructive azoospermia (NOA) includes primary or secondary and incomplete testicular failure. Before testicular sperm extraction (TESE), donor insemination is the only option available in men with NOA. The combination of microTESE and intracytoplasmic sperm injection has considerably increased the fertilization rate. However, mature spermatozoa can be found in half of the patients. This situation prompted experts to use spermatids to assist in reproductive techniques. Elongated spermatid injection (ELSI) and round spermatid injection (ROSI) are among the possible treatments for couples who cannot find mature spermatozoa after microTESE in patients with NOA. This review provides an updated summary of the most recent available topics on ELSI and ROSI in the literature.
Keywords: Infertility, spermatogenesis, spermatids, testicular function

Introduction

Infertility is a significant health problem affecting ~20% of couples. Azoospermia is seen in ~15% of infertile men and is divided into two classes, obstructive azoospermia (OA) and non-obstructive azoospermia (NOA) (1). Patients with OA have normal spermatogenesis in the testis; however, spermatozoa are absent in the semen due to an obstruction in any part of the genital system. Patients with NOA have insufficient or hesitant spermatogenesis. Spermatogenesis is a complex process starting from mitosis of the spermatogonia to haploid round spermatid meiosis. Spermatogenesis then undergoes condensation and elongation in the spermiogenesis stage, where the head and tail of the sperm cell are formed (2). These structural changes are critical stages for a living sperm cell. Should there be pauses in these stages, mature spermatozoa do not form.

NOA is often due to primary testicular insufficiency [increased follicle-stimulating hormone (FSH) and luteinizing hormone (LH) levels accompanying small testicles], secondary testicular insufficiency (low FSH and LH levels associated with small testicles due to hypogonadotropic hypogonadism), or incomplete or ambiguous genitals (increased FSH levels or small testicular size accompanying average FSH levels) (1). Before the availability of microdissection testicular sperm extraction (microTESE) and intracytoplasmic sperm injection (ICSI), the only recommended option for patients who did not respond to medical treatment was donor insemination. Gratifyingly, because of the combination of microTESE and ICSI accompanying

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laboratory and genetic tests, the possibility to obtain sperm has increased considerably (3). However, spermatozoa are found in only approximately half of the cases after microTESE, even in experienced centers; therefore, the transfer of cells before maturation was tried in spermiogenesis to achieve fertilization in patients without spermatozoa, and evidence has shown that fertilization was achieved with elongated spermatid (ELS) and round spermatids (ROS) (4,5).

Spermiogenesis

Spermiogenesis is the final stage of spermatogenesis, where haploid ROS turns into mature motile spermatozoa (6). Spermatids contain Golgi apparatus, mitochondria, centrioles, and a nucleus. These formations are important in the shape of mature spermatozoa. The function of the Golgi apparatus plays an especially crucial role in spermiogenesis (7). Spermiogenesis can be divided into four basic stages: 1) the Golgi phase; 2) acrosome formation; 3) tail formation; and 4) maturation. Acrosome formation, which provides the egg's penetration into the protein sheath, is an early and essential stage performed by the Golgi apparatus. While vesicles within the cell unite to form the acrosome, the radially symmetrical spermatids become polarized. The Golgi apparatus then creates enzymes that will make up the acrosome. Later, the confluent acrosome vesicle begins to grow on the nuclear membrane surface and covers half of the membrane surface. The Golgi apparatus takes a cap by covering the core that passes to the center's other side. Once the acrosome is formed, a centriole of the sperm cell elongates to form the tail. This tail becomes a modified and mobile cilium (8). As spermiogenesis continues, the core is compressed and elongated. Cuff formation develops in the distal part with core densification and elongation. In the last stage of maturation, Sertoli cells phagocytose excess cytoplasm.

Cell Selection for ELSI and ROSI

The probability of finding viable spermatozoa after microTESE varies between 40% and 60% in patients with NOA; however, no mature spermatozoa can be found in half of these patients. This situation prompted experts to use spermatids to assist in reproductive techniques, resulting in a breakthrough in infertility treatments. Research showed that pregnancy could be achieved after the injection of spermatids into oocytes (4,9).

Fertilization success rates vary after elongated spermatid injection (ELSI) and round spermatid injection (ROSI), which can be obtained due to abnormal progression in spermiogenesis or maturation arrest. Early studies used the Papanicolaou test, fluorescence labeling, Pisum sativum agglutinin binding, and antiacrosin antiserum immune labeling for cell selection; however, living cells could not be obtained by employing these separation methods (10). Then, protocols, such as the Percoll gradient centrifuge, which enables the separation based on cell density, the STA-PUT velocity sedimentation based on miRNA, fluorescence-assisted cell sorting (FACS) based on DNA content, or propidium iodide, a DNA intercalation dye, were implemented for the effective and specific isolation of pure germ cells at different developmental stages (11-14). Differentiating them using the FACS method is difficult because the cell DNA content is similar. Instead, the selection of germ cells according to cell density is more efficient.

Currently, the most successful method for cell selection employs discernment under an electron microscope. Cells are selected based on their fundamental structural differences. Since ELS cells have a different head structure, they can be identified more easily than ROS cells. ROS are the smallest spermatogenic cells with a dimension of nearly 6-8 µm. ROS cells do not have distinct nucleoli, and the edge of the cytoplasm surrounding the nucleus is thinner than in spermatogonium. Active pseudopods seen in spermatogonia are also absent in round spermatocytes. Additionally, the cytoplasm of ROS is easily separated from the nucleus when pulled back and forth in the pipette. The fluorescence in situ hybridization (FISH) method is also helpful in identifying ROS cells. Mendoza et al. (15) used immunochemical imaging of proacrosis and autosomal DNA FISH to identify ROS. All ROS spermatids with pro-acrosine activity were haploid in the FISH. When the authors expanded their research, they emphasized that cell size is the main criterion for ROS selection. Computer-aided identification of live spermatids is predicted to be available soon.

ELSI and ROSI Success Rates

ELSI and ROSI success rates in patients with NOA are essential factors in transferring these cells. The literature showed that fertilization can be achieved with ROSI; however, early studies demonstrated the low efficiency of this process (10,16). The popularity of these procedures has decreased over time, especially since the American Reproductive Medicine Practice Committee defines ROSI as an experimental study (17). Similar fertilization rates were reported in ROSI and ELSI. However, these rates are lower than the fertilization rates obtained with mature spermatozoa obtained from microTESE (16,17). Data showed that fertilization rates after the transfer of the ELS cells with better maturation are slightly better than ROSI (18). A retrospective study by Sousa et al. (19) revealed that fertilization rates were 71.4%, 53.6%, and 17% in patients with ICSI, ELSI, and ROSI, respectively, and clinical pregnancy rates were 31.7%, 26.3%, and 0%, respectively. Additionally, in the same study, when the literature was reviewed, fertilization rates after ELSI and ROSI were 48.4% and 21.8%, and pregnancy rates were 28.9% and 2.8%, respectively. In seminal work by Tanaka et al. (5), the fertilization rate after ROSI was applied to 86 female patients was 76.4%, with a total pregnancy rate of 16.2% in cells whose spermatids were cryopreserved before transfer. In their later study, they showed that the fertilization

rate was 60.2% in those who were cryopreserved and with a low total number of pregnancies (9.4%) (17).

The most important factor affecting the success is correct cell selection (5,17,20). In animal models, ROS were defined as cells formed that contain central chromatin. Yet, human ROS do not contain central chromatin, and this situation supports that early studies' failure was the wrong cell selection. ELS can be selected more easily based on their DNA material and structural features; however, this selection is difficult for ROS. The morphological structure of ROS has been defined. According to the changes it has undergone, the terms early-ROS and late-ROS are used (21).

Another important factor affecting the success is the incomplete activation of oocytes due to insufficient activation ability of ROS; therefore, Tanaka et al. (5,17) reported that success rates increased when they activated oocytes after transfer. Another factor affecting the success was when the transfer was made, whether fresh spermatid or after freezing. The literature shows that transfer made after freezing the spermatids increased fertilization success since the uterine endometrium can be better prepared and the transfer can occur when it is in the best condition (5).

Safety of ELSI and ROSI

The reliability of assisted reproductive techniques depends on another important step. Spermatids may be susceptible to genetic disorders, which may occur in late gametogenesis and contribute to embryonic development (22). An early study showed that DNA methylation, essential for genomic imprinting, was not completed at the ROS stage; however, DNA methylation can still be completed after injection. This theory is supported by the observation of DNA methylation fluctuations that were completed during early embryonic development. DNA methylation and demethylation occur throughout spermatogenesis and mostly before meiosis I (23). Some researchers thought that the failure of ROSI was due to a lack of DNA methylation in ROS. Still, in animal models, DNA methylation is complete in ROS (23,24). In a study by Bonduelle et al. (25), which included 2889 pediatric patients with ICSI and 2995 with IVF, malformation rates were 1.69% and 1.31%, respectively. A review by Ludwig and Diedrich (26) reported that the rate of major malformation increased by 8.6% and the relative risk increased by 1.25% in the ICSI cases. In Tanaka et al. (17) study, which included 90 infants from ROSI with a 2-year follow-up, congenital anomalies were found in 3 (3.3%) of them (1 cleft palate, 1 ventricular septal defect, and 1 omphalocele). The authors stated that they did not evaluate whether there was a statistical difference between the standard delivery groups during this period due to the small number of ROSI groups. However, ROSI babies did have a low birth weight. At the end of the 2 years, no significant difference was found between the groups in terms of syndrome (Prader-Willi syndrome, Angelman syndrome, Wiskott-Alrich syndrome, etc.) or abnormal physical or mental developmental disorders. Nevertheless, healthcare providers should explain parents in planning the pregnancy before the spermatid transfer the risks of possible hereditary diseases, such as Prader-Willi and Angelman syndromes (17,22).

Conclusion

ELSI and ROSI are among the possible treatments for couples who cannot find mature spermatozoa after micro-TESE in patients with NOA. The success rates of ROSI are not as high as ELSI; however, the most critical factor affecting the success is correct cell selection and proper transfer. Thus, ROSI success rates can approach ELSI when performed correctly. Congenital anomalies are rarely reported after spermatid injection; however, the risk is higher than in natural conception. With this method, couples who plan to have children should undertake genetic counseling before the procedure to be informed of the risk of congenital anomalies.

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Uses of Mobile Phone Language Translation Applications in Surgery

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Abstract

Globalization has resulted in the proliferation of multi-lingual communities worldwide. Local health agencies nowadays cater to the increasing demand for interpretation services, which can be an expensive effort. Professional interpretation services also have limitations in availability and convenience. With the widespread use of smartphones in the medical workplace, software applications with the ability to translate between languages represent a potentially convenient and inexpensive adjuvant to professional interpretation services. It may also be a useful option for clinicians working in rural areas devoid of professional interpreter services. Current data suggests that current translation software applications provide variable accuracy of translation depending on the language, some are acceptable and others are not. More research is required to improve the accuracy and consistency of these translation applications. Using these translation applications on mobile phones for minor or non-medicolegal tasks may help improve the efficiency of the health system by reserving professional interpreting services for important tasks with potential medicolegal implications.

Keywords: Interpretation, language, mobile phone, software, translation

Introduction

Globalization has encouraged the spread of languages worldwide and the proliferation of multi-cultural communities. A 2011 census by the Australian National Audit Office reported that 19% of Australia's population spoke a non-English language at home, and 17% from this cohort (almost 700,000 people) could not adequately speak English (1). This increases the need to provide health services in a multilingual settings. The demand for interpretation services was estimated to grow at approximately 20% annually, from 1.1 million phone interpreting services in 2011-2012 to 1.5 million in 2013-2014 (1). This increasing demand for professional interpreting services thus leads to increasing financial expenditure. For example, the Australian Translating and Interpreting Service received more than AU$153 million in one year between 2013 and 2014 (1). Similarly, large sums of more than £20 million on average were spent each year from 2008 to 2011 by the United Kingdom (UK) National Health Service (NHS) (2). More money spent on language translation services means less money for investment into other health sectors. Unfortunately, language barriers or the inability to speak the local language is still one of the major contributing factors to health disparities in communities with low English proficiency (3-5).

The desired solution is to provide inexpensive and accurate translation options, which are not as accurate as a medical doctor who is fluent in the same language or a professional interpreter, but accurate and consistent enough to be an alternative when the aforementioned options are unavailable. Such situations may arise especially in poorer countries or in rural areas where access to a professional interpreter is limited, either in person or via phone. One possible solution is to use translation software applications on portable electronic devices, such as smartphones, tablet computers, or laptops. Thus, this study aimed to highlight the potential issues that can arise during the care of a patient who does not speak the local language and how current translation software technology can play an adjuvant role in the communication and medical care improvement of such patients.

Role of Professional Interpreting Services

The best way to communicate important medical information is to have a doctor who speaks the same language as the patient. The next best thing to communicate with patients who do not

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speak the local language is the professional interpreting services, which can be provided in person or via telecommunication but commonly via phone conversation. In countries with established infrastructure and an adequate workforce of professional interpreters, these services can be provided even to doctors working in remote communities. Clinical care can be benefited from the use of professional interpreters. A systematic review by Karliner et al. (6) in 2007 concluded the association of the use of professional interpreters with better positive outcomes and improved quality of healthcare than that of ad hoc interpreters (such as family members or clinical staff). Similarly, Ribera et al. (7) concluded that the use of professional interpreters can improve patient satisfaction and access to healthcare, reduce the risk of medical errors, and reduce the cost of unnecessary investigations and erroneous treatments. Besides patients, clinicians themselves have been more satisfied with their delivery of healthcare as they used professional interpreting services. Clinicians with previous training on interpreter use were more likely to use professional interpreters [odds ratio (OR) 3.2; 95% confidence interval (CI) 1.4-7.5] and report increased satisfaction with the medical care that they have provided (OR 2.6; 95% CI 1.1-6.6) (8).

Potential Issues in Using Professional Interpreters

Professional interpreting services have an important role in ensuring the appropriate provision of healthcare services to patients who do not speak the local language. The importance of this service cannot be questioned for essential tasks such as history-taking and obtaining informed consent for surgeries. However, the effort of using professional interpreting services does have several limitations, namely cost, availability, and convenience. Providing professional interpreting services can be an expensive effort. The Australian Translating and interpreting service reported revenue of over AU$153 million in 2013-2014 alone (1). Similarly, large expenses were also found in other countries. In the UK, NHS trusts spent an estimated £23.3 million on interpretation services in the 2010/2011 financial year and £64.4 million over 3 years before and including the 2010/2011 financial year (2). In Australia, the government-affiliated translating and interpreting service in 2021 charged rates approximately twice the base pay rate of doctors with several years of working experience (Table 1) (9,10).

The issue of availability may be due to the non-availability of interpreters who speak uncommon minority languages. Furthermore, interpreters in Australia predominantly work on a casual basis (1), thus anyone may not be available to interpret certain languages at certain times. The lack of professional interpreters after normal working hours brings inconvenience for hospital teams to see patients outside the normal working hours or even during early morning ward rounds, as is common with the surgical teams. Planned interpreter sessions can be a potential solution to this issue; however, finding meeting times that suit the patient, medical staff, and interpreter can be challenging. Physicians often tend to multiple patients and have to address unplanned emergencies, be it personal or professional. Patients themselves could have an unexpected event, thus arranging an interpreter immediately may not be feasible. Furthermore, interpreters themselves may be already booked ahead to provide their services at a separate time and location, thus making it difficult for them to overstay during the meeting and even stay before the meeting concludes to attend to their next booking. Hiring an interpreter for 24-hour care will be geographically and financially inconvenient. Not so much in Australia, but in some poorer countries, professional interpreter services may be limited in rural areas, including phone interpretation services either due to lack of communication infrastructures or lack of professional interpreters.

Despite 1 in every 35 Australians having low English proficiency (11), studies suggest that the use of interpreters in a clinical scenario remains uncommon (11,12). Diamond et al. (13) found that the underuse of interpreters was due to complexity and that physicians often have to weigh the importance of communication in clinical decision-making against time pressures. Medical practitioners gauged the need for interpreters on a case-to-case basis and whether the perceived benefit of the exact situation will outweigh the hassle factor, have a high yield, and is worth the time invested (13). Therefore, arranging for professional interpreting services in a small and simple need, such as asking the type of food suitable to the patient's religion or explaining the need to perform minor procedures, like intramuscular injections, can be inconvenient. In addition, for patients to not be able to describe their pain or other symptoms immediately to the treating team is inconvenient if professional interpreting services had to be organized each time the patient tries to communicate.

Interpreting Services Available on Mobile Phones

Several applications are available on mobile phones to provide interpreting services, some of which require payment and others are free. Currently, one of the most popular translation applications is Google Translate (Google Inc., California, USA), which is also free of charge. As of December 2015, this application was able to translate into 90 languages via typing on the mobile phone, which also supports automatic speech translation in 40 languages that would be particularly helpful in patients who are uncertain nationality and could not even tell their spoken language. Translated text can either be read on-screen or spoken aloud by the mobile device. More recently, the text can also be translated using the phone camera in 26 languages. The majority of doctors and other healthcare workers are found to use a smartphone at work nowadays, enabling convenient and rapid access to interpreting services via their phones.

With technological advances and updated statistical translation techniques, Google Translate has other helpful features. The translation process can be improved using the list of synonyms with corresponding definitions in Google Translate to effectively form a coherent sentence. A higher level of accuracy can be achieved using the "sanity check" feature, which makes Google back translate the text enabling the user to determine if the translated work makes sense. Furthermore, patients with different language scripts can respond using Google Translate's on-screen keyboard. This keyboard icon allows them to type or virtually handwrite non-Roman alphabets. Google Translate also has a simple and user-friendly web interface, which further allows easier usage by most patients and doctors alike.

Google Translate was the software application of choice in most studies that were conducted to compare the degree of accuracy and consistency of machine versus human language translation. Other translation software/systems are also available, such as the Moses-based system used by Pecina et al. (14) in their study, but these applications were not as commonly used or available to the general public, thus they were not investigated as much as Google Translate. Therefore, most of the current data and statistics presented in the following discussions are related to Google Translate.

Potential Uses of Interpreting Services on Mobile Phones

Using a free interpreting service on a mobile device can be a convenient, inexpensive, and effective alternative way of communication when other methods of translation are unavailable or inadequate. Translation tools may even be used as an initial mode of communication, particularly in rural- or regional-based practices where the immediate availability of professional interpreters is limited aside from phone services. Even with phone interpretation services, several physicians nowadays communicate with the use of images and anatomical models to illustrate their explanations. Communicating and illustrating simultaneously using the translation application on a mobile device can be easier rather than via a phone interpreter who cannot see and describe the illustration or anatomical model.

Patient review and ward rounds can be done impromptu at the convenience of the treating team even after standard working hours. Simple procedures such as an indwelling catheter change and intravenous cannulation could be conveniently performed by describing the procedure using Google Translate instead of having to arrange a telephone or on-site interpreting services. In addition, Google Translate-enabled smartphones, tablets, or computers have no shortage, as nowadays, most members of the treating team had access to one in the workplace. The simple and quick access to automated translation technologies via mobile devices allows doctors to customize their questions and responses appropriately at the patient's bedside.

Patients unable to speak the local language also stand to benefit from easily-accessible interpretation software on mobile devices. Using this technology, nursing staff could also describe the medications prescribed to the patient and respond better to patient requests for analgesia and antiemetics. Furthermore, some of the older patients who do not speak the local language may have difficulties with mobilization and have their bed railings set up to prevent any falls. However, these patients will have difficulty in communicating their desire to go to the bathroom with their nurse without readily available

Table 1. Indicative cost of professional interpreting services in Australia within regular business hours compared with base hourly pay rates for doctors in Western Australia

Indicative cost of professional interpreting service in Australia*			
Service	**Description**	**Charge in Australian dollars**	**Equivalent hourly rate**
Immediate phone interpreting	Every 15 minutes	$27.50	$110.00
Pre-booked telephone interpreting	First 30 minutes	$73.59	$147.18
	Each additional 15 minutes	$20.24	$80.96
On-site interpreting	First 90 minutes	$157.52	$105.01
	Each additional 30 minutes	$32.67	$65.34
Telehealth video	First 90 minutes	$157.52	$105.01
	Each additional 30 minutes	$32.67	$65.34
Base hourly pay rate of doctors in Western Australia**			
Year 3 resident medical officer	Standard business hours	$50.06	$50.06
Year 3 registrar	Standard business hours	$59.33	$59.33
Year 7 registrar	Standard business hours	$72.11	$72.11

*Note: Bookings that start at 10.00 a.m. were used to represent regular business hours. These cost quotations exclude cancellation charges, services after regular business hours, and pre-reading before the appointment. **Base working hours of 40 hours per week were used to calculate the hourly pay rate of doctors

language translation service, especially if they have diarrhea or urinary urgency, as they not uncommonly do. Making the patient wait while organizing for phone interpreters each time the patient wants to talk to the nurse is possible; however, it quickly adds up to the burgeoning cost to the health system and the added inconvenience to both the patient and the nursing staff. Kitchen staff could discuss appropriate food options with the patient using these translation applications when patients have religious food restrictions or allergies. Patients are unlikely to express dissatisfaction with their care if Google Translate was utilized wisely along with good non-verbal communication skills to answer most, if not all, of their questions.

Validity of Using Interpreting Services on Mobile Phones

Accuracy of interpreting services is very important to ensure appropriate healthcare delivery. The available data on the accuracy of professional interpreters and translation software on electronic devices is somewhat conflicting. A study by Flores et al. (15) revealed that ad hoc interpreters were significantly more likely to make errors with potential clinical consequences than professional interpreters (77% vs. 53%, $p<0.0001$). However, a rate of 53% for professional interpreters is still worrisomely high, even if they were to be the next best thing after a doctor who speaks the same language as the patient. The same study found no statistically significant difference in the mean number of errors committed by hospital and ad hoc interpreters in each clinical encounter; however, professional interpreters were more likely to use an incorrect or non-existent word/phrase than ad hoc interpreters (22% vs. 9%, $p=0.007$) (15).

A wide variance is found in the accuracy of translation between different languages. A study on the accuracy of Google Translate in 51 languages revealed a wide variation of Bilingual Evaluation Understudy (BLEU) scores, ranging from 0 up to 93 out of a possible 100. In terms of translating to/from English, languages with the highest BLEU scores (>90) were Danish (93), Indonesian (93), Estonian (93), French (92), Bulgarian (91), Greek (91), Norwegian (91), and Swedish (91) (16). However, the translation accuracy in this study was not checked by human translators but rather was compared with a single "correct" reference text, thus languages with very different grammatical structures may suffer lower BLEU scores (16). The accuracy of translations made with Google Translate also varied based on the geographical origins of languages, with the best accuracy for Western European languages, followed by Eastern European, Asian, and African languages (17).

The impact of grammar on translation accuracy was also reported in a study by Beh and Canty (18), in which English-Mandarin/Chinese translation via Google Translate deteriorated with longer phrases compared with short phrases (grammar has smaller roles with shorter phrases). Similarly, the study by Anazawa et al. (19,20) found Google Translate to be mostly just partially useful in English-Japanese translation of scientific abstracts, but performed better with Korean-Japanese translations, presumably due to similar grammatical structure. A recent study showed that it was possible to improve the accuracy of translations made by machine translators by configuring its system data up to an average of 55% from its baseline BLEU scores (14). The same machine translator also achieved consistently higher BLEU scores compared with Google Translate for translations between English and French, German, and Czech languages (14).

In a direct comparison between machine translation and professional interpreters, a randomized controlled trial involving a small cohort of French-speaking Burundians found that patient satisfaction outcomes were comparable between using machine translation and trained interpreters during patient-doctor encounters (21). This study suggested that machine translation is a suitable alternative in the absence of a trained professional interpreter (21). Examples include use in clinical practice in rural areas where little or no services are provided by professional interpreters. These automated translation tools are timely and attractive language technology that can be well-utilized in times of need within the healthcare system (22,23).

A study reported by the agency for healthcare research and quality (United States of America) compared the accuracy of translations performed by Google Translate against clinicians who are fluent in the language assessed and found that >60% of articles in Portuguese and German that were translated into English by Google Translate had high levels of agreement with the translations made by clinicians who are fluent in these languages (24). In the same study, none of the scientific papers in Chinese translated into English by Google Translate had at least 80% of agreement with the translations made by the clinicians (24). Similarly, most of the papers in Hebrew, which is written from right to left, were not satisfactorily translated using Google Translate (24). These findings illustrate the impact of grammatical differences on the accuracy of Google Translate. In a follow-up study a year later, the investigator group found that Spanish articles were instead translated with the highest accuracy into English, versus Chinese, French, German, and Japanese (25). The change in accuracy level between English-German and English-Spanish in the space of one year was less likely to be due to sample selection bias and may probably be due to improvement in the translation engine for the Spanish language.

Conclusion

Professional interpreting services are an important resource in healthcare, especially for patients who are unable to speak

the local language. Like all resources in hospitals, it needs to be used efficiently to minimize unnecessary costs. Outside of metropolitan hospitals, it can be quite useful for inter-language communication between a clinician and a patient if professional interpretation services are lacking, such as in poorer countries or rural areas. Google Translate has been shown to have variable translation accuracies depending on the language, with better results for languages with similar grammatical structures. Therefore, it is reasonable to suggest that language interpretation software applications on portable electronic devices may be used in certain situations that require rapid or convenient translation services for minor or non-medicolegal tasks while reserving professional interpretation services for major or medicolegal tasks. More research is required to substantiate the currently available data on the subject. The accuracy and consistency of applications such as Google Translate can be improved to support an adjunctive role in clinical settings in the future.

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Authorship Contributions

Concept: D.C., Design: D.C., M.M., Data Collection or Processing: D.C., M.M., Analysis or Interpretation: D.C., M.M., Literature Search: D.C., M.M., Writing: D.C., M.M.

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ORIGINAL RESEARCH
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Variant Histology: The Impact on Oncological Outcomes of Patients with Urothelial Carcinoma of The Bladder Treated with Radical Cystectomy

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What's known on the subject? and What does the study add?

The association of variant histologies of bladder cancer with prognosis is a current debate in the literature. Our study illustrates that variant histologies of bladder cancer are related to poor survival rate. However, lymph node metastasis have been identified as the most significant factor for overall and cancer-specific survival.

Abstract

Objective: To investigate the impact of variant histology (VH) of urothelial carcinoma (UC) of the bladder on oncologic outcomes after radical cystectomy (RC).

Materials and Methods: We identified 125 patients with cT2-T4N0M0 UC who underwent RC without perioperative systemic therapy between 2014 and 2019 at a single tertiary care referral center. The Mann-Whitney U test and chi-square test were used to compare the statistically significant differences in medians and proportions, respectively. The Kaplan-Meier method and Cox regression analyses tested the effect of different VH on cancer-specific survival (CSS) and overall survival (OS).

Results: Of 125 patients, 70 (56%) had pure UC, whereas 55 (44%) had VH. The mean patient age and the median follow-up were 63.6±9.7 years and 12.5 (3-72) months. The female to male ratio was 13/112. The presence of lymphovascular invasion, locally advanced stage (≥pT3), and recurrence status were significantly higher in patients with VH than those with pure UC. In all patients, the presence of VH was not significantly associated with the presence of lymph node (LN) metastasis. In the multivariable Cox regression analyses, the type of UC [hazard ratio (HR) 1.80, 95% confidence interval (CI) 1.00-3.24, p=0.050] and age (HR=1.050, 95% CI 1.016-1.086, p=0.004) was associated with the OS, whereas the LN metastases was associated the CSS (HR=2.962, 95% CI 1.456-6.027, p=0.003) and OS (HR=3.211, 95% CI 1.778-5.799, p<0.001).

Conclusion: Our study demonstrated that VH in bladder cancer was associated with unfavorable clinicopathological features and a poorer OS prognosis. However, VH is not independently significant with the CSS. In addition, this study confirms that the LN metastasis represents a robust and independent predictor of inferior CSS and OS.

Keywords: Variant histology, survival, urothelial carcinoma

Introduction

Bladder cancer (BC) is a common malignancy. It rates seventh in males, whereas eleventh when both genders are considered (1). The most common histology of BC is urothelial carcinoma (UC) (2). Except for pure UC, several different variant histologies (VH) are present, which include urothelial and non-urothelial, and were found in up to 33% of radical cystectomy (RC) specimens (3).

VH is associated with determined predictors of aggressive behavior (4). Several studies have identified a relationship with the adverse outcome; however, this adverse outcome does not remain significant on the multivariable analysis (4,5). These variants gained attention for their aggressiveness; however,

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the studies investigating the impact of VH on the oncologic outcomes have obscure results (3,5,6).

This research was single-institutional and involved pure UC and VH containing pure variant type and mixed-type UC with a variant pattern. Furthermore, this study aimed to assess the clinicopathological features and prognosis in patients with pure UC and VH who underwent RC and lymph node (LN) dissection (LND).

Materials and Methods

This study included 192 patients who underwent RC and bilateral pelvic LND from January 2014 to December 2019 due to BC after the institutional review board approval (no: GO 21/30). All surgeries were performed at a single tertiary referral center. Patients' preoperative evaluation comprised chest and pelvic/abdominal imaging. While patients underwent X-ray or computed tomography for chest imaging, computed tomography scan and magnetic resonance imaging was used for pelvic/abdominal imaging. Pelvic LND was performed routinely with RC, and different surgeons used standard techniques over the study's timeframe. Patients with clinically metastatic disease (cN1 or cM1) were excluded when these data were being created. Patients with non-urothelial histology (e.g., pure squamous cell carcinoma and adenocarcinoma) (n=45) were excluded. Furthermore, patients who received systemic neoadjuvant chemotherapy were excluded (n=22).

Expert genitourinary pathologists examined every surgical specimen. Our analyses on VH classification included micropapillary, sarcomatoid, lymphoepithelial, small cell, squamous, plasmacytoid, trophoblastic, nested, and glandular. The uropathological assessment of more than one VH was classified as mixed variants. Due to patient scarcity, all variant types were grouped under one group and compared with pure UC. LN status and tumor stage were divided into two groups [(N0-Nx and N1-N2), (≤pT2 and ≥pT3), respectively].

The two groups were compared in terms of gender, age, comorbid disease, smoking history, surgical margin, adjuvant chemotherapy, LN involvement, accompanying CIS, lymphovascular invasion (LVI), tumor stage, recurrence, cancer-specific survival (CSS), and overall survival (OS). Univariate and multivariate statistical analyses were conducted to define the factors affecting CSS and OS.

The follow-up data of all patients were complete. Clinic and radiological follow-up were started about three months after surgery. Computed tomography was conducted in examinations of all patients as radiological imaging. Physical examination accompanied laboratory analysis, abdominal ultrasonography, neobladder cystoscopy, urine cytology, and urethral washings. A bone scan was performed with any present indication.

Statistical Analyses

Frequencies and proportions were the focal points of descriptive statistics of categorical variables. Mean ± standard deviation was used for parametric variables, while the median and interquartile range were used for non-parametric variables. The t-test and chi-square test were used to compare the statistical significance of variances in means and proportions, respectively. The effect of different histopathological variants on CSS and OS was tested by the Kaplan-Meier method and Cox regression analyses. Statistical significance was taken at $p<0.05$. The Statistical Package for the Social Sciences v.22.0 was used to conduct statistical analyses (IBM Corp., Armonk, NY).

Results

The mean patient age and the median follow-up period were 63.6±9.7 years and 12.5 (3-72) months. The female to male ratio was 13/112. The pure UC and VH percentages and frequencies were shown in Table 1, and patient demographics and pathological characteristics are illustrated in Table 2. Patients with VH had a higher locally advanced stage disease (≥pT3) ($p<0.001$), LVI ($p<0.001$), and recurrence ($p=0.008$) than those with pure UC. Nevertheless, the similarity was found between patients with VH and those with UC regarding age, gender, surgical margin, adjuvant chemotherapy, accompanying CIS, comorbid disease, smoking history, and LN involvement.

Concerning prognostic values, patients with VH had worse CSS and OS than those with pure UC in the Kaplan- Meier analyses ($p=0.013$ and $p=0.035$, respectively; see Figure 1).

The 2-year CSS and OS were 65.5% and 56.3%, respectively. The type of UC, LVI, T stage, LN metastasis, and positive surgical

Table 1. Frequencies and percentages of pathological variants

	N	%
Pure urothelial	70	56
Variant histology	55	44
Micropapillary	14	11.2
Sarcomatoid	9	7.2
Lymphoepithelial	2	1.6
Small cell	1	0.8
Squamous	13	10.4
Plasmositoid	3	2.4
Trophoblastic	1	0.8
Nested	5	4
Glandular	3	2.4
Mixt	4	3.2

Table 2. Patient demographics and clinical features of pathologic variants

		Pure urothelial carcinoma	Variant histology	p
n, (%)		70 (56)	55 (44)	-
Age, year, mean (± SD)		63.4 (10.3)	63.7 (9)	0.845
Gender (%)	Female	7.1	14.5	0.178
	Male	92.9	85.5	
Surgical margin (%)	Positive	21.4	30.9	0.228
	Negative	78.6	69.1	
Adjuvant chemotherapy (%)	Yes	18.6	25.5	0.353
	No	81.4	74.5	
Lymph node status (%)	pNx-N0	71.4	58.2	0.122
	pN1-2	28.6	41.8	
Accompanying CIS (%)	Yes	48.6	47.3	0.885
	No	51.4	52.7	
Lymphovascular invasion (%)	Positive	44.3	76.4	**<0.001**
	Negative	55.7	23.6	
Tumor stage (%)	≤pT2	49.3	18.2	**<0.001**
	≥pT3	50.7	81.8	
Recurrence (%)	Positive	22.9	40.7	**0.032**
	Negative	77.1	59.3	
Comorbid disease (%)	Positive	45.7	45.5	0.977
	Negative	54.3	54.5	
Smoking history (%)	Positive	44.3	49.1	0.593
	Negative	55.7	50.9	

SD: Standard deviation

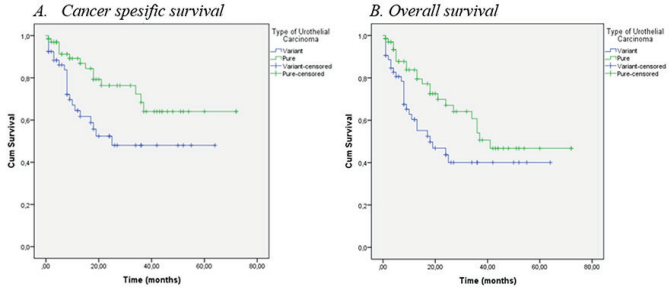

Figure 1. Survival analyses using Kaplan-Meier methods for pure urothelial carcinoma and histologic variants

margin (PSM) were associated with the CSS in the univariate analysis (p=0.013, p=0.004, p=0.006, p<0.001, p=0.011, respectively). The type of UC, LVI, T stage, LN metastasis, PSM, and age were associated with OS in the univariate analysis (p=0.035, p=0.004, p=0.005, p<0.001, p=0.018, and p=0.009, respectively) (Table 3).

Only LN metastasis was identified as a significant prognostic factor for the CSS in the multivariate analysis (p=0.003). The type of UC, LN metastasis, and age were identified as significant prognostic factors for the OS in the multivariate analysis (p=0.05, p<0.001, p=0.004, respectively) (Table 4).

Table 3. Univariate analysis for factors affecting cancer-specific survival and overall survival

Parameters		Univariate analysis			
		2-year CSS (%)	p	2-year OS (%)	p
Gender	Female	55.4	0.395	48.5	0.529
	Male	66.4		57.1	
Type of urothelial carcinoma	Pure	76.4	**0.013**	67	**0.035**
	Variant	52.4		43.7	
Lymphovascular invasion	Yes	55.4	**0.004**	45.1	**0.004**
	No	79.7		71.8	
T-stage	≤pT2	82.9	**0.006**	78.2	**0.005**
	≥pT3	55.6		44	
Lymph node metastasis	Nx-N0	81.2	**<0.001**	74.5	**<0.001**
	N1-N2	40.6		28.1	
Adjuvant chemotherapy	Yes	57.8	**0.717**	49.2	0.852
	No	68.2		58.9	
Surgical margin	Negative	72.3	**0.011**	63	**0.018**
	Positive	49.6		41.2	
Accompanying CIS (%)	Yes	63.5	0.848	52	0.810
	No	68.8		61.7	
Age (± SD)	CSS	63.1 (10)	0.440	66.4 (9)	**0.009**
	CSD	64.6 (9.2)		61.7 (9.9)	

CSD: Cancer-specific death, CSS: Cancer-specific survival, SD: Standard deviation, OS: Overall survival

Discussion

Given the development of literature about the importance of variant tumors as one of the crucial factors of therapeutic approach, our referral center has a current series that includes nonmetastatic BC that are treated with RC and focuses on the incidence and histological variant effect on survival in patients.

Our study revealed that VH was remarkably high at the time of RC, contrary to previous studies (7-9). This may be related to the fact that our data is more recent than previous studies and the increased knowledge and awareness of genitourinary pathologists in VH (3,10). In our study, most patients who had VH were diagnosed with micropapillary and squamous differentiation. Our results are consistent with prior findings on this issue (11-13). Monn et al. (11) investigated a patient cohort that includes patients who underwent RC from 2008 to 2013. VH incidence was 26%. In addition, squamous and

Table 4. Multivariate analysis for cancer-specific survival (CSS) and overall survival (OS)

Parameters	CSS		OS	
	HR (95% CI)	p	HR (95% CI)	p
Gender (female/male)	-	-	-	-
Type of urothelial carcinoma (pure/variant)	1.611 (0.785-3.308)	0.194	1.801 (1.000-3.244)	**0.050**
Lymphovascular invasion (yes/no)	1.495 (0.633-3.532)	0.359	1.700 (0.857-3.374)	0.129
T-stage (≤pT2/≥pT3)	0.411 (0.164-1.028)	0.057	0.786 (0.344-1.798)	0.569
Lymph node metastasis (Nx-N0/N1-N2)	2.962 (1.456-6.027)	**0.003**	3.211 (1.778-5.799)	**<0.001**
Adjuvant chemotherapy (yes/no)	-	-	-	-
Surgical margin (negative/positive)	1.524 (0.754-3.082)	0.241	1.299 (0.718-2.351)	0.387
Accompanying CIS (%)	-	-	-	-
Age (± SD)	-	-	1.050 (1.016-1.086)	**0.004**

CSS: Cancer-specific survival, SD: Standard deviation, HR: Hazard ratio, OS: Overall survival, CI: Confidence interval

micropapillary variants were the most common variants. Other data is presented in the literature, including 1,984 patients who underwent RC with bilateral LND from 2000 to 2008 at five referral centers (13). The VH incidence was reported to be 24.6%, with squamous variants being the most frequent.

VH was confirmed to harbor biologically aggressive disease characteristics, such as the presence of LVI, advanced tumor stage, and recurrence development (7,8). Regrettably, our data size is not adequately large to provide sufficient statistical power. Thus, individual variant subgroups could not be analyzed in the variant population. The presence of VH was associated with both CSS and OS in the univariable Kaplan- Meier analysis. However, the association was not found with CSS in a multivariable analysis adjusted for standard clinicopathological predictors such as LN parameters, advanced T stage, and surgical margin. Overall, the influence of VH on survival is still a disputable issue. Few previous studies found an association of VH with unfavorable pathological characteristics including LN status (8,9,14); however, these results were not associated with low survival metrics in adjusted outcome analyses of contemporary series (13,14). In our study, only LN involvement influenced the prognosis of both the CSS and OS independently. Regardless of variant differentiation, LN metastasis is the imperative risk factor for the systemic spread and subsequently fatal disease course. Therefore, early diagnose of LN metastasis by genetic and molecular characterization might be a popular topic in the future. Thus, possible multimodal treatments will be individually modified in UC, as previously demonstrated in oral squamous carcinoma (15).

Contrarily, the quality of LN dissection might explain this paradoxical observation between adverse pathology in VH but no association with LN positivity, which appeared as the most critical factor for survival in this study. The surgeon's experience and the patient's anatomy might be significant factors for quality. Unfortunately, the quality was not similar between the patient groups.

Our study found no significant difference in the oncological outcomes in terms of adjuvant chemotherapy. This result corresponds with previous literature (9,11,16). However, Bellmunt et al. (17) conducted a randomized phase III trial. They compared observation with four paclitaxel, gemcitabine, and cisplatin (PGC) courses in the clinical setting. This study strongly recommends that PGC adjuvant therapy ameliorates the CSS and OS in high-risk invasive BC. Thus, we could not certainly answer whether adjuvant chemotherapy would have an advantage for prognosis or not. This treatment can be considered with the clinician's preference.

Study Limitations

Our study has several limitations. First, this study was retrospectively conducted and provided a limited sample size due to its single-center nature. Second, the VH percentage was not evaluated since it was not reported in pathological specimens. Additionally, we did not determine a cut-off value for the amount of dedifferentiated tissue that is required for a specimen to be categorized as mixed histological type. However, evidence does not exist about the possible survival forecast of this parameter (18). Third, the follow-up time was short, and we were unable to evaluate the effect that significant findings may have had on oncologic or survival outcomes with long follow-up times. Fourth, due to the rarity of VH subgroups, they were incorporated into the same group during analysis. Fifth, due to retrospective analysis, the status of the smokers was not determined. Some studies found that current smokers had a higher risk of recurrence or progression than former smokers (19). Finally, the patients who received neoadjuvant chemotherapy were excluded due to the low number of patients, and the decision of neoadjuvant chemotherapy was

surgeon and patient-dependent in our clinic. Thus, this situation can cause a risk of bias.

Conclusion

This current research confirmed that VH incidence is frequent at RC specimens; moreover, the presence of VH correlated with a high risk of recurrence and worse clinical outcomes for OS. However, VH did not significantly change the incidence of the LN metastases. Our study confirmed that the LN metastasis represents a robust and independent predictor of lower CSS and OS.

Ethics

Ethics Committee Approval: This study included 192 patients who underwent RC and bilateral pelvic LND from January 2014 to December 2019 due to BC after the institutional review board approval (no: GO 21/30).

Informed Consent: Retrospective study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: B.A., C.Y.B., M.S.Y., Concept: B.A., C.Y.B., M.S.Y., Design: B.H., Data Collection or Processing: B.H., K.E.B., P.S., Analysis or Interpretation: H.B.H., Literature Search: B.H., Writing: B.H., H.B.H., M.S.Y.

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Efficacy Study of Mitomycin C Pre-infusion in Addition to Periodic Bacillus Calmette-Guerin Infusions in the Management of Non-muscle Invasive Bladder Cancers

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What's known on the subject? and What does the study add?

Adjuvant intravesical therapies for the treatment of non-muscle invasive bladder cancers have been consistently recommended, which include intravesical immunotherapy with "bacillus Calmette-Guerin (BCG)" or intravesical chemotherapy with "mitomycin C (MMC), epirubicin, or doxorubicin." BCG holds superiority over MMC, but the additional efficacy of the combination of pre-infusion of MMC in BCG protocol has been seldom studied. Thus, this study aimed to determine the differences between the two different protocols and show that combination therapy (MMC followed by BCG infusion) holds no advantage over BCG alone.

Abstract

Objective: To determine the benefits of the combination of bacillus Calmette-Guerin (BCG) and mitomycin C (MMC) in comparison to BCG alone in the treatment of patients with non-muscle invasive (NMI) bladder cancer.

Materials and Methods: The randomized comparative study was conducted on 54 patients with NMI bladder cancer. Following the transurethral resection, patients were randomly grouped into two: Group A (n=27) included patients who received postoperative MMC at 40 mg diluted in 50 mL of normal saline on postoperative day 1, followed by intravesical BCG at 60 mg per week for 6 weeks and BCG monthly for 1 year, and group B (n=27) included patients who received intravesical BCG at 60 mg postoperatively per week for 6 weeks followed by BCG monthly for 1 year. The outcome measures were time to recurrence, progression of the disease to muscles or other organs, overall survival, and treatment-related side effects.

Results: Compared to BCG alone, perioperative MMC in combination with BCG had comparable disease-free survival (85.18% vs. 66.66%, p=0.202), recurrence of disease (14.81% vs. 33.33%, p=0.202), and progression rate (11.1% vs. 25.9%, p=0.293). Side effects were minor and comparable between the study groups, which included dysuria, bacterial cystitis drug-induced cystitis, macroscopic hematuria prostatitis epididymitis fever, influenza-like symptoms, and fatigue.

Conclusion: Overall, both protocols were found comparable in safety and efficacy in reducing the progression and recurrence of NMI bladder cancers without any significant superiority of MMC in combination with BCG in comparison to BCG alone.

Keywords: BCG, mitomycin C, non-muscle invasive bladder cancer

Introduction

Bladder cancer is one of the rare cancers that ranks ninth in the global list of cancers. In the majority of patients (approximately 80%), the cancer is superficial at presentation. However, despite being superficial [Ta, T1, or carcinoma *in situ* (CIS)], the outcome remains varied (1).

The usual initial management of non-muscle invasive (NMI) bladder cancers includes cystoscopy and transurethral resection (TUR). Despite this, the spread of cancers to the muscle tissue and the recurrence rate are high, which carries a poor prognosis (1).

Given this, the use of adjuvant intravesical therapies has been practically recommended, which include intravesical

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immunotherapy with "bacillus Calmette-Guerin (BCG)" or intravesical chemotherapy with "mitomycin C (MMC), epirubicin, or doxorubicin" (2). They have been proposed to delay the tumor progression and recurrence with minimal side effects (3).

The use of BCG in bladder cancer began after it proved efficacious in melanoma. The effect is based on the mechanism that BCG binds and internalizes in the bladder tumor cells and induces cell death by (1) apoptosis-inducing pathways and (2) stimulation of local inflammation and macrophage-induced destruction. Since an adequate host immunity is required for the BCG immunotherapy to be effective, BCG has been much used in NMI bladder cancers only, that is, with low cancer load and good host immunity (4). The dosage regime of BCG has been decided as per its delayed immunity effects, which begin to show in 3 weeks, and its side effects profile, which subsides within 1 week. Therefore, a weekly regime of 6 weeks has been practically unanimously agreed (5,6). This regime showed to reduce tumor progression and recurrence for up to 10 years (7), after which increased recurrence rates have been reported in a follow-up study of 15 years (8).

MMC, hydrophobic in nature, is an antitumor antibiotic, among others, like epirubicin and doxorubicin, which by local instillation, works as an immediate chemotherapy measure to provide a longer recurrence-free period (9,10). It is minimally absorbed in a dose of 40 mg in saline or water and thus carries minimal side effects (11,12). Unlike BCG multi-dosage regime, MMC shows no superiority in efficacy by multi-dosage in comparison to single immediate instillation (12,13). Thus unanimously, a single dose of 40 mg within 1 h of TUR has been accepted (11).

Among the two, BCG has shown superior efficacy in reducing the recurrence (14-19). With the ongoing medical advancements, combinations of therapies have been tried against monotherapy. However, no consensus was found as to combination therapies are safe and efficacious compared to monotherapy. Some studies showed that BCG in combination with MMC is far better in achieving tumor-free interval and lowering disease progression (20-22), whereas some studies fail to see any significant difference with the combination therapy (23,24).

Therefore, the present study was conducted to determine the benefits of a combination of BCG and MMC compared to BCG alone in the treatment of patients with NMI bladder cancer.

Materials and Methods

The randomized comparative study was conducted in the department of urology of a tertiary care hospital. The study recruitment period was of 1 year with a follow-up of 2 years. The institutional ethical committee approved the study (IEC/SNMC/1210/2010). All patients aged 18 years or older with freshly diagnosed and histologically proven stage pT1 transitional cell carcinoma of the bladder, whether papillary or solid, were included in the study. Any patient with muscle invasion, previous or ongoing treatment with intravesical agents, bladder capacity <2 L, a urethral stricture that would prevent endoscopic procedures and repeated catheterization, diseases of the upper urinary tract, history of tuberculosis, tumor recurrence, cardiac disease, other malignancies, psychiatric or neurological disorder, contraindications to spinal or general anesthesia as required for a TUR, and known hypersensitivity to BCG or MMC were excluded from the study.

Informed written consent was obtained from all patients before enrolling them into the study. The sample size calculation of the study was based on the research of Hurle et al. (25), who observed that in the BCG group, estimated recurrence-free survival was 58.1 months, whereas 34.6 months for the MMC group. Taking these values as a reference and assuming a standard deviation of 30 months, the minimum required sample size with 80% power of study and 5% level of significance is 26 patients in each study group. The total sample size taken is 27 (54 patients per group) to reduce the margin of error.

The enrolled patients underwent an investigative protocol of urine exfoliative cytology, ultrasonography of the upper urinary tract, intravenous urogram, cystoscopy, and biopsy. TUR of bladder tumor (TURBT) for all visible tumors was performed on cystoscopy. The detailed methodology of TURBT has been shown in Supplementary File 1.

Following TURBT, patients were randomly grouped into two using a sealed envelope system. In this, ten sealed opaque envelopes were prepared, assigning A and B in 5 envelopes each, where A is represented by perioperative MMC and BCG and B by BCG alone. Once a patient consented to enter a trial, an envelope was opened, and the patient was then offered the allocated group. In this technique, patients were randomized in a series of blocks of 10. Once 25 patients were allocated to each group, then we used four sealed opaque envelopes, assigning A and B in 2 envelopes each.

Group A (n=27) included patients who received postoperative MMC at 40 mg diluted in 50 mL of NS within 6 h of operation, followed by intravesical BCG at 60 mg per week for 6 weeks followed by monthly BCG for 1 year. BCG therapy was begun 2-4 weeks after the tumor resection to allow time for re-epithelization.

Group B (n=27) included patients who received intravesical BCG at 60 mg postoperatively (after 2-4 weeks) per week for 6 weeks, followed by BCG monthly for 1 year.

The detailed steps of drug instillations are shown in Supplementary File 2, and the procedural flow is shown in Figure 1.

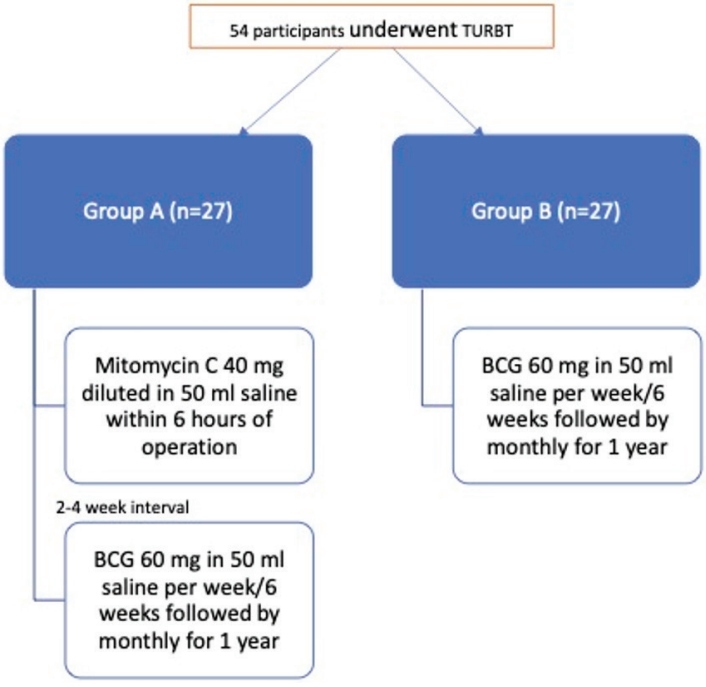

Figure 1. Fifty-four participants underwent TURBT

TURBT: Trans urethral resection of bladder tumour, BCG: Bacillus Calmette-Gu

Follow-up

All patients were properly followed for the next 2 years to fulfill the objectives of the study. Adverse events were recorded according to the World Health Organization toxicity grading (26) after each instillation and a week after the 6th dose. In case of persistent fever for >72 h and sterile urine culture, antitubercular treatment was started depending on the severity of the symptoms, and all records were maintained of the total dose and duration. Follow-up cystoscopy with three urine cytology was done every 3 months for 2 years. Histopathological types and grades were recorded for each recurrence.

The outcome measures were time to recurrence, progression of the disease to muscles or other organs, overall survival, and treatment-related side effects. Recurrence (or persistent disease) was defined as biopsy confirmed CIS or non-invasive papillary carcinoma, or malignant cytology and progression defined as pT1 tumor or more advanced disease. Patients were considered to have a complete response at 1 year if they had no progression during the first 9 months and no recurrent/persistent disease or progression at 12±3 months. The treatment failure was defined as progression or change in therapy resulting from recurrence or side effects during the first year or as recurrence, progression, or change in therapy after the first year.

Statistical Analysis

The categorical variables were presented in the form of numbers and percentages (%). Contrarily, the continuous variables were presented as mean ± standard deviation and median values. Mann-Whitney U test was used to compare quantitative variables, and the chi-square test and Fisher's Exact test were used to compare qualitative variables. The data entry was done in the Microsoft Excel spreadsheet, and the final analysis was done with the use of Statistical Package for Social Sciences software version 21.0. For statistical significance, a p-value of <0.05 was considered significant.

Results

The demographic distribution of the two groups was comparable (Table 1). The median age in the group of perioperative MMC with BCG was 65 years and in BCG alone was 67 years (p=0.361). The gender distribution showed slight male predominance in both groups (p=0.573). All patients were of NMI bladder cancer with T1 stage in both the groups (p=0.967). The majority of tumors were the papillary type of transitional cell carcinoma (88.89% in group A and 92.59% in group B) with others being the solid type of transitional cell carcinoma, with no significant difference (p>0.05). The tumors were majorly low grade (85.19% in group A and 88.89% in group B) with well-differentiated morphology. Among all the cases belonging to T1, 2 cases in group A and 3 cases in group B were CIS.

Compared to BCG alone, perioperative MMC in combination with BCG had comparable disease-free survival (85.18% vs. 66.66%, p=0.202), disease recurrence (14.81% vs. 33.33%, p=0.202), and progression rate (11.1% vs. 25.9%, p=0.293) (Table 2).

The side effects profile of the study participants was comparable in both the study groups (Table 3). The side effects included

Table 1. Demographic characteristics of study groups

Variables	Group A (n=27)	Group B (n=27)	p
Age	65 (58-72) years	67 (64-70) years	0.361
Gender			0.573
Male	16 (59.26%)	18 (66.67%)	
Female	11 (40.74%)	9 (33.33%)	
Histological variant of the tumor			
Papillary	24 (88.89%)	25 (92.59%)	1
Solid	3 (11.11%)	2 (7.41%)	
Carcinoma *in situ*	2 (7.41%)	3 (11.11%)	1
Grade of tumor			
Low grade	23 (85.19%)	24 (88.89%)	1
High grade	4 (14.81%)	3 (11.11%)	
Disease characteristics			0.967
pT1-G2 (multifocal)	15 (55.56%)	16 (59.26%)	
pT1-G3	12 (44.44%)	11 (40.74%)	

dysuria, bacterial cystitis, drug-induced cystitis, macroscopic hematuria, prostatitis, epididymitis, fever, influenza-like symptoms, and fatigue, due to which treatment had to be temporarily stopped in 5 patients in group A and 4 patients in group B. However, overall, they were minor side effects and were effectively managed without any mortality.

Table 2. Comparison of outcomes in the study groups

Variables	Group A (n=27)	Group B (n=27)	p
Disease-free survival	23 (85.18%)	18 (66.66%)	0.202
Recurrence of disease	4 (14.81%)	9 (33.33%)	0.202
Progression rate	3 (11.1%)	7 (25.9%)	0.293
Mortality	0 (0%)	0 (0%)	-

Table 3. Side effects of study groups

Event	Group A (n=27)	Group B (n=27)	p
Dysuria	17 (62.96%)	13 (48.15%)	0.902
Bacterial cystitis	7 (25.93%)	6 (22.22%)	0.869
Drug-induced cystitis	15 (55.56%)	14 (51.85%)	0.984
Macroscopic hematuria	20 (74.07%)	17 (62.96%)	0.743
Prostatitis	0 (0%)	1 (3.70%)	1
Epididymitis	1 (3.70%)	0 (0%)	1
Fever	9 (33.33%)	8 (29.635)	0.914
Influenza-like symptoms	13 (48.15%)	12 (44.44%)	0.984
Fatigue	13 (48.15%)	16 (59.26%)	0.951

Discussion

The present study was a randomized comparative trial on 54 patients (27 patients in each group), where we determined the benefits of a combination of BCG and MMC in comparison to BCG alone in the treatment of patients with NMI bladder cancer by comparing progression-free survival rates in patients.

The randomization ensured that age, gender, and cancer stage were comparable among the two groups and that any difference in outcome is purely due to differential intervention and not due to chance bias (27).

Despite the developments in diagnosis and treatment modalities, a high recurrence rate in bladder tumors is reported. Generally, the progression from non-muscle to muscle-invasive urinary bladder cancer results in metastasis and is considered a bad prognosis. Approximately 70-80% are NMI, which usually recur without aggressive histopathological features, and a subgroup of high-risk lesions that usually progress to invasive forms (MI). Recurrent relapses, disease progression, and chemoresistance lead to urinary bladder cancer that becomes difficult to manage from the diagnosis till death (28).

Our study revealed a comparable progression rate in perioperative MMC in combination with BCG compared to BCG alone (11.1% vs. 25.9%, p=0.293). Among the previous studies that compared the combination therapy with BCG alone, similar findings were reported by Solsona et al. (29), who found no statistically significant difference between MMC + BCG and BCG alone in terms of 5-year PFI (12.3% vs. 12.2%; hazard ratio: 1.05; 95% confidence interval, 0.61-1.83; p=0.852). Even Oosterlinck et al. (30) reported that alternating chemoimmunotherapy schedules with MMC and BCG demonstrated comparable efficacy compared to BCG alone in reducing the rate of progression. In contrast, Di Stasi et al. (23) reported that sequential BCG in combination with electromotive MMC showed lesser progression of the disease than BCG alone [9.3% (3.8-14.8) vs. 21.9% (17.9-25.9); p=0.004].

Disease-free survival is an important landmark in cancer treatment. Our study revealed a comparable disease-free survival in perioperative MMC in combination with BCG compared to BCG alone (85.18% vs. 66.66%, p=0.202), as well as in disease recurrence (14.81% vs. 33.33%, p=0.202). The findings were comparable to Oosterlinck et al. (30), who found that alternating chemoimmunotherapy schedules with MMC and BCG had similar efficacy compared to BCG alone in reducing the rate of recurrence. Contrary to the present study, Di Stasi et al. (23) found a combination of the sequential BCG with electromotive MMC to be superior to BCG alone, as sequential BCG and electromotive MMC had lower recurrence [41.9% (32.7-51.5) vs. 57.9% (48.7-67.5); p=0.0012]. Solsona et al. (29) also reported similar findings as a combination of sequential BCG with MMC significantly reduced the disease relapse at 5 years compared to BCG alone (20.6% vs. 33.9%, p<0.05).

The side effects of both protocols were minor without any mortality. They were mainly macroscopic hematuria, dysuria, and drug-induced cystitis in the BCG + MMC group and macroscopic hematuria, fatigue, and drug-induced cystitis in the BCG alone group (p>0.05). A similar comparable side-effect profile was observed in the study by Di Stasi et al. (23). Kaasinen et al. (31) found significantly more local side effects with BCG monotherapy, which also resulted in premature cessation of instillation treatment compared to the MMC + BCG. However, the difference in serious side effects in both groups was not significantly different. Contrarily, Solsona et al. (29) found that the MMC + BCG had significantly more local toxicity compared to BCG alone (80.4% vs. 69.7%, p<0.05). Even after reducing the dose of MMC to 10 mg, toxicity was still higher compared to BCG alone, specifically in local side effects grade 3 (28.4% vs. 10.9%; p<0.001).

Overall, we found that both protocols were comparable in safety and efficacy in reducing the progression and recurrence of NMI bladder cancers without any significant superiority of MMC in combination with BCG compared to BCG alone. Our

findings were in line with the studies by Solsona et al. (29), who found comparable PFI, and were in contrast to the studies by Oosterlinck et al. (30) and Di Stasi et al. (23), who showed that combination is a better protocol compared to BCG alone in terms of recurrence, progression, and disease-free survival. Among other studies, Kaasinen et al. (31) found that 1-year BCG monotherapy was more effective than the alternating therapy of BCG and MMC for reducing recurrence rates and disease-free survival and similar progression rate.

The difference in the results of various studies could be due to the difference in the schedule of instilling MMC with BCG. In studies by Oosterlinck et al. (30) and Kaasinen et al. (31), MMC plus BCG was administered on a weekly alternating schedule. In a study by Solsona et al. (29), MMC was administered sequentially, 1 d before the BCG instillation. In the study by D i Stasi et al. (23), patients who were assigned to BCG + MMC had electromotive MMC once a month. The comparable reduction in the progression and recurrence of NMI bladder cancers noted in the present study might be because MMC was given only once immediately after the TURBT, whose effect might be overpowered by the continuous instillation of BCG for 1 year given in both the groups.

Thus, combination therapy is proposed to depend specifically on the infusion timing. In contrast to the present study, where MMC was given initially and followed by BCG in due course, better outcomes have been seen with initial treatment with BCG followed by MMC. With the initial treatment with BCG, the immune response is initiated, and the tumor cells get exposed to infiltration of cytokines (some of which exert an antiproliferative action), cytotoxic T-lymphocytes, helper T-lymphocytes, and specifically, non-specific BCG-induced responses. These cascades play an important role for MMC introduction, which by enzymatic reduction, enhances the anticancer effects by crosslinking of DNA to all tissue layers of the bladder wall, which are affected by NMI bladder cancer (such as urothelium and lamina propria). In addition, MMC attacks cancer cells that are resistant to BCG (23).

Study Limitations

One of the limitations of the study was the insufficient long-term maintenance schedule, which is recommended as per the guidelines (32). Another limitation was that this study was conducted at a single center; thus, results cannot be generalized. Lastly, no comparison was made on BCG infusion followed by MMC on the disease-free interval in NMI bladder cancers.

Conclusion

Perioperative MMC in combination with BCG was comparable to BCG alone in the effectiveness in terms of disease-free survival, disease recurrence, and progression rate in patients with NMI bladder cancer. In addition, side effects were also similar in patients who received MMC with BCG and BCG alone, thereby suggesting that the combination therapy (MMC followed by BCG infusion) holds no advantage over BCG alone.

Ethics

Ethics Committee Approval: The institutional ethical committee approved the study (IEC/SNMC/1210/2010).

Informed Consent: Informed written consent was obtained from all patients before enrolling them into the study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: N.K., S.J., D.A., Design: N.K., Data Collection or Processing: N.K., S.J., D.A., Analysis or Interpretation: N.K., S.J., D.A., Literature Search: S.J., D.A., Writing: N.K., S.J.

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Supplementary File 1

Operative Steps of TURBT:

- A preliminary cystoscopy was performed to assess the shape and size of the tumor.
- An Otis urethrotomy was performed if the urethra was narrow to allow easy passage of a resectoscope.
- A preliminary assessment of whether the tumor could be easily resected completely or not was made. This was possible in those tumors that had not infilterated more deeply than superficial muscle.
- The aim was to resect the tumor level to the rest of the bladder wall.
- With small tumors, it was often best to begin the resection towards the base of tumor, particularly when a papillary growth had a relatively small stalk. On other occasions when the tumor had a wide base, it was necessary to resect from the top or the side of the tumor downwards, towards the base.
- A continuous flow Iglesias system was used, so that the position of the bladder tumor remains static.

- In tumors of the anterior wall, which tend to become inaccessible as the bladder filled, a suprapubic pressure on a half filled bladder was done to bring the tumor into view.
- Diathermy alone was sufficient for small areas of tumor, provided that adequate biopsies had been taken elsewhere.
- During the resection bleeding points were coagulated. Visualizing a small ring of white coagulation confirmed homeostasis and yielded less damage to the bladder than that occurring when the biopsy area was painted with cautery.
- It was important to include muscle in the resection biopsy specimens, so that any invasion could be identified histologically. The resulting bladder defect was inspected carefully for bleeding and for perforation.

Supplementary File 2

- Method of instillation of perioperative chemotherapy.
  1. Intent to administer perioperative chemotherapy (and agent) on actual operative schedule was included.
  2. It was insured that the pharmacy had the medication available. A written prescription was given to all patients.
  3. After resection, absence of clinical perforation was confirmed. Then 3 ways catheter was placed in bladder while patient was still in operating room. Inflow port was attached to saline infusion bag and inflow was clamped.
  4. Mitomycin C 40 mg diluted in 50 mL of NS was administered through catheter outflow port in recovery room within 6 hours of operation and outflow tubing was clamped with hemostat to allow retention.
  5. Outflow tubing was opened for irrigation 1 hour after administration, so that gravity drainage occurs in next 30 to 60 minutes.
  6. Foley catheter was removed and discarded in biohazard container.
  7. Gloves were worn throughout the procedure.
- Method of instillation of BCG.
  1. The vaccine was reconstituted with 50 mL of saline and administered through a urethral catheter under gravity drainage soon thereafter in order to prevent aggregation.
  2. Treatment was begun 2 to 4 weeks after tumor resection, allowing time for reepithelialization to minimize the potential for intravasation of live bacteria.
  3. In the event of a traumatic catheterization, the treatment was delayed for several days.
  4. After instillation, the patient retained the solution for 2 hours.
  5. After 2 hours gravity drainage of the drug was done by opening the catheter opening, followed by removal of catheter.

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Stage pT0 Prostate Cancer: A Single-Center Study and Literature Review

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What's known on the subject? and What does the study add?

Stage pT0 prostate cancer (PCa) after radical prostatectomy is a rare phenomenon with unclear significance. Patients with a Gleason score of 6 and tumors in a single core and length of <2 mm in the biopsy have a higher risk of stage pT0 PCa.

Abstract

Objective: To report our experience with biopsy positive T0 prostate cancer (PCa) and perform a literature review to determine the frequency, clinical outcomes, and predictors of pT0 PCa after radical prostatectomy (RP).

Materials and Methods: The records of 497 patients who underwent robot-assisted RP at our institution between 2015 and 2020 were retrospectively reviewed. No patients were diagnosed after the transurethral prostate resection or received preoperative hormone therapy. Clinicopathological features including age, prostate-specific antigen (PSA), body mass index, digital rectal examination, biopsy results, clinical T stage, D'Amico risk, prostate weight, prostatectomy pathology, and follow-up data were analyzed.

Results: Overall, 3 patients were classified as pT0 on pathologic examination of the RP. The biopsy re-evaluation revealed that 1 patient did not have PCa. Subsequently, the entire RP specimens were re-analyzed, wherein 2 cases were signed out with no identified carcinoma. The incidence of the pT0 PCa was 0.4% in our series. The median age of patients was 64 years. The median PSA was 14.27 ng/mL. Biopsy Gleason score of 2 patients was reported as 3 + 3. All patients had a tumor in only one core and all were in clinical stage T1c. No biochemical recurrence was found in a mean 21-month follow-up. Eleven studies were identified involving 26,228 patients, wherein 122 (0.46%) were reported with pT0 cases. Most patients with stage pT0 have been reported to have a Gleason score of <7, only one positive core biopsy, and a tumor length of <2 mm.

Conclusion: Patients with a Gleason score of 6 and tumors in a single core and length of <2 mm in the biopsy should be informed about the risk of stage pT0.

Keywords: Prostate cancer, residual cancer, surgical pathology, prostatectomy

Introduction

Prostate cancer (PCa) is the most commonly diagnosed cancer in men and is also second-ranked cancer that results in death in the United States (1). Currently, radical prostatectomy (RP) remains the gold standard surgical treatment for localized PCa. Widespread use of prostate-specific antigen (PSA) screening has resulted in an increased number of patients diagnosed with small-volume and low-grade tumors. Correspondingly, the volume of residual cancer in RP specimens has decreased (2). In some cases, no demonstrable cancer is identified in the entire RP specimen despite prior positive biopsy. The inapperent cancer after the RP has been referred to as the 'vanishing cancer phenomenon' that was first described by Goldstein et al. in 1995 (3). The vanishing cancer phenomenon is defined as stage pT0 according to the Tumor, Node, and Metastasis classification. The rate of pT0 cystectomy specimens has ranged between 5.1% and 20.1% (4). However, the unusual event occurs in <1% of all RPs (5). Patients who have had neoadjuvant hormonal therapy or prior transurethral resection of the prostate (TURP) experience

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more commonly pT0 disease after the RP (2,6). The finding of pT0 disease following the RP is a challenging situation with unclear significance.

This study aimed to report the results of pT0 tumors after the RP at our institution. Additionally, the literature review was performed to determine the incidence, clinicopathological characteristics, and follow-up data of no residual cancer following RP.

Materials and Methods

Study Population

After the local institutional review board approval (approval number: 2021-007), we retrospectively identified the prospectively maintained robotic surgery database records of 497 patients who underwent robot-assisted RP (RARP) between March 2015 and June 2020 in our institution. The study was approved by Antalya Training and Research Hospital Ethics Committee (approval number: 2021-007). Patients who received hormonal therapy before the surgery (n=2) or who were diagnosed with PCa after TURP (n=4) were excluded from the study.

Acquisition and Definition of Data

For each case, patient age, PSA level, body mass index, digital rectal examination (DRE) finding, prostate biopsy results (number of biopsy core, number of positive core, length of positive core, percentage of cancer, and Gleason score), clinical T-stage, D'Amico risk group, prostate weight, prostatectomy pathology results (pathological N stage, RP diagnosis), last visit PSA level, and follow-up time were recorded.

PubMed, Web of Science, Scopus/Science Direct, Wiley Online, and Google Scholar databases were scanned for the literature review. Scanning the literature was performed using the keywords: vanishing cancer, pT0, PCa, and no residual tumor.

Surgical Technique and Follow-up

Radionuclide bone scans were performed in symptomatic patients and patients with PSA levels of >10 ng/mL. The multiparametric magnetic resonance imaging was performed in all patients. All patients had a clinically localized PCa at the time of surgery. All patients underwent RARP. Our surgical technique of RARP has been described (7). Bilateral pelvic lymphadenectomy was performed in all high-risk and selected intermediate-risk patients according to the Briganti nomogram. Patients were followed up postoperatively with PSA every 3 months for the first year, every 6 months for the second year, and annually thereafter. The biochemical recurrence (BCR) was defined by two consecutive PSA levels of ≥0.2 ng/mL.

Pathological Examination

All RP specimens were sampled and examined using a standard protocol (8,9). Prostate needle biopsies were re-evaluated when no residual tumor was found following the histological review. After excluding false-positive prostate needle biopsy, entire RP specimens are re-analyzed. The slides of the surgical specimens were reviewed for residual cancer by a dedicated pathologist. The remaining prostate tissue was processed in toto if the RP specimen was not embedded. Three additional deeper sections of the RP tissue block corresponding to the tumor area of the biopsy were re-cut. After block-flipping, additional deeper sections were prepared. Immunohistochemical analysis was done if a lesion suspicious for cancer was present. The RP specimen was signed out as showing no residual cancer if cancer is not found after all of these steps. Cases were included in this study after confirmation of no residual tumor (pT0).

Statistical Analysis

Our study performed no statistical analysis due to insufficient data groups requiring statistical analysis. The data of patients were expressed as mean, minimum-maximum, and percentage.

Results

The clinical data of all cases with a postoperative pT0 stage were extracted from the database, wherein 3 cases were identified. All prostate biopsies corresponding to the pT0 tumors were reviewed by a second pathologist, and PCa diagnosis was not confirmed in 1 patient. After excluding this patient, RP specimens of 2 patients were re-analyzed. No residual tumor was found. The patient characteristics are listed in Table 1. The median age of patients was 64 years (range, 62-66). No abnormal findings were detected in the DRE of these patients. The median PSA was 14.27 ng/mL (range, 3.93-24.62). In all cases, PCa was diagnosed in the first biopsy. Prostate needle biopsy Gleason score of 2 patients was reported as 3 + 3. All patients had a tumor in only one core and all were clinical stage T1c. The final pathology was reported as high-grade prostatic intraepithelial neoplasia in patient 1, whereas nodular hyperplasia in patient 2. (Figure 1,

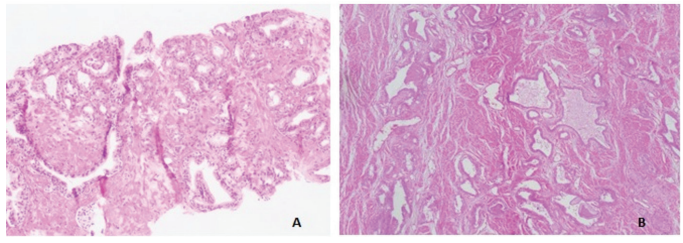

Figure 1. A- Crowded small glands of prostatic adenocarcinoma have amphophilic cytoplasm and enlarged nuclei with prominent nucleoli on needle core tissue. (Gleason score 3+3=6). B- Invasive tumor has not been determined at radical parostatectomy of the same patient

Figure 2) The mean prostate weight was 118 g (range, 110-126). The BCR was not detected in any patient.

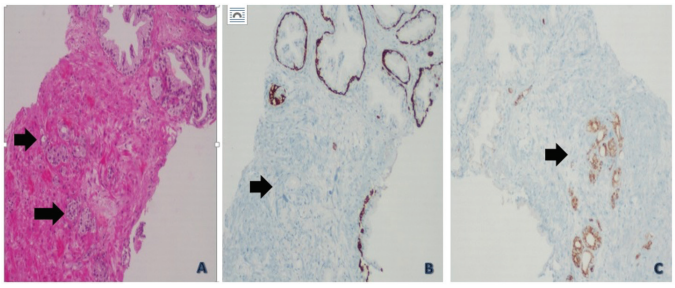

Figure 2. A- Small glands of adenocarcinoma (arrow), compared with benign glands (above) B- Basal cells of benign glands reactive with high-molecular weight cytokeratin (HMWK). Tumoral glands (arrow) do not express HMWK because basal cells are absent in invasive adenocarcinoma of the prostate. C- Neoplastic prostatic epithelial cells show over-expression of AMACR (arrow)

Table 1. Characteristics of patients with pT0

	Patient 1	Patient 2
Age, years	62	66
BMI, kg/m^2	29.74	28.40
Abnormal DRE	No	No
PSA, ng/mL	24.62	3.93
Biopsy Gleason score	3+3	3+3
Total number of cores, n	10	12
Number of positive core, n	1	1
Length of positive core, mm	2	1
Percentage of cancer, %	5	1
Preoperative stage	T1c	T1c
D' Amico risk group	High	Low
Specimen weight, g	126	110
Final pathology result	HGPIN	Nodular hyperplasia
Pathological N-stage	N0	Nx
Follow-up, months	24	17
BCR	No	No
Last visit PSA, ng/mL	0.02	<0.0008

BMI: Body mass index, DRE: Digital rectal examination, PSA: Prostate-specific antigen, HGPIN: High-grade prostatic intraepithelial neoplasia, BCR: Biochemical recurrence

Discussion

The absence of residual tumor in RP specimens is called the "vanishing cancer phenomenon" (pT0) (3). This phenomenon, which is very rare and challenging for both clinicians and patients, is also important from a medicolegal perspective. The incidence of stage pT0 PCa ranges from 0.1% to 2.12% (10-26). The frequency of pT0 PCa in our cohort was 0.4%. This incidence is higher in patients diagnosed with incidental PCa during TURP or open prostatectomy performed to treat benign prostatic hyperplasia or patients who receive neoadjuvant hormonal therapy (17,27). In these patients, a small tumor focus may be removed during a surgical procedure or obscured by hormonal therapy. The final true incidence rate is 0.1%-1.3% in patients diagnosed with PCa on prostate needle biopsy and who do not receive preoperative hormonal therapy (10,12,13,15,16,18-20,23-25). The incidence and clinical outcomes of this group of patients are summarized in Table 2. Patients with tumors detected after the re-evaluation of RP specimen and prostate needle biopsy were not included in Table 2. Thus, the final true incidence was determined.

Most patients with stage pT0 have been reported to have lower PSA levels, biopsy Gleason scores, and tumor burden. Park et al. (15) compared patients with and without stage pT0 and revealed that patients with pT0 had significantly lower Gleason scores, a smaller number of positive cores, smaller tumor length, and larger prostate volume. Another study noted lower Gleason scores, a higher rate of lower-risk disease, and fewer positive cores in patients with pT0 (11). A study that compared patients with stage pT0 with a control group revealed statistically significantly lower Gleason scores, tumor length in the biopsy, and the number of positive cores in the pT0 group. Prostate volume was significantly larger (13). Schirrmacher et al. (21) compared patients with and without stage pT0 and reported that Gleason scores, tumor length, and the number of positive cores were significantly lower in patients with pT0. Moreira et al. (17) showed that the PSA level of patients with pT0 was significantly lower than that of the control group. No comparative analysis was performed in our study. The mean PSA level of patients was 14.27 ng/mL. Based on previous studies, a high mean PSA level can be associated with the fact that one of the two patients had a PSA of 24.62 ng/dL. Two patients had a Gleason score of 6. In addition, the tumor was detected in a single core in both. The mean tumor length in the positive core was 1.5 mm.

The prognosis of patients with stage pT0 is assumed to be satisfactory. Several studies have indicated no local recurrence or clinical progression in the follow-up period (10,12-16,20,23,24). This study observed no BCR or disease progression in any patients during the mean follow-up period of 21 months. In a population-based study conducted by Knipper et al. (11), cancer-specific death was observed in only 3 patients with pT0 during a 9-year follow-up period. The cancer-specific survival rate in the 9 years was 99.5% in patients with pT0; however, it was 98.8% in those without pT0. In a study including 62 patients with pT0, 7 (11%) had disease relapse during the median of 10.9 years of follow-up (17). However, all these patients had received treatment before surgery. Compared with patients without pT0, those with pT0 were reported to have longer recurrence-free survival. Prayer-Galetti et al. (26) reported PSA progression in

3 (12.5%) patients in their pT0 cohort study that included 24 patients. All patients who experienced PSA progression had undergone preoperative hormonal therapy. The absence of PSA progression in studies including patients who did not receive preoperative hormonal therapy indicates a favorable prognosis in these patients. However, caution must be exercised in the follow-up of these patients. Patients with pT0 PCa should be followed up routinely. Thwaini et al. (28) reported that bone metastasis was detected during the follow-up of a patient with pT0 who did not receive hormonal therapy before the surgery.

Some researchers have investigated variables that can be used to predict stage pT0 before RP. In the study by Park et al. (15), no multivariate logistic regression analysis could be performed, as the number of patients was low. However, they chose four criteria to predict pT0 disease: (1) Gleason score of ≤6, (2) positive cores of ≤2, (3) tumor size in biopsy of ≤2 mm, and (4) prostate volume of ≥30 cm^3. When these four criteria were combined, they calculated that the sensitivity of pT0 in predicting the disease was 88.8%, specificity was 93.4%, positive predictive value (PPV) was 12.7%, and negative predictive value

Table 2. Literature data of patients with pT0 prostate cancer

References	Study period	Total, n	pT0, n	Incidence, %	Follow-up	Oncological outcomes	Predictors of pT0
Bessede et al. (10)	1991-2010	2462	19	0.77	Median follow-up of 41 months	No clinical or biochemical recurrence	N/A
Bream et al. (12)	1991-2011	1635	2	0.12	Ranging 3 months to 10 years follow-up	No clinical or biochemical recurrence	N/A
Descazeaud et al. (13)	1996-2005	1950	11	0.56	Mean follow-up of 30 months	No clinical or biochemical recurrence	One positive core only, overall tumor length of ≤2 mm, biopsy Gleason score of <7, and prostate weight of 60 g. A combination of 4 variables had a sensitivity of 82% and a specificity of 99%. The PPV value was 31% and the NPV was 99%.
Park et al. (15)	2004-2008	702	9	1.3	Mean follow-up of 23.6 months	No clinical or biochemical recurrence	Gleason score of 6 or less, two or fewer positive cores, a tumor size of 2 mm or less, and prostate volume of ≥30 cm^3 A combination of the 4 criteria had a sensitivity of 88.8% and a specificity of 93.4%. The PPV value was 12.7% and the NPV was 99.8%.
Bessède et al. (16)	1998-2006	7693	30	0.39	Median follow-up of 82 months	No clinical or biochemical recurrence	N/A
Mazzucchelli et al. (18)	1995-2006	1328	3	0.22	N/A	N/A	N/A
Kosarac et al. (19)	2004-2009	1741	5	0.28	N/A	N/A	N/A
Trpkov et al. (20)	2000-2005	1351	9	0.67	Mean follow-up of 714 days	No clinical or biochemical recurrence	N/A
Mehta et al. (23)	1998-2010	1060	11	1	Median follow-up of 64 months	No clinical or biochemical recurrence	N/A
Herkommer et al. (24)	1990-2004	3609	13	0.36	Median follow-up of 62 months	No clinical or biochemical recurrence	N/A
Duffield and Epstein (25)	2005-2007	2200	8	0.36	N/A	N/A	N/A
Present study	2015-2020	497	2	0.4	Mean follow-up of 20.5 months	No clinical or biochemical recurrence	N/A
Total		26.228	122	0.46			

(NPV) was 99.8%. Similarly, Descazeaud et al. (13) identified four criteria (i.e., single positive core, total tumor length in the biopsy of ≤2 mm, Gleason score of <7, and prostate volume of ≥60 g). The sensitivity of the combination of these criteria was 82%, specificity was 99%, PPV was 31%, and NPV was 99%. In a population-based study, the number of biopsy cores taken, a Gleason score of ≤6, and the detection of tumors in a single core was shown as independent variables in multivariate logistic regression analysis to predict pT0 disease (11). In a study of 20,222 patients, a multivariate analysis determined low PSA levels, low Gleason score, and preoperative hormonal therapy as independent variables in predicting pT0 disease (17). In this study, the Gleason score of two patients was 6. The tumor was detected in a single core in both patients, and the tumor length was <2 mm. Our results are also consistent with the multivariate logistic regression analysis (11). Although the patient's PSA level is high, it should be considered that there is a risk of pT0.

Several reasons may be present for the absence of residual tumor in RP specimens following positive biopsy results. The possibility of a false-positive result on prostate needle biopsy should be considered first. Prostate needle biopsy tissue should be re-examined by a second pathologist, and the diagnosis of PCa should be confirmed. Another possibility is that the diagnosis of the RP specimen is a false negative. The specimen should be examined again for an overlooked residual tumor. If a tumor is still absent, the entire prostate tissue should be sampled. Further deeper re-cutting should be performed in the prostate tissue corresponding to the areas with positive biopsy results. Immunohistochemical staining should be used for minimal residual tumor and suspected foci. This step is critical to detect the tumor that has become a small focus as a result of preoperative hormonal treatment. As these steps were followed meticulously, tumors were detected in some patients with pT0. When the RP specimens of 8 patients with pT0 were examined closely, it was determined that 6 of them had tumors (18). Similarly, in one study, no residual tumor was detected in 28 patients in the first examination, whereas the second examination revealed the presence of tumor in 10 patients (21). In a study by Duffield and Epstein (25), among 2,200 patients who underwent RP, 34 showed to have pT0 in the first pathological examination and a further examination revealed that 8 patients have pT0. In our study, both biopsy tissue and prostatectomy specimen results were meticulously reviewed and false positivity was noted in one patient biopsy result. Another possibility for the vanishing cancer phenomenon is the diagnostic treatment of the tumor. Tumor focus might have been removed during TURP and open prostatectomy. Moreover, a small tumor area might be completely regressed with hormonal therapy. However, this is unclear in prostate biopsy. Kommu introduced the curative biopsy theory and claimed that the malignancy focus might be completely removed by biopsy (29). Some researchers argue that necrosis may develop in tumor tissue due to vasospasm or hematoma and the tumor may disappear after a biopsy (30,31). Evidence on this issue is insufficient. The last possible reason for the absence of a residual tumor is misnomenclature or confusion regarding the specimen. To eliminate this possibility, some researchers performed DNA analysis of the biopsy and surgical specimens (3,10,20,22). DNA mismatch was detected in only 1 of the patients in these studies. No DNA analysis was performed in our study.

Study Limitations

Our study has some limitations. First, the study has a retrospective design. Furthermore, the number of patients in our study was small, and the follow-up period was relatively short. Owing to the small number of patients, no regression analysis could be performed for variables that could be used to predict pT0. Finally, the needle biopsy and RP pathology reports were verified by a second pathologist; however, no DNA analysis was performed.

Conclusion

No residual tumor after RP is extremely rare. Consensus about its clinical importance is unclear; however, patients should be routinely followed up. Patients with a Gleason score of 6 and tumors in a single core and length of <2 mm in the biopsy should be informed about the risk of stage pT0, and active surveillance option should be explained.

Ethics

Ethics Committee Approval: The study was approved by Antalya Training and Research Hospital Ethics Committee (approval number: 2021-007).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: E.İ., K.Y., M.A., Ş.Y., Concept: K.K., M.T.Ö., M.A., Design: K.K., M.T.Ö., M.A., Data Collection or Processing: K.K., K.Y., O.A., Analysis or Interpretation: K.K., M.T.Ö., K.Y., O.A., Ş.Y., Literature Search: K.K., E.İ., Writing: K.K., M.T.Ö., E.İ., Ş.Y.

Conflict of Interest: No conflict of interest was declared by the authors.

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ORIGINAL RESEARCH
Reconstructive

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Sacral Neuromodulation Treatment for Non-neurogenic Urological Disorders: Experience of a Single Center in Turkey

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What's known on the subject? and What does the study add?

Sacral neuromodulation (SNM) has been proven by many studies to be an effective and safe minimal invasive therapy for the treatment of overactive bladder, bladder pain syndrome/interstitial cystitis, and idiopathic non-obstructive urinary retention. Efficacy and safety results of this study is similar with the literature. On the other hand, this study is presenting the experience of a center in Turkey with regard to SNM treatment in non-neurogenic urological disorders.

Abstract

Objective: We evaluated the success rate and complications of sacral neuromodulation (SNM) in patients with non-neurogenic urological disorders.
Materials and Methods: We retrospectively evaluated patients with an overactive bladder (OAB), bladder pain syndrome/interstitial cystitis (BPS/IC), and idiopathic non-obstructive urinary retention (IUR), who underwent SNM between 2015 and 2020. SNM was recommended for patients with OAB and BPS/IC who previously had unsuccessful conservative and medical therapies and botulinum toxin injections. Success was defined as more than 50% improvement in clinical symptoms or voiding diary parameters in patients with OAB; more than 50% improvement in storage symptoms or subjective pain improvement or improvement after pain medications in patients with BPS/IC; more than 50% reduction in urethral catheterization rate in patients with IUR. We reviewed the success rates and complications.
Results: Twenty-four patients underwent the first stage of SNM and 16 patients (66.6%) received permanent implantation. Ten patients were female (62.5%) and six were male (37.5%). The mean age was 36.9 years. Seven patients (43.7%) had OAB, three patients (18.7%) had BPS/IC, and six patients (37.5%) had IUR. After a mean follow-up of 42.3 months, the overall success rate was 87.5% for all indications. The success rate was 100%, 100%, and 66.7% for OAB, BPS/IC, and IUR, respectively. Four patients underwent surgical reintervention: two had their devices removed due to failure (50%), one had their implantable pulse generator (IPG) repositioned due to serious pain (25%), and one changed IPG due to malfunction (25%).
Conclusion: SNM is a safe and effective minimally invasive therapy for patients with non-neurogenic urological disorders.
Keywords: Bladder pain syndrome, idiopathic urinary retention, interstitial cystitis, overactive bladder, sacral neuromodulation

Introduction

Sacral neuromodulation (SNM) has proven to be an effective treatment option for refractory overactive bladder (OAB) and idiopathic nonobstructive urinary retention (IUR) (1). The Food and Drug Administration has approved SNM for treating OAB and IUR (2). Additionally, SNM has been widely used for treating bladder pain syndrome/interstitial cystitis (BPS/IC) and neurogenic bladder (3). Several SNM studies are present in the current literature, reporting long-term success and safety (1,4). Currently, there are no articles on the success and complications of SNM in urological disorders in the English literature published from Turkey. This is the first study from Turkey, where we present our experience with SNM for treating OAB, IUR, and BPS/IC.

Materials and Methods

Our institutional ethical board approved this study (University of Health Sciences Turkey, Gülhane Training and Research Hospital, approval number: 19/80, date: 28.05.2019). Following

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the ethical approval, we retrospectively reviewed the medical records of all patients who underwent implantable pulse generator (IPG) placement (Interstim™, Medtronic, Minneapolis, USA) in our center between January 2015 and May 2020. Patients' demographics, indications for SNM, treatment success, follow-up period, and complications (including revisions) were recorded.

We assessed all patients using a thorough medical history, physical examination, cystoscopy, urodynamic testing, neurological and psychiatric examination, and seven-day voiding diary (frequency, urgency, incontinence episodes, voided volume, and self-catheterization episodes and volume). Inclusion criteria were as follows: patients in the age range of 18 to 55 years, urinary urgency, frequency, urgency incontinence, pain related to the urinary bladder, dysuria, and urinary retention. Exclusion criteria were as follows: patients older than 55 years bladder outlet obstruction, urethral stricture, urinary tract cancer, urinary tract infection, pregnancy, and neurological or psychiatric pathology. SNM treatment indications included refractory OAB, refractory BPS/IC, and IUR.

OAB was diagnosed according to the definition of the International Continence Society (5). BPS/IC was diagnosed according to the definition of the European Society for the Study of Interstitial Cystitis (ESSIC) (6). IUR was defined as "neurologically healthy patients who are unable to urinate or had difficulty urinating with a significant residual urine volume, greater than 300 mL, without urethral stricture or bladder outlet obstruction." Patients defined as "refractory OAB" were those who experienced no improvement using one antimuscarinic drug or more for three months or those who were unable to tolerate the side effects of antimuscarinics (7). All patients with OAB and BPS/IC had botulinum toxin injections before SNM treatment. In patients with OAB, failure of intradetrusor botulinum toxin injections was defined as less than 50% improvement or worsening of symptoms following the injections. Refractory BPS/IC was defined as less than 50% improvement or worsening of symptoms following oral and intravesical treatments, hydrodistension, fulguration, or intradetrusor botulinum toxin injections.

All patients underwent two-stage SNM implantation. The first stage was performed in the operating room under local anesthesia and sedation. A 22-G spinal needle was placed percutaneously into each S3 foramen under fluoroscopic guidance, and stimulation was then performed. Proper needle location was assessed using sensorial (vaginal or perineal sensation) and motor (bellow-like contraction of the anal sphincter or plantar flexion of the great toe) responses during stimulation. The needle with the best stimulation responses was retained and the other one removed. Then, a small incision was made and the tined permanent lead was placed through the needle tract. Proper tined lead placement was confirmed using fluoroscopy and repeat stimulation. The tined lead was then connected to an extension wire, which was tunneled subcutaneously to the contralateral upper lateral side of the hip and connected to an external temporary generator. Patients were taught how to work the external generator. During the test stimulation period (7-30 days), patients were seen daily for the first five days to assess the sensorial response and symptom improvement. Patients completed a seven-day voiding diary (frequency, urgency, incontinence episodes, voided volume, and self-catheterization episodes and volume). After seven days, the patients were contacted by phone. If a patient reported a decreased vaginal or perineal sensation, reprogramming was done. Reprogramming was also done for patients who experienced no clinical improvement after the first week and repeated if necessary. Success was defined as more than 50% improvement in clinical symptoms or voiding diary parameters in patients with OAB; more than 50% improvement in storage symptoms or subjective pain improvement or improvement after pain medications in patients with BPS/IC; less than 50% reduction in urethral catheterization rate in patients with IUR. If successful results were achieved during the test stimulation period, then the patients underwent permanent IPG placement under local anesthesia. Improvement of less than 50% or worsening of the symptoms was defined as failure for all indications.

All patients were followed up at three, six, and twelve months postoperatively and yearly thereafter, or if clinically indicated. Overall symptom improvement was reported using a voiding diary and direct interview on each visit. Symptom scores were not used. Also, PVR measurement was performed for patients with IUR. During the follow-up, SNM was considered successful if there was an initial improvement of more than 50% in clinical symptoms or voiding diary parameters persisted compared with baseline. Due to the small number of patients and retrospective design, descriptive statistical data (percentage, mean, and range) were used.

Results

Twenty-four patients underwent the first stage of SNM from January 2015 to May 2020 in our urology department. Eight patients (33.3%) failed the test period, and 16 patients (66.6%) received permanent IPG implantation. During implantation, motor responses were achieved in 15/16 patients (93.7%) and sensory responses were achieved in 12/16 patients (75%). Our implantation rate was 66.6%. Of these 16 patients, 10 were female (62.5%) and six were male (37.5%). The mean age was 36.9 (range: 20-55) years. Seven patients (43.7%) had OAB, three patients (18.7%) had BPS/IC, and six patients (37.5%) had

IUR. After a mean follow-up of 42.3 months (range: 5-80), our overall success rate was 87.5% for all indications. The success rate was 100%, 100%, and 66.7% for OAB, BPS/IC, and IUR, respectively (Table 1).

No local wound complication (hematoma, infection, etc.) occurred in the early postoperative period. Also, no serious complications occurred. Four patients (25%) experienced complications during the follow-up period: Two patients experienced device failure, one patient had IPG site pain, and one patient experienced IPG malfunction. Four patients underwent surgical reintervention: Two had their devices removed due to failure (50%), one had their IPG repositioned due to serious pain (25%), and one changed IPG due to malfunction (25%) (Table 1). Failure occurred in two patients with IUR at three and 47 months after implantation. Follow-up with clean intermittent catheterization was recommended for these patients.

Table 1. Patients' demographics, success rate, and complications

	All	OAB	BPS/IC	IUR
Number of patients, n (%)	16	7 (43.7)	3 (18.7)	6 (37.5)
Mean age (range), years	36.9 (20-55)	31.1	49	37
Gender: female/male, n	10:6	3:4	3:0	4:2
Mean follow-up, months	42.3	37.8	37.6	42.5
Success, %	87.5	100	100	66.7
Complications, n • Failure • IPG site pain • IPG malfunction	4 2 1 1	0 0 0 0	0 0 0 0	4 2 1 1

OAB: Overactive bladder, BPS/IC: Bladder pain syndrome/interstitial cystitis, IUR: Idiopathic non-obstructive urinary retention, IPG: Implantable pulse generator

Discussion

SNM is a safe and long-term effective therapy for patients with nonneurogenic lower urinary tract dysfunction (LUTD) (2). The precise mode of action of SNM still remains largely unknown (4). It is thought that SNM works by modulating reflexes at the cord level; however, supraspinal pathways also have a role (8).

Our overall success rate was 87.5% at a mean follow-up 42.3 months, and the success rates for OAB, BPS/IC, and IUR were 100%, 100%, and 66.7%, respectively. These results are similar to those of other SNM studies. In a retrospective study by Sutherland et al. (4), a 69% success rate was reported after SNM implantation in patients with voiding dysfunction with a mean follow-up of 22 months. Peeters et al. (8) reported a 70% success rate in patients with urgency incontinence and a 73% success rate in patients with IUR at a mean follow-up of 47 months. In another retrospective study with a median follow-up of 9.7 years, Ismail et al. (9) reported a 63% success rate in patients with OAB. Siegel et al. (10) reported an 83% success rate of SNM in patients with OAB (10). Zhang et al. (3) reported that the success rates in patients with OAB, BPS/IC, and IUR were 42.5%, 72.4%, and 51.6%, respectively. Gajewski and Al-Zahrani (11) reported that the rate of permanent IPG implantation was 59%, and the success rate in patients with BPS/IC was 72%, at a mean-follow-up of 61.5 months.

The most common adverse event reported in the literature was pain at the implant site (15%-42%) (2). No serious complications were reported (2,4). van Kerrebroeck et al. (1) reported that 20% of the patients experienced adverse events resulting in surgical intervention at the one-year follow-up. This rate increased to 42.1% at five-year follow-up. The most common surgical complications requiring surgical intervention were IPG site pain, suspected lead migration, and new pain or undesirable change in stimulation. Other complications reported in the literature were loss of efficacy, device problem, adverse change in bowel function, infection, and suspected neuropraxia (12). The surgical revision rate was between 13-47% (9,13). The most common reason for surgical revision was pain at the site of implantation (2,13). The reintervention rate is high in long-term follow-up and tends to be within the first two years after the implantation (2). Our complication rate was 25%. Four patients underwent surgical intervention: Two had their devices removed due to failure (50%), one had their IPG repositioned due to serious pain (25%), and one changed IPG due to malfunction (25%). All complications occurred in patients with IUR. Additionally, none of our patients experienced serious complications.

The number of our patients is small because we cannot provide SNM to every patient with refractory OAB and BPS/IC. SNM and botulinum toxin injections are both effective and recommended for treating patients with OAB and BPS/IC who failed conservative and initial therapies. No hierarchy has been implied between botulinum toxin and SNM (14,15). In our country, the social security institution allows implantation of SNM in neurologically and psychologically healthy patients with OAB and BPS/IC, who failed conservative and initial medical therapies and intradetrusor botulinum toxin injection. Therefore, it is mandatory to use intradetrusor botulinum toxin injections in patients with OAB and BPS/IC before SNM implantation. In fact, this clinical practice is performed to reduce the treatment costs of patients with OAB and BPS/IC since SNM is an expensive treatment option. In randomized studies conducted on patients with OAB, it has been shown that SNM treatment is more expensive than botulinum toxin injections (16,17).

In our study, a previous history of psychiatric disease was an exclusion criterion since, in some studies, psychiatric disorders

were associated with poor results and adverse events. In a study by Weil et al. (18) that reported SNM treatment results in 36 patients with chronic voiding dysfunction, all patients with a previous history of psychological disorder or sexual abuse had a good response to temporary stimulation. However, the median duration of the therapeutic effect was only 12 months in patients with a previous psychiatric history, and 82% of these patients showed poor results compared with 28% of the patients without a history of psychiatric disorders (18). White et al. (19) reported a high rate of implant removal in patients with a psychiatric disease history but could not show a significant relationship between psychiatric history and adverse events (19). Marcelissen et al. (20) reported that a history of psychiatric disease was unrelated to the outcome of the test stimulation. However, patients with a history of psychiatric disease more likely encounter adverse events with permanent SNM treatment.

Age was associated with the success rate of SNM. Peters et al. (21) reported that advanced age was negatively associated with SNM success. Amundsen et al. (22) reported in a prospective study that, in patients with refractory urge incontinence who were treated with SNM, age older than 55 years and more than three chronic conditions were independent factors associated with a lower cure rate. Sherman et al. (23) reported that an age less than 55 years was positively associated with SNM treatment. Therefore, we included patients younger than 55 years old in our study.

When placing the quadripolar electrode, it is important to obtain sensory and motor responses. Cohen et al. (24) investigated whether intraoperative motor or sensory response is more predictive of a successful SNM treatment. The authors concluded that a positive test stimulation is more likely when intraoperative lead placement causes a positive motor response compared with sensory response (24). Peters et al. (21) evaluated the impact of assessing sensory responses during quadripolar lead placement in patients with refractory voiding symptoms. They found that, during permanent lead placement, routinely assessing the sensory response insignificantly impacts the success rate of IPG implant and the clinical outcomes of SNM (22). We tried obtaining motor and sensory responses in each patient, and we achieved motor responses in 93.7% of patients and sensory responses in 75% of patients.

Study Limitations

The main limitations of this study were its retrospective design and a small number of patients. However, this is the first study from Turkey reporting on SNM treatment outcomes in urological disorders.

Conclusion

SNM is a safe and effective minimally invasive therapy in patients with OAB, BPS/IC, and IUR and should be considered before any invasive surgical intervention is planned. Several studies are published in English literature, but this is the first study from Turkey reporting on SNM treatment outcomes in urological disorders.

Ethics

Ethics Committee Approval: Our institutional ethical board approved this study (University of Health Sciences Turkey, Gülhane Training and Research Hospital, approval number: 19/80, date: 28.05.2019).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: A.E.C., S.Y., M.G., Concept: A.E.C., M.G., Design: A.E.C., M.G., Data Collection or Processing: A.E.C., Analysis or Interpretation: A.E.C., Literature Search: A.E.C., S.Y., B.T., M.Z., E.K., Writing: A.E.C., M.G.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declare that they have no relevant financial.

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ORIGINAL RESEARCH
Transplantation

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The Quality of Randomized Controlled Trial in Cochrane Kidney and Transplant Group

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What's known on the subject? and What does the study add?

Misconduct is an important issue on research integrity. Cochrane systematic reviews are known for their best level of evidence. Cochrane Kidney and transplant group is one of the chief review groups of this database. A total of 267 systematic reviews and their understudies 3213 RCTs were evaluated. All of the systematic reviews in kidney and transplant group had high quality. In the understudies RCTs of these review, the highest risk of bias had been seen in allocation concealment bias, and the most common bias was unclear allocation concealment (selection bias). It's recommended observing integrity principles for preventing research misconduct.

Abstract

Objective: Misconduct is one of the important issues in research integrity. Cochrane systematic reviews are known for their best level of evidence. Since kidney failure is a major public health problem worldwide, the Cochrane Library provides a robust and reliable database to upgrade medical knowledge and make the best medical decisions. Therefore, this study aimed to assess the quality of randomized controlled trials (RCTs) that are included in the Cochrane systematic reviews of kidney and transplant groups.

Materials and Methods: This analytic cross-sectional study was conducted on systematic reviews of kidney and transplant group of Cochrane reviews. All types of biases in the understudied RCTs or quasi-RCTs of these systematic reviews were evaluated using the Cochrane appraisal checklist. The types of biases in included studies were also separated and stratified. Descriptive statistics were used for data analysis using the Statistical Package for the Social Sciences 16.

Results: A total of 267 systematic reviews and their understudied 3213 RCTs were evaluated. In the kidney and transplant group, the highest risk of bias was seen in allocation concealment bias, whereas the most common bias was unclear allocation concealment (selection bias). From 2008 to 2009, high random sequence generation bias has dramatically increased, and after decreasing, the gradual growth has been continuing over time. Furthermore, the low detection bias has reduced surprisingly in 2011 then decreased in 2012-2013.

Conclusion: Regarding high risks of performance and random sequence generation biases in understudied RCTs, critical structure deficiencies were obvious. Therefore, observing integrity principles to prevent research misconduct is recommended.

Keywords: Risk of bias, randomized controlled trial, Cochrane, systematic review

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Introduction

Misconduct is an important issue on research integrity (1). In recent decades, a dramatically increased number of published articles in different fields of medical sciences have been reported. As a result, the structure of published articles in medical journals and their adaptation to provide reporting standards and research methodology have been considered more than ever (2). However, the main concern has always been the presence of quantitative growth of research with their qualitative development. In the study's pyramid, the highest levels of best evidence belong to meta-analysis and systematic reviews (3). Cochrane Library provides a robust and reliable database for upgrading medical knowledge and helps to make the best medical decisions. Cochrane reviews are systematic research reviews in healthcare and health policy published in the Cochrane Database consisting of 52 review groups that focus on specific topics (4). Cochrane kidney and transplant group is one of the chief review groups of this database and is responsible for identifying all renal disease trials, trials quality assessment, collecting and analyzing trial data, and preparing organized reports for inclusion in reviews working on 214 items (5). The activity area of this group includes acute renal failure (ARF), chronic renal failure (pre-dialysis, hemodialysis, and peritoneal dialysis), diabetes mellitus, glomerulonephritis (including nephrotic syndrome, immunoglobulin A nephropathy, lupus nephritis, Henoch–Schönlein purpura, and other glomerular diseases), kidney transplantation, solid organs transplantation, urinary tract infections, and the effects of drugs on renal function (6). Kidney failure is a major public health problem worldwide, with increasing incidence and prevalence, high costs, and poor outcomes (7). A significantly higher prevalence of chronic kidney disease (CKD) in earlier stages and adverse consequences, such as loss of kidney function, premature death, and cardiovascular disease, was reported (8). Moreover, many heterogeneous disease pathways led to CKD that irreversibly altered the function and structure of the kidney in months or years (9). CKD is a frequent phenomenon that affects 1 out of 10 cases (10) in the general population and increases the risk of morbidity and mortality (11). An analysis in 2017 estimated the global prevalence of CKD as 9.1% or 697.5% cases. The age-standardized global prevalence of this disease was higher in females (9.5%) than that in males (7.3%). More than 10 million cases were detected in 10 countries, and more than 1 million cases have been identified in 79 countries. An increase of 29.3% in the all-age global prevalence of CKD was reported between 1990 and 2017, whereas a significant change was not observed in the age-standardized global prevalence (12). These diseases increased globally due to elevation in the prevalence of hypertension, obesity, diabetes mellitus, and most importantly, aging (13). Renal diseases are the ninth most common cause of death in the United States with a higher mortality rate compared to breast and prostate cancers (14,15). In the United States, the unadjusted prevalence of CKD in 2011 through 2014 was estimated at 14.8%. A total of 120,688 new cases of end-stage renal diseases (ESRD) were reported in 2014 (a 1.1% increase compared to 2013). A total of 678,383 individuals were treated for ESRD at the end of 2014 (up 3.5% from 2013), a number that continues to rise due to falling mortality rates among those with ESRD (16). CKD is associated with increased cardiovascular mortality and disability (17). However, the lack of kidney disease registry in many low and middle-income countries has made it difficult to determine the true CKD load. In low and middle-income countries, higher mortality rate is usually due to expensive services of kidney replacement therapy (18). In Iran, according to the result of Safarinejad (19) study (2009), the prevalence of CKD was reported at 12.6%. Other kidney-related disease includes ARF (20) with an incidence of 5%-20% in adolescents admitted to the care unit (21). ARF is associated with high morbidity and mortality, and >70% of people with ARF need supportive care. Despite advances in clinical care, people with ARF have a high risk of mortality and morbidity that needs significant health care resources (22).

The Cochrane systematic reviews are known for their best level of evidence. The Cochrane International Foundation uses a precision instrument to evaluate randomized clinical trials (RCTs) to examine the types of possible bias in each study that distort the credibility and accuracy of the regular Cochrane reviews (23). The Cochrane kidney and transplant group are responsible for identifying all trial-related kidney diseases and transplant, evaluating the relevance and trial quality, collecting and analyzing trial data, and preparing reports including systematic reviews of the Cochrane Database. The Cochrane Library provides a robust and reliable database to upgrade medical knowledge and make the best medical decisions since kidney failure is a major public health problem worldwide with increasing incidence and prevalence, high costs, and poor outcomes. Therefore, this study aimed to assess the quality of understudied RCTs or quasi-RCTs included in the Cochrane systematic reviews of kidney and transplant groups.

Materials and Methods

This analytic cross-sectional study was conducted on published systematic reviews of kidney and transplant groups of the Cochrane reviews to evaluate the quality of their understudied RCTs or quasi-RCTs.

After proposal approval and Ethics Committee confirmation of Research Deputy of Tabriz University of Medical Sciences, Tabriz, Iran (code: IRTBZMED.REC.1396.577), all systematic reviews that were published in kidney and transplant group, were prepared. The quality of Cochrane kidney and transplant group systematic reviews or meta-analysis and their understudied RCTs were

evaluated at the presents study, thus informed consent was not applicable.

The Cochrane Library is a collection of databases that contain different types of high-quality and independent evidence to inform healthcare decision-making. Related topics include CKD, hypertension, end-stage kidney disease, kidney transplant, acute kidney injury, and urology.

The current study selected all systematic reviews that focus on the kidney and transplant after an electronic search in the Cochrane Library. Firstly, all included systematic reviews were listed in Table 1. Then, the general information, including title, year of publication, author name, study location, and other necessary information was extracted from each study (supplementary file 1). Next, all of the understudied RCTs of these systematic reviews were evaluated. Therefore, the number of RCTs that were included in the systematic reviews was counted. Then, all kinds of bias, which were evaluated by the authors of these systematic reviews were counted and listed on the column of the related topic of bias.

All included RCTs in the Cochrane reviews were appraised by the authors of systematic reviews using the standard risk of bias tool developed by the Cochrane group. This tool consisted of six dimensions, including the method of random sequencing, random assignment of samples, selective report of consequences, blindness, the existence of any probabilistic suppression of results, and reporting of incomplete data.

Each of the cases examined in the tool was reported in three ways, including low-risk, high risk, and unclear-risk bias. The standard risk of bias tool is a valid and reliable tool for evaluating all RCTs, regardless of the language, time, and location of article publication (24). All types of evaluated biases were counted based on the results of "Risk of bias summary: Review author judgments about each risk of bias item for each included study." And then, all types of biases were counted for all systematic reviews, listed in appropriate columns, and calculated the sum of all kinds of biases.

Statistical Analysis

All types of biases in RCTs or quasi-RCTs were gathered and finally, all types of biases in included studies were separated according to the publication date. Descriptive statistics were used to analyze data. Data were analyzed using the Statistical Package for the Social Sciences software (SPSS 16, SPSS Inc., Chicago, IL, USA).

Results

A total of 267 systematic reviews, which were published in the Cochrane kidney and transplant group until October 2019, and their understudied 3213 RCTs or quasi-RCT were included.

All published systematic reviews and meta-analyses followed the preferred reporting items for systematic review and meta-analysis for their report (24).

Among the several biases, the highest risk of bias belonged to the allocation concealment. However, the most common bias was the unclear allocation concealment (selection bias). Then unclear random sequence generation (selection bias) and selective reporting bias were in the next ranks. According to the findings, in 2008-2009, high random sequence generation bias dramatically increased and after decreasing, continued to grow gradually over time. Furthermore, low detection bias has decreased in 2011 and 2012-2013, respectively (Figure 1).

From 2014 to 2018, the unclear allocation bias was the most common bias among others. However, the highest risk of bias was seen in 2014 to 2018 in attrition, performance, and reporting, respectively in the included studies.

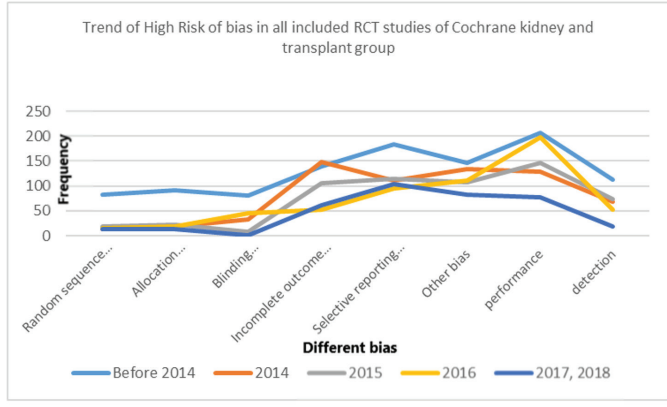

Figure 1. The trend of all high risk of bias in the Cochrane kidney and transplant group

The number (%) of all kinds of bias in published studies in the Cochrane kidney and transplant group are summarized in Table 1 (Supplementary file 1).

Discussion

Misconduct is one of the most important issues in research integrity of clinical research, which is defined as poor management or administration. The most common causes of misconduct in clinical research are financial interest, professional ambitions to become famous, complex study design, and consequently, the lack of researcher motivation or laziness and expectations of organization or government (25).

The medical literature is an essential and also helpful resource to make the best clinical decision. Hence, improper clinical outcome reporting can influence the health care system at all levels, from patient treatment to modifying and developing

national public health policies (26). Therefore, methodological quality assessment of studies is a crucial stage in the best clinical literature selection process. The methodological quality evaluation of the study should be based on evaluating internal and external validity, which characterizes the design conduction, data analysis, or degree of study result generalization, respectively (27). The highest level in the evidence pyramid belongs to meta-analysis and systematic review of RCTs (26). These study types present the best evidence for beneficial treatment in clinical research. Furthermore, the most robust clinical evidence constitutes the systematic reviews of homogeneous RCTs. Therefore, these types of studies had the highest impact on the guidelines, as well as decision-making. However, any misconduct could have a remarkable influence on caregiving quality. In addition, studies with a high risk of bias can lead to false evidence, which affects both the patients and the healthcare system in different aspects.

The use of their results will also be effective in advancing science by promoting the quality of research. Additionally, poor-quality research may lead to inaccurate conclusions. Thus, compliance with research and reporting methodology standards is necessary for the quality improvement of published articles. Incorrect reporting of clinical outcomes can affect health care at all levels, from the design of national public health policies to the treatment of the patient. Therefore, the quality confidence of these articles seems to be critical (28).

A systematic review attempts to identify, appraise, and synthesize all the empirical evidence that meets pre-specified eligibility criteria to answer a given research question. Researchers who conduct systematic reviews use explicit methods to minimize bias and produce more reliable findings that can be used to inform decision-making (29). The Cochrane Library provides a robust and reliable database to improve and develop medical knowledge and, most importantly, to make the best medical decisions (30). Therefore, preserving the quality of such studies, which will be utilized in the development of guidelines, is crucial.

Bias can occur in any phase of the conducted research, including planning, data collection, analysis, and publication. Understanding research bias and consequently, its effect on study results allows readers to critically and independently review the scientific literature and avoid suboptimal or potentially harmful treatment (31).

Our study results revealed that among different types of bias in all dates, the highest risk of bias belonged to selection. Unclear allocation concealment was the most common bias in our study in this Cochrane group. Selection bias or systematic differences between baseline characteristics of the groups that are compared may occur during study population identification. It means that the ideal study population was not clearly defined, accessible, reliable, and at increased risk to develop the outcome of interest (32). Prospective studies (particularly RCTs), where the outcome is unknown at the time of enrolment, are less prone to selection bias (33).

However, the evaluation of RCTs in our study showed that the unclear allocation concealment was the most common bias, explaining that the authors did not describe the used method to conceal the allocation sequence in detail to determine the prediction of intervention allocations in advance or during the enrolment. Our study results emphasized that the researchers should focus on preventing various types of misconduct. Therefore, observing integrity principles to prevent research misconduct is recommended. In addition, governments, institutions, and other committees need to take steps for better training and education for the researcher. The strength of this study is the quality assessment of all published systematic reviews and their understudied RCTs or quasi-RCTs, which was conducted in the field of kidney and transplantation in terms of the six-criterion risk of bias for the first time.

Study Limitations

However, our study had limitations, which include the utilization of descriptive statistics, including the frequency of all kinds of biases, to report the outcomes. In addition, the sum of all reported types of bias in understudied RCTs or quasi-RCTs included in the Cochrane kidney and transplant review group was reported. The effect of factors, such as group, year, and type of work is recommended to be examined with the Generalized Linear Models structure in future studies.

Conclusion

The high risks of performance and random sequence generation biases in understudied RCTs have critical structure deficiencies. Therefore, observing the integrity principles to prevent research misconduct is recommended.

Ethics

Ethics Committee Approval: After proposal approval and Ethics Committee confirmation of Research Deputy of Tabriz University of Medical Sciences, Tabriz, Iran (code: IRTBZMED.REC.1396.577).

Informed Consent: The quality of Cochrane kidney and transplant group systematic reviews or meta-analysis and their understudied RCTs were evaluated at the presents study, thus informed consent was not applicable.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: H.S.P., S.H., Design: H.S.P., Data Collection or Processing: A.Mo., Z.S., Analysis or Interpretation: A.Mo., S.H., Literature Search: A.M., L.H., Writing: Z.S., N.A.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declare that they have no relevant financial.

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Article	Year	Random sequence generation (selection bias)			Allocation concealment (selection bias)			Blinding (performance & detection bias)			Incomplete outcome data (Attrition bias)			Selective reporting (Reporting data)			Other bias			Performance			Detection			Article number
Risk of bias	Total	2127			2363			362			2007			1923			1899			1603			1564			
		Low	High	Unclear	Low	High	Unclear	Low	High	Unclear	Low	High	Unclear	Low	High	Unclear	Low	High	Unclear	Low	High	Unclear	Low	High	Unclear	
Pascual J, Zamora J, Galeano C, Royuela A, Quereda C	2009	-	-	-	14	1	14	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	29
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Braun N, Schmutzler F, Lange C, Perna A, Remuzzi G, Willis NS	2008	-	-	-	4	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	4
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Webster AC, Pankhurst T, Rinaldi F, Chapman JR, Craig JC	2006	-	-	-	2	16	3	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	21
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Strippoli GFM, Tong A, Johnson DW, Schena FP, Craig JC	2004	-	-	-	2	2	13	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	17
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Michael M, Elliott EJ, Ridley GF, Hodson EM, Craig JC	2009	-	-	-	9	-	4	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	13

Ruospo M, Palmer SC, Natale P, Craig JC, Vecchio M, Elder GJ, Strippoli GFM	2018	27	-	77	23	7	88	-	-	-	31	52	21	69	35	-	40	44	20	27	73	4	104	-	-	104
Zalmanovici Trestioreanu A, Green H, Paul M, Yaphe J, Leibovici L	2010	9	-	12	4	-	17	12	5	4	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	21
Rabindranath KS, Adams J, MacLeod AM, Muirhead N	2007	-	-	-	12	-	3	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	15
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Pohl A	2007	-	-	-	8	-	7	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	15
Perrotta C, Aznar M, Mejia R, Albert X, Ng CW	2008	-	-	-	1	-	8	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	9
Palmer SC, McGregor DO, Craig JC, Elder G, Macaskill P, Strippoli GFM	2009	12	3	45	5	5	50	10	12	37	-	-	-	-	-	-	-	21	39	-	-	-	-	-	-	60
Palmer SC, McGregor DO, Craig JC, Elder G, Macaskill P, Strippoli GFM	2009	4	-	12	3	-	13	2	2	12	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	16
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Cavalcanti AB, Goncalves AR, Almeida CS, Bugano DDG, Silva E	2010	-	-	-	6	1	17	-	-	-	8	15	1	-	-	-	-	-	-	6	13	5	-	-	-	24
Bravo Zuñiga JI, Loza Munárriz C, López-Alcalde J	2016	-	-	1	-	1	-	-	-	-	-	1	-	-	1	-	-	-	-	-	1	-	-	-	1	1
Webster AC, Ruster LP, McGee RG, Matheson SL, Higgins GY, Willis NS, Chapman JR, Craig JC	2010	16	1	54	15	1	55	1	24	46	36	13	22	41	12	18	8	30	33	-	-	-	-	-	-	71
Suckling, R. J., He, F. J. and MacGregor, G. A.	2010	-	-	-	4	-	16	-	-	-	-	-	-	-	-	-	-	-	-	9	8	3	12	1	7	13
McMahon EJ, (28) Campbell KL, Bauer JD, Mudge DW	2015	5	-	3	2	-	6	-	-	-	4	-	4	4	-	4	2	2	4	2	-	6	2	-	6	8
Reid S, Cawthon PM, Craig JC, Samuels JA, Molony DA, Strippoli GFM	2011	8	-	48	4	-	52	-	-	-	-	-	-	-	-	-	-	-	-	9	13	34	1	3	52	56
(158) Lee BSB, Bhuta T, Simpson JM, Craig JC	2012	3	2	8	2	1	10	-	-	-	3	3	7	-	-	-	-	-	-	4	7	2	1	-	12	13
Badve SV, Beller EM, Cass A, Francis DP, Hawley C, Macdougall IC, Perkovic V, Johnson DW	2013	1	-	1	-	-	2	-	1	1	2	-	-	-	-	2	-	2	-	-	-	-	-	-	-	2
Chen Y, Gong Z,Chen X, Tang L, Zhao X, Yuan Q,Cai G	2013	10	-	-	-	10	-	-	10	-	10	-	-	10	-	-	-	-	10	-	-	-	-	-	-	10
Palmer SC, Navaneethan SD, Craig JC, Johnson DW, Perkovic V, Nigwekar SU, Hegbrant J, 3Strippoli G-FM	2013	3	-	23	4	-	22	-	-	-	10	5	11	9	17	-	-	-	-	14	7	5	3	4	19	26
Lim AKH, Manley KJ, Roberts MA,- Fraenkel MB	2016	1	-	16	2	-	15	-	-	-	9	2	6	6	10	1	-	-	-	9	3	5	3	2	12	17
Wang H, Deng JL, Yue J, Li J, Hou YB	2010	-	-	6	-	-	6	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-6	-	-	-	6
Palmer SC, Saglimbene V, Craig JC, Navaneethan SD, Strippoli GFM	2014	7	1	24	6	-	26	-	-	-	4	19	9	10	22	-	1	19	12	5	17	10	1	16	15	32

Smart NA, DiebergG, Ladhani M, Titus T	2014	30	6	4	-	-	-	-	-	-	-	-	-	-	23	15	2	8	30	2	-	-	-	23	3	14	40
Nagler EV, Haller MC, Van Biesen W, Vanholder R, Craig JC, Webster AC	2018	14	-	21	12	-	23	-	-	-	18	9	8	16	18	1	3	27	5	16	11	8	31	1	3	35
Arechabala MC, Catoni MI, Claro JC, RojasNP, RubioME,Calvo MA,LetelierLM	2018	17	2	20	7	1	31	-	-	-	23	1	15	28	1	10	3	1	35	9	7	23	7	4	28	39
Bell S, Rennie T, Marwick CA,Davey P	2018	9	-	17	14	-	11	-	-	-	15	6	5	25	1	-	13	5	8	15	2	9	8	1	17	26
Tam KW, Wu MY,Siddiqui FJ, Chan ESY,Zhu Y, Jafar TH	2018	3	-	2	2	-	3	-	-	-	-	-	5	3	-	2	2	-	3	5	-	-	5	-	1	5
Webster AC, Lee VWS, Chapman JR,Craig JC	2006	-	-	-	10	3	23	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	36
Chen Y, Schieppati A, Chen X, Cai G, Zamora J, Giuliano GA, Braun N, Perna A	2014	22	-	17	16	-	13	-	-	-	-	-	-	-	-	-	-	-	-	7	19	3	-	-	-	39
(83) Palmer SC, Saglimbene V, Craig JC, Navaneethan SD, Strippoli GFM	2014	7	1	24	6	-	6	-	-	-	4	19	9	10	22		1	19	12	5	17	10	1	16	15	32
(134) Yahaya I, Uthman OA, Uthman MMB	2013																									0
(192) Krogsbøll LT, Jørgensen KJ, Gøtzsche PC	2015																									0
Adamu B, Abdu A, Abba AA, Borodo MM, TleyjehIM	2014	2	-	1	-	1	2	-	3	-	2	1	-	3	-	-	2	1	-	-	-	-	-	-	-	3

Ballinger AE,Palmer SC, Wiggins KJ, Craig JC, Johnson DW, Cross NB, Strippoli GFM	2014	4	6	32	7	9	26	-	-	-	27	5	10	6	35	1		8	34	3	34	5	1	6	35	42
Nagler EV, Haller MC, Van Biesen W, Vanholder R, Craig JC, Webster AC	2018	14	-	21	12	-	13	-	-	-	18	9	8	16	18	1	3	17	5	16	11	8	31	1	3	35
Rabindranath KS, Kumar E, Shail R, Vaux EC	2011	3	-	4	-	-	7	-	-	-	6	-	1	4	-	3	6	-	1	7	-	-	-	-	-	7
Palmer SC, Palmer AR,Craig JC,Johnson DW, Stroumza P, Frantzen L, Leal M, Hoischen S, Hegbrant J, Strippoli GFM	2014	1	-	-	1	-	-	-	-	-	1	-	-	1	-	-	-	1	-	-	1	-	1	-	-	1
(75) Zeng X, Zhang L, Wu T, Fu P	2014	-	1	2	-	3	-	-	3	-	2	-	1	-	-	3	-	-	3	-	-	-	-	-	-	3
Ruospo M, Saglimbene VM, Palmer SC, De Cosmo S, Pacilli A, Lamacchia O, Cignarelli M, Fioretto P, VecchioM, Craig JC, Strippoli GFM	2017	8	-	6	7	-	7	-	-	-	9	2	3	11	3	-	6	6	2	2	3	9	7	-	7	14
Aboumarzouk OM, Kata SG, Keeley FX, McClinton S, Nabi G	2012	3	3	1	-	-	7	-	7	-	7	-	-	7	-	-	7	-	-	-	-	-	-	-	-	7
(36) Adamu B, Abdu A, Abba AA, Borodo MM, Tleyjeh IM	2014	2	-	1	-	1	2	-	3	-	2	1	-	3	-	-	2	-	1	-	-	-	-	-	-	3
(163) Afshar K, Jafari S, Marks AJ, Eftekhari A, MacNeily AE	2015	17	-	33	10	-	40	37	7	6	41	9	-	46	4	-	40	2	8	-	-	-	-	-	-	50
Bai ZG, Yang K, Tian JH, Ma B, Liu Y, Jiang L, Tan J, Liu TX, Chi I	2014	-	-	1	-	-	1	-	-	1	-	1	-	-	-	1	-	-	1	-	-	-	-	-	-	1

Ballinger AE, (62) Palmer SC, Nistor I, Craig JC, Strippoli GFM	2014	4	-	14	7	-	11	-	-	-	6	12	-	11	7	-	-	18	-	13	5	-	2	1	15	18
Bao Y, Wei Q	2012	-	-	1	-	-	1	-	-	-	-	-	1	-	-	1	-	-	1	-	-	1	-	-	-	1
Batterink J, Cessford TA, Taylor RAI	2015	1	-	6	1	-	6	-	-	-	5	-	1	3	4	-	1	-	6	2	-	5	2	-	5	7
Bolignano D, Palmer (27) SC, Navaneethan SD, Strippoli GFM	2014	9	-	18	4	-	23	-	-	-	18	1	8	13	-	14	8	1	18	1	4	12	1	4	22	27
Bolignano D, Palmer (115) SC, Ruospo M, Zoccali C, Craig JC, Strippoli GFM	2015	12	2	16	13	-	17	-	-	-	9	11	10	6	-	24	4	11	15	12	8	10	7	8	15	30
Botero Aguirre JP, Restrepo Hamid AM	2015	7	-	5	3	-	9	-	-	-	11	-	1	10	1	-	2	9	1	3	9	-	-	12	-	12
Strippoli GFM, Tong A, Johnson DW, Schena FP, Craig JC	2004	-	-	-	1	2	16	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	19
Chaturvedi S, Jones C	2007	-	-	-	-	-	3	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	3
Chen Y, Gong Z, Chen X, Tang L, Zhao X, Yuan Q, Cai G	2013	10	-	-	-	10	-	-	10	-	10	-	-	-	-	-	-	-	10	-	-	-	-	-	-	10
Cody JD, Daly C, Campbell MK, Khan I, Rabindranath KS, Vale L, Wallace SA, MacLeod AM, Grant AM, Pennington S, Nistor I, Bolignano D, Webster AC	2005	-	-	-	3	-	12	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	15
Coronado Daza-J,Martí-Carvajal AJ,Ariza GarciaA,RodeloCeballos J,YomayusaGonzález N, Páez-CanroC,Loza-Munárriz C,Urrútia G	2015																									0

Couchoud C	1998																											0
(38) Zalmanovici Trestioreanu A, Lador A, Sauerbrun-Cutler MT, LeiboviciL	2015	2	5	2	2	2	5	-	-	-	6	-	3	9	-	-	4	-	5	4	3	2	1	3	5	9
Cross NB, Webster AC, Masson P, O'Connell PJ, Craig JC	2009	8	55	1	8	1	55	-	-	-	30	7	27	1	-	63	53	2	9	-	-	-	-	-	-	64
Escribano J, Balaguer A, Pagone F, Feliu A, Roqué i Figuls M	2009	-	-	-	-	-	5	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	5
(86) Escribano J, Balaguer A, Roqué i Figuls M, Feliu A, Ferre N	2014	2	-	3	2	-	3	1	4	-	1	1	3	5	-	-	2	2	1	-	-	-	-	-	-	5
Fayad AI, Buamscha DG, Ciapponi A	2016	6	-	-	5	-	1	-	-	-	6	-	-	6	-	-	3	-	3	-	-	6	6	-	-	6
Fayad AII, Buamscha DG, Ciapponi A	2018	4	-	1	4	-	1	-	-	-	4	1	-	5	-	-	3	-	2	-	-	5	5	-	-	5
Feng M, (69) Yuan W, Zhang R, Fu P, Wu T	2013	8	1	-	-	9	-	-	-	-	9	-	-	7	-	2	-	-	9	-	9	-	-	-	9	9
Fitzgerald A, Mori R, Lakhanpaul M	2012	1	-	2	1	-	2	2	-	1	2	-	1	3	-	-	-	-	-	-	-	-	-	-	-	3
(41) Fitzgerald A, Mori R, Lakhanpaul M, Tullus K	2012	2	-	14	1	-	15	2	1	13	9	3	4	13	-	3	-	-	-	-	-	-	-	-	-	16
Flower A, (68) Wang LQ, Lewith G, Liu JP, Li Q	2015	7	-	-	-	-	7	-	-	-	4	1	2	-	-	7	-	-	7	-	6	1	-	-	7	7

Fortin PM, Bassett K, Musini VM	2010	1	-	-	1	-	-	1	-	-	1	-	-	1	-	-	1	-	-	1	-	-	-	-	-	-	-	-	1
Gupta A, Ahmed K, Kynaston HG, Dasgupta P, Chlosta PL, Aboumarzouk OM	2016	3	-	-	2	-	1	-	-	-	2	1	-	3	-	-	1	-	2	1	-	2	3	-	-	3
(104) Hahn D, Cody JD, Hodson EM	2014	9	-	24	14	-	19	-	-	-	16	8	9	5	20	8	1	21	11	33	-	-	33	-	-	33
Hahn D, Hodson EM, Craig JC	2015	13	1	6	13	2	5	-	-	-	9	9	2	11	9	-	13	5	2	4	15	1	20	-	-	20
Hahn D, (79) Hodson EM, Willis NS, Craig JC	2015	18	6	10	16	8	10	-	-	-	14	14	6	16	16	2	12	1	21	7	27	-	8	26	-	34
Hahn D, (140) Hodson EM, Willis NS, Craig JC	2015	6	-	8	8	-	6	-	-	-	5	3	6	8	3	3	4	2	8	3	10	1	3	4	7	13
Heiwe S, Jacobson SH	2011	11	-	34	11	-	34	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	45
Hewitt J, Uniacke M, Hansi NK, Venkat-Raman G, McCarthy K	2012	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	0
(53) Hodson EM, Ladhani M, Webster AC, Strippoli GFM, Craig JC	2013	12	1	24	12	1	24	-	-	-	34	1	2	7	26	4	5	14	8	10	26	1	10	26	1	37
Hodson EM, Willis NS, Craig JC	2012	-	-	18	4	-	14	-	-	-	9	6	3	11	-	7	-	14	4	5	13	-	-	-	18	18
Hodson EM, Willis NS, Craig JC	2010	7	-	7	8	-	6	-	10	4	4	5	5	9	1	4	4	4	6	-	-	-	-	-	-	14

Hong T, Zhang M, Fan J	2015	2	-	3	-	-	5	-	-	-	5	-	-	-	-	5	-	-	5	-	-	5	5	-	-	5
Cho Y, Johnson DW, Craig JC, Strippoli GFM, Badve SV, Wiggins KJ	2014	14	3	19	10	3	22	-	-	-	7	18	11	20	12	5	-	5	30	19	8	9	3	-	33	36
(81) Jepson RG, Mihaljevic L, Craig JC	1998	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	0
(80) Jepson RG, Williams G, Craig JC	2012	14	1	9	15	2	7	-	-	-	12	9	3	21	-	3	10	2	12	17	6	1	11	1	12	24
Jiang L, Zeng R, Yang K, Mi DH, Tian JH, Ma B, Liu Y	2012	1	-	-	-	-	1	-	-	1	-	-	1	-	1	-	-	-	1	-	-	1	-	-	1	1
Jun, M., Venkataraman, V., Razavian, M., Cooper, B., Zoungas, S., Ninomiya, T., Webster, A. C. and Perkovic, V.Perkovic V	2012	4	-	6	3	-	7	7	-	3	8	-	2	5	1	4	1	5	4	-	-	-	-	-	-	10
Kang A, Nigwekar SU, Perkovic V, Kulshrestha S, Zoungas S, Navaneethan SD, Cass A, Gallagher MP, Ninomiya T, Strippoli GFM, Jardine MJ	2015	1	-	-	1	-	-	-	-	-	-	-	1	1	-	-	1	-	-	1	-	-	1	-	-	1
Kimachi M, Furukawa TA, Kimachi K, Goto Y, Fukuma S, Fukuhara S	2017	4	-	1	4	-	1	-	-	-	-	-	5	5	-	-	-	5	-	4	-	1	5	-	-	5
Kong X, (153) Yuan H, Fan J, Li Z, Wu T, Jiang L	2013	-	-	5	1	-	4	-	-	-	4	1	-	-	5	-	-	-	5	2	3	-	2	3	-	5
Kosa SD, Al-Jaishi AA, Moist L, Lok CE	2015	2	1	1	2	1	1	-	-	-	2	2	-	1	2	1	1	1	2	1	1	2	1	1	2	4
(115) Lewicki M, Ng I, Schneider AG	2015	3	-	4	2	-	5	7	-	-	7	-	-	1	5	1	4	1	2	7	-	-	7	-	-	7

(46) Lv J, Perkovic V, Foote CV, Craig ME, Craig JC, Strippoli GFM	2012	13	-	13	12	-	14	-	-	-	14	8	4	15	8	3	-	-	-	18	6	2	7	-	19	26
Lutters M, Vogt-Ferrier NB lower urinary tract infections in elderly women (Review)	2008	-	-	-	5	1	9	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	15
Lo, C., Toyama, T., Wang, Y., Lin, J., Hirakawa, Y., Jun, M., Cass, A., Hawley, C. M., Pilmore, H., Badve, S. V. and et al.	2018	23	-	21	24	-	20	-	-	-	24	18	2	25	-	19	7	31	6	27	9	8	12	8	24	44
Lo C, Jun M, Badve SV, Pilmore H, White SL, Hawley C, Cass A, Perkovic V, Zoungas S	2017	3	-	4	2	2	3	-	-	-	2	4	1	4	2	1	4	2	1	2	5	-	1	2	4	7
Liu Z, Su G, Guo X,)85) Wu Y, Liu X, Zou C, Zhang L, Yang Q, Xu Y, Ma W	2015	1	-	8	-	-	9	-	-	-	4	3	2	6	2	1	-	-	9		2	7	1	-	8	9
(172) Liu LR, Li QJ, Wei Q, Liu ZH, Xu Y	2013	-	-	2	-	-	2	-	-	-	2	-	-	2	-	-	1	-	1	-	2	-	2	-	-	2
Liu L, Zhang L, Liu GJ, Fu P	2017	3	-	3	3	-	3	-	-	-	4	-	2	3	1	2	1	2	3	-	6	-	-	-	6	6
(102) Lim AKH, Manley KJ, Roberts MA, Fraenkel MB	2007	-	-	-	2	-	15	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	17
(166) Li Y, Tang X, Zhang J, Wu T	2012	2	-	6	-	-	8	2	-	6	6	2	-	6	1	1	8	-	-	-	-	-	-	-	8	8
Li T, Wu HM, Wang F, Huang CQ, Yang M, Dong BR, Liu GJ	2011	1	-	1	-	-	2	1	1	-	2	-	-	-	2	-	-	-	2	-	-	-	-	-	-	2
Li J, Wu HM, Zhang L, Zhu B, Dong BR	2010	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	0

Nistor I, Palmer SC, Craig JC, Saglimbene V, Vecchio M, Covic A, Strippoli GFM	2015	11	4	25	1	3	36					5	23	12	3	35	2	4	36		1	16	23	4	15	21	40
(202) Nigwekar SU, Strippoli GFM, Navaneethan SD	2013	-	-	2	-	-	2	-	-	-	1	-	1	2	-	-	-	-	2	-	-	2	-	-	2	2	
Nigwekar SU, Navaneethan SD, Parikh CR, Hix JK	2009	5	-	14	3	-	16	1	15	3	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	19	
(118)Mutter TC, Ruth CA, Dart AB	2013	24	2	16	19	2	21	-	-	-	30	7	5	38	1	3	26	13	3	-	-	-	-	-	-	42	
Moreno G, (205) Corbalán J, Peñaloza B, Pantoja T2014	2014	2	-	10	-	-	12	-	-	-	8	2	2	-	1	11	-	-	12	2	1	9	1	-	11	12	
(197) Montero N, Webster AC, Royuela A, Zamora J, Crespo Barrio M, Pascual J	2014	-	-	3	1	-	2	-	3	-	-	-	3	2	-	1	1	-	2	-	-	-	-	-	-	3	
Montero N, Favà A, Rodriguez E, Barrios C, Cruzado JM, Pascual J, Soler MJ	2018	3	-	7	4	-	6	-	-	-	8	2	-	8	2	-	10	-	-	-	10	-	-	1	9	10	
McCann M, Moore ZEH	2010	5	1	4	4	1	5	5	1	4	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	10	
Masson P, Henderson (57) L, Chapman JR, Craig JC, Webster AC	2014	2	-	3	4	-	1	5	-	-	5	-	-	2	3	-	-	3	2	-	-	-	-	-	-	5	
MacLeod AM, Campbell MK, Cody JD, Daly C, Grant A, Khan I, Rabindranath KS, Vale L, Wallace SA	2005	-	-	-	4	3	25	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	32	

Palmer SC, Saglimbene V, Mavridis D, Salanti G, Craig JC, Tonelli M, Wiebe N, Strippoli GFM	2014	7	-	49	10	-	46	-	-	-	7	31	18	23	23	-	27	29	-	16	37	3	2	-	54	56
Palmer SC, Rabindranath KS, (111) Craig JC, Roderick PJ, Locatelli F, Strippoli GFM	2012	5	2	26	5	3	25	-	-	-	19	6	8	8	22	3	5	6	22	2	31	-	2	5	26	33
Palmer SC, Navaneethan SD, Craig JC, Perkovic V, Johnson DW, Nigwekar SU, Hegbrant J, Strippoli GFM	2014	3	1	18	2	-	20	-	-	-	5	11	6	-	-	-	-	-	-	11	6	5	4	5	13	22
Palmer, S. C., Natale, P., Ruospo, M., Saglimbene, V. M., Rabindranath, K. S., Craig, J. C. and Strippoli, G. F. M	2016	1	-	3	-	-	4	-	-	-	3	1	-	3	1	-	4	-	-	2	1	1	-	1	3	4
Palmer SC, Nand K, Strippoli GFM	2008	-	-	-	-	-	3	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	3
Palmer SC, McGregor DO, Strippoli GFM	2007	-	-	-	6	-	17	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	23
Palmer SC, Maggo JK, Campbell KL, Craig JC, Johnson DW, Sutanto B, Ruospo M, Tong A, Strippoli GFM	2017	3	-	16	1	-	18	-	-	-	7	3	9	3	16	-	8	5	6	-	19	-	1	1	17	19
Palmer SC, Navaneethan SD, Craig JC, Johnson DW, Perkovic V, Hegbrant J, Strippoli GFM	2014	12	-	38	14	-	36	-	-	-	14	20	16	-	-	-	16	10	24	21	19	10	12	12	26	50
Owers DS, Webster (180) AC, Strippoli GFM, Kable K, Hodson EM	2013	5	-	10	4	1	10	-	-	-	15	-	-	8	7	-	4	5	6	1	13	1	-	13	2	15
Albaramki J, Hodson EM, Craig JC, Webster AC	2012	12	-	16	6	2	20	28	-	-	12	6	10	12	7	9	-	12	16	-	-	-	-	-	-	28
O'Kane, D. B., Dave, S. K., Gore, N., Patel, F., Hoffmann, T. C., Trill, J. L. and Del Mar, C. B.	2016																									0

Ravani P, Quinn RR, Oliver MJ, Karsanji DJ, James MT, Mac-Rae JM, Palmer SC, Strippoli GFM	2016	6	-	8	4	4	6	-	-	-	6	4	4	13	1	-	2	10	2	4	4	6	1	13	-	14
(155) Sarai M, Tejani AM	2015	2	-	2	2	-	2	-	-	-	2	-	2	-	4	-	4	-	-	2	2	-	2	2	-	4
Sampson AL, Singer RF, Walters GD	2017	4	-	8	2	-	10	-	-	-	7	3	2	5	4	3	1	2	9	2	6	4	1	-	11	12
(78) Roderick PJ, Willis NS, Blakeley S, Jones C, Tomson C	2007	-	-	-	1	-	2	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	3
Raval AD, Thakker (212) D, Rangoon-wala AN, Gor D, Walia R	2015	6	-	3	6	-	3	-	-	-	7	1	1	7	1	1	3	4	2	2	2	5	2	2	5	9
(187) Rabin-dranath KS, Daly C, Butler J, Roderick PJ, Wallace SA, MacLeod AM	2005																									0
(161) Prav-itsitthikul N, Willis NS, Hodson EM, Craig JC	2013	11	1	19	16	1	14	-	-	-	26	3	2	19	9	3	11	3	17	6	25	-	6	25	-	31
Prabhu RA	2015	3	-	7	2	2	6	-	-	-	6	2	2	6	3	1	3	2	5	2	4	4	7	-	3	10
Phillips R, Hanchanale VS, Myatt A, Somani B, Nabi G, Bi-yani CS (70)	2015	6	-	1	1	-	6	6	-	-	5	2	-	7	-	-	2	-	5	-	-	-	-	-	-	7
: Penninga, L., Penninga, E. I., Møller, C. H., Iversen, M., Stein-brüchel, D. A. and Gluud, C.	2013	2	-	1	-	-	3	-	-	-	2	-	1	3	-	-	1	2	-	3	-	-	2	1	-	3
(42) Penninga L, Møller CH, Penninga EI, Iversen M, Gluud C, Steinbrüchel DA	2013	1	-	5	-	-	6	-	-	-	4	1	1	6	-	-	4	1	1	-	-	6	-	2	4	6

Saglimbene VM, Palmer SC, Ruospo M, Natale P, Craig JC, Strippoli GFM	2017	4	3	25	4	3	25	-	-	-	4	21	7	8	22	2	-	22	10	2	28	2	-	-	32	32
Schwenger EM, Tejani AM,Loewen PS	2015	3	-	6	4	-	5	-	-	-	-	4	5	1	2	6	2	4	3	2	2	5	3	1	5	9
Shakiba, B., Heidari, K., Jamali, A. and Afshar, K.	2014	1	-	3	-	-	4	-	-	-	2	1	1	-	-	4	-	-	4	-	4	-	-	-	4	4
Shan D, Wu HM, Yuan QY, Li J, Zhou RL, Liu GJ	2012	4	-	13	-	-	17	3	-	14	13	4	-	9	-	8	-	-	17	-	-	-	-	-	-	17
Sharma P, Blackburn RC, Parke CL, McCullough K, Marks A, Black C	2011	2	1	1	2	1	1	3	1	-	4	-	-	4	-	-	-	3	1	-	-	-	-	-	-	4
Srisubat A, (100) Potisat S, Lojanapiwat B, Setthawong V, Laopaiboon M	2014	3	-	2	-	-	5	-	-	5	-	5	-	5	-	-	-	2	3	-	-	-	-	-	-	5
(37) Strohmeier Y, Hodson EM, Willis NS, Webster AC, Craig JC	2014	12	3	12	6	3	18	-	-	-	19	7	1	13	13	1	4	11	12	-	27	-	17	9	1	27
(59Tian JH, (59) Ma B, Yang K, Liu Y, Tan J, Liu TX	2015	2	-	2	1	-	2	-	1	3	4	-	-	-	4	-	-	-	4	-	-	-	-	-	-	4
Vale L, Cody JD, Wallace SA, Daly C, Campbell MK, Grant AM, Khan I, MacLeod AM	2004		-	-	-	-	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1
Wang H, Song H, Yue J, Li J, Hou YB, Deng JL	2012	-	-	9	-	-	9	-	-	9	7	-	2	3	-	6	2	-	7	-	-	-	-	-	-	9
(191) Wilson CH, Rix DA, Manas DM	2013	-	-	-	4	1	2	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	7

Wilson CH, Sanni A, Rix DA, Soomro NA	2011	4	-	2	4	-	2	1	4	1	1	-	5	5	-	1	2	-	4	-	-	-	-	-	-	6
Worster AS, Bhanich Supapol W	2012	-	-	2	-	-	2	1	-	1	-	1	1	-	-	2	-	-	-	-	-	2	1	-	1	2
Wu HM, Tang JL, Cao L, Sha ZH, Li Y	2012	-	1	11	-	-	12	-	-	12	11	-	1	1	6	5	-	-	12	-	-	-	-	-	-	12
(31) Yang Q, Abudou M, Xie XS, Wu T	2014	2	-	6	2	-	6	-	-	-	7	1	-	2	-	6	3	1	4	2	1	5	1	-	7	8
Zhang HW, Lin ZX, Tung YS, Kwan H, Mok CK, Leung C, Chan LS	2014	2	3	17	-	4	18	-	19	3	18	1	3	2	-	20	-	2	20	-	-	-	-	-	-	22
Zhang (55) HW, Lin ZX, Xu C, Leung C, Chan LS	2014	1	2	19	-	2	20	-	-	-	22	-	-	-	-	22	3	4	15	-	22	-	-	-	22	22
(34) Zhang L, Zeng X, Fu P, Wu HM	2014	4	-	2	4	1	1	5	-	1	1	3	2	-	-	6	1	-	5	-	-	-	-	-	-	6
Webster AC, Wu S, Tallapragada K, Park MY, Chapman JR, Carr SJ	2017	6	2	23	4	2	25	23	6	2	25	3	3	18	9	4	4	7	20	-	-	-	-	-	-	31
(198) Webster AC, Taylor RRS, Chapman JR, Craig JC	2005	-	-	-	4	2	24	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	30
(146) Walters G, Willis NS, Craig JC	2015	18	-	13	15	-	16	-	-	-	25	4	2	21	5	5	14	9	8	26	-	5	-	1	30	31

Vecchio M, Navaneethan SD, Johnson DW, Lucisano G, Graziano G, Saglimbene V, Ruospo M, Querques M, Jannini EA, Strippoli GFM M, Querques M, Jannini EA, Strippoli GFM	2010	2	-	13	3	-	12	9	1	5	8	2	5	11	2	2	-	-	15	-	-	-	-	-	-	15
(32) Strippoli GFM, Bonifati C, Craig ME, Navaneethan SD, Craig JC	2006	-	-	-	10	-	39	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	49
Toh SL, Boswell-Ruys CL, Lee BSB, Simpson JM, Clezy KR	2017	2	-	1	2	-	1	-	-	-	-	3	-	-	3	-	3	-	-	3	-	-	3	-	-	3
Tunnicliе DJ, Palmer SC, Henderson L, Masson P, Craig JC, Tong A, Singh-Grewal D, Flanc RS, Roberts MA, Webster AC, Strippoli GFM	2018	25	4	44	18	3	53	-	-	-	52	3	19	36	35	3	35	29	10	14	48	12	9	-	65	74
Vecchio M, Bonerba B, Palmer SC, Craig JC, Ruospo M, Samuels JA,Molony DA, Schena FP,Strippoli GFM	2015	9	1	22	7	1	24	-	-	-	14	12	6	21	10	1	13	4	15	2	21	9	1		31	32
Wagner M, Earley AK, Webster AC, Schmid CH, Balk EM, Uhlig K	2015	2	2	19	2	2	19	-	-	-	9	7	7	15	6	2	3	9	11	2	21	-	2	-	21	23
Hahn D, Hodson EM, Fouque D	2018	13	-	10	11	-	12	-	-	-	13	5	5	8	13	2	10	-	13	-	22	1	19	-	4	23
Wang Y, Ivany JN, Perkovic V, Gallagher MP, Woodward M, Jardine MJ	2016	12	2	12	5	2	19	-	-	-	19	5	2	7	17	2	9	4	13	8	10	8	4	8	14	26
(169) Wu HM, Sun HJ, Wang F, Yang M, Dong BR, Liu GJ	2014	2	-	13	1	-	14	-	1	14	6	4	4	1	-	14	-	2	13	-	-	-	-	-	-	15
Karpe, K. M., Talaulikar, G. S. and Walters, G. D.	2017	27	3	53	25	4	54	-	-	-	54	7	22	55	8	20	9	55	19	1	81	1	4	24	55	83

Kennard AL, Walters GD, Jiang SH, Talaulikar GS	2017	6	1	1	3	3	2	-	-	-	1	6	1	3	4	1	2	6		1	5	2	1	5	2	8
Kim, K. H., Lee, M. S., Kim, T. H., Kang, J. W., Choi, T. Y. and Lee, J. D.	2016	6	5	15	-	12	14	-	-	-	6	6	14		1	25	22	1	3	-	18	8	5	-	-	26
Menting TP, Wever KE, Ozdemir-van Brunschot DMD, Van der Vliet DJA, Rovers MM, Warle MC	2017	23	2	4	16	-	13	-	-	-	11	2	16	19	5	5	17	5	7	16	1	12	10	4	15	29
Thompson ER, Hosgood SA, Nicholson ML, Wilson CH	2018	3	-	2	3	-	2	-	-	-	4	-	1	3	1	1	3	1	1	4	-	1	-	4	1	5
Hahn D, Esezobor CI, Elserafy N, Webster AC, Hodson EM	2017	3	-	11	2	-	12	-	-	-	8	4	2	6	8	-	2	8	4	1	10	3	13	-	1	14
Gopaluni S, Sherif M, Ahmadouk NA	2016	3	-	6	3	-	6	-	-	-	9	-	-	7	1	1	3	1	5	4	4	1	4	4	1	9
Lim CED, Ng RWC, Cheng NCL, Cigolini M, Kwok C, Brennan F	2016	1	1	-	1	-	1	-	-	-	1	1	-	-	2	-	-	1	1	-	2	-	-	-	2	2
Wan S, Roberts MA, Mount P	2016	5	-	1	3	-	3	-	-	-	-	-	-	1	-	5	-	2	4	5	-	1	-	1	5	6

CASE REPORT
Urooncology

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Nephrectomy and Tumor Thrombectomy with Concurrent Coronary Artery Bypass Graft for an HMB-45-Negative Giant Classical Renal Angiomyolipoma with Venous Extension

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Abstract

A 72-year-old woman was found to have a giant right renal mass (11.5 cm) suggestive of an angiomyolipoma (AML) on computed tomography imaging with atypical heterogeneity and grade III tumor thrombus extension into the inferior vena cava (IVC). Significant ischemic heart disease prompted a right radical nephrectomy on cardiopulmonary bypass with tumor thrombectomy and concurrent coronary artery bypass grafts. The patient recovered well and her histopathology confirmed a benign classical (non-epithelioid) renal AML, which was HMB-45 negative. AMLs are benign mesenchymal renal neoplasms, but surgical excision is indicated if malignant characteristics are present on imaging. HMB-45-negative AMLs are exceedingly rare, and to our knowledge, this is the first nephrectomy for an AML of this size and immunohistochemistry profile with IVC extension.

Keywords: Renal tumor, nephrectomy, angiomyolipoma

Introduction

Angiomyolipomas (AMLs) are the most common benign mesenchymal renal neoplasm, which are comprised of typical "triphasic" mature adipose tissue, smooth muscle, and dysmorphic blood vessels (1). Renal AMLs occur in 0.2-3.0% of the population, represent 1-2% of all resected renal masses, and have a female predominance (estimated 4:1) (1,2). They are associated with tuberous sclerosis complex (TSC), and rarely with lymphangioleiomyomatosis (LAM), although most occur sporadically (1). "Giant" AMLs are defined as >10 cm in size. Epithelioid variants (8% of all renal AMLs) are listed separately in the World Health Organization classification of renal tumors as they are characterized by aggressive behavior and are the only AMLs with malignant potential (2). For classical AMLs to have significant venous extension and malignant-appearing characteristics on imaging is extremely rare.

Case Report

A 72-year-old female patient was found to have incidental findings of cystic lung disease, and a large right renal mass (maximum diameter of 11.5 cm) on staging computed tomography (CT) during the workup of breast cancer, for which she had a left radical mastectomy. Her only other background was ischemic heart disease and hypertension. No prior imaging was available for comparison.

The CT appearance was consistent with an AML, and hypodensity indicated high-fat content. However, the mass demonstrated several atypical features, including heterogeneity with prominent central vessels from the right renal artery, grade III tumor thrombus extension into the inferior vena cava (IVC) causing >50% occlusion, and displacement of the right ureter, though without obstructive features (Figure 1). Thus, concern for malignancy prompted consideration of nephrectomy.

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The routine preoperative investigation included spirometry, carotid Doppler ultrasound, echocardiogram, and a CT, which was followed by a percutaneous coronary angiogram that confirm significant coronary artery disease. Following the multidisciplinary discussion with the urology and cardiothoracic teams, the patient proceeded to an open right radical nephrectomy with IVC thrombectomy and coronary artery bypass graft (CABG).

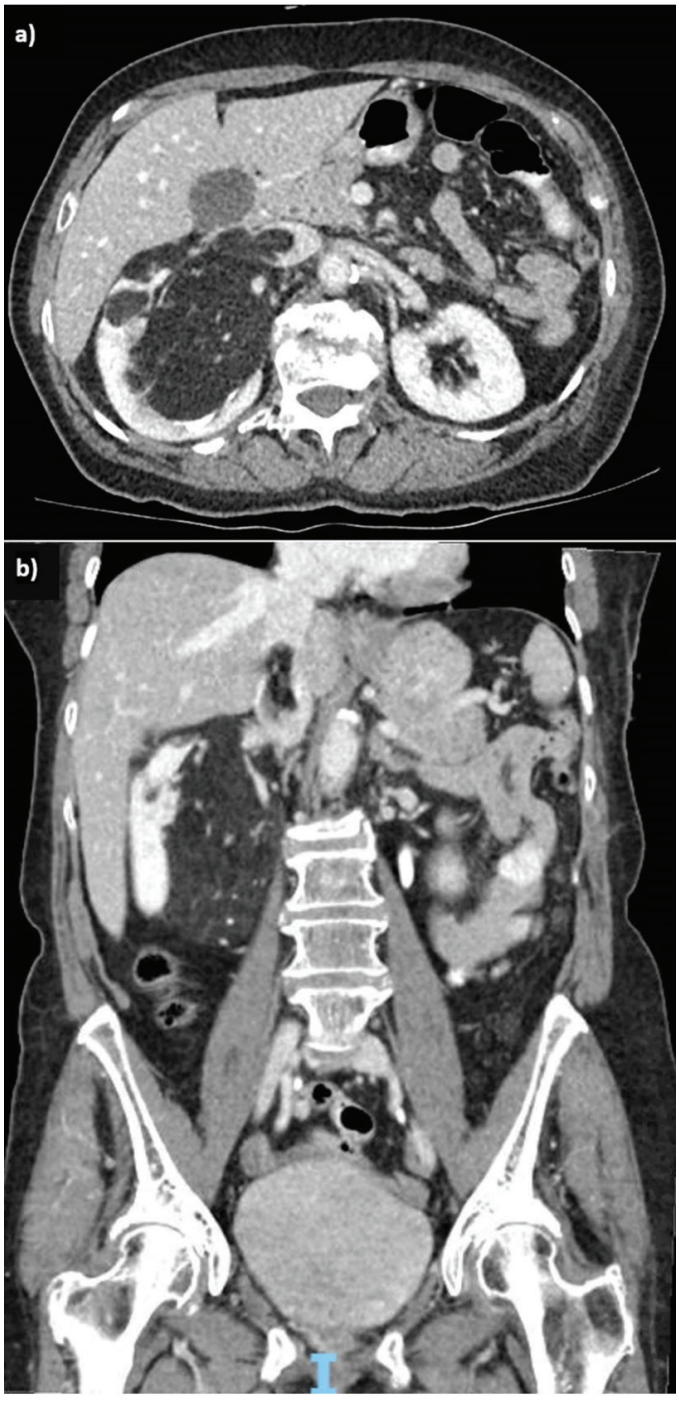

Figure 1. a) CT venous phase axial view demonstrating right renal tumor with venous extension, b) CT venous phase coronal view

CT: Computed tomography

A midline laparotomy was performed and the second part of the duodenum was kocherized, demonstrating an 11 cm right renal mass. The right renal artery was isolated in the inter-aortocaval region and ligated between vicryl ties. The liver was mobilized before the incision was extended to include sternotomy. The right saphenous vein was harvested and then the patient was placed on cardiopulmonary bypass, with deep hypothermic arrest, and CABG was completed by the cardiothoracic team (saphenous vein graft-obtuse marginal artery-right posterior descending artery). The aorta was clamped, the perfusion pump stopped, and the IVC was opened. The tumor thrombus was extended beyond the level of the hepatic veins (level III according to the Mayo staging system) but was not adherent and was milked back and removed; no reconstruction was required. The nephrectomy was then completed and the IVC was closed with 5-0 prolene. A drain was placed in the renal bed before closing in layers.

The total cardiopulmonary bypass time was 1 h and 39 min, with a cross-clamp time of 40 min and deep hypothermic arrest for 16 min at a temperature of 25 °C.

The patient was extubated on postoperative day 1 and recuperated well in the intensive care unit with only brief transaminitis and mild acute renal impairment, which improve as evidenced by a creatinine of 94 µmol/L and glomerular filtration rate of 52 mL/min/1.73 m^2 at discharge. She was discharged home after an uneventful inpatient recovery including a period of rehabilitation.

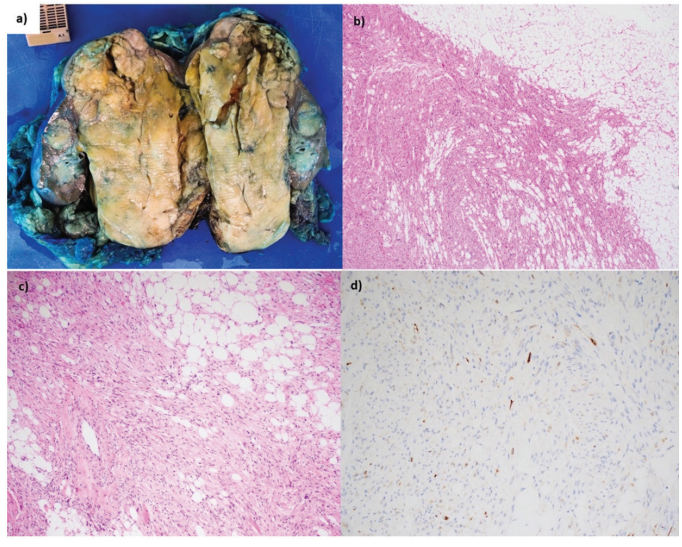

Figure 2. a) Macroscopic view of divided nephrectomy specimen exhibiting central pale yellow tumor, b) 40× magnified view of the lipomatous and myoid tumor (hematoxylin & eosin staining), c) 100× magnified view of the smooth muscle, fat, and vessel components of the tumor, d) HMB-45 staining

Pathological examination of the excised kidney demonstrated no extension into the perinephric fat (no lymph nodes were included). The tumor did not infiltrate the identified adrenal gland but invaded the renal sinus and the IVC. The tumor was composed primarily of mature adipose cells, as well as smooth muscle and blood vessels. No epithelioid component was identified, thus confirming a classical AML (Figure 2). The immunoprofile of the tumor was predominantly negative for HMB-45 and desmin, with positive focal cytoplasmic melan-A.

Cystic lung lesions that were seen on initial CT suggest the possibility of associated LAM in TSC. LAM is more typically diagnosed by the fourth decade and is characterized by desmin and HMB-45 positivity. Perioperative spirometry was superior to age-adjusted values, therefore no intervention had been deemed necessary preoperatively, and the patient was referred to the Respiratory team for further investigation.

Discussion

Giant AMLs with venous extension past the level of the hepatic veins pose a unique management dilemma. HMB-45 negative AMLs are exceedingly rare, and to our knowledge, this is the first nephrectomy for an AML of this size with IVC extension and immunohistochemistry profile.

Imaging is often adequate for diagnosis. AMLs tend to be highly echogenic on ultrasound, and the presence of macroscopic fat with a typical appearance on CT is considered diagnostic (although not pathognomonic). Magnetic resonance imaging, biopsy, or excision may be required for the diagnosis of the 5% of AMLs that are fat-poor, as carcinoma cannot otherwise be excluded (1-3). AMLs are the most common renal neoplasm associated with spontaneous perirenal hemorrhage, followed by renal cell carcinomas. Venous extension of AMLs is extremely atypical, but risk factors include right-sided tumors and large size (2,4). In very rare cases, intra-cardiac extension has also been reported (at least six case reports in the literature). Large AMLs with venous extension may include complications such as hypertension and its secondary complications and pulmonary fat embolism in some cases, which prompt the insertion of a preoperative IVC filter (2,4).

Several treatment options are available; if AMLs meet the criteria for intervention, a minimally invasive and nephron-sparing approach is preferred where feasible. Options include angioembolisation, partial (including laparoscopic or robotic approach) nephrectomy, and radiofrequency/cryo/microwave ablation (3,5). However, radical surgical intervention is indicated if malignancy is suspected (5). Complete excision may also be preferred in the presence of symptomatic hemorrhage, risk of aneurysmal rupture, and factors precluding minimally invasive options (5).

Histopathology in this case notably confirmed a classical rather than epithelioid AML, although interestingly with a rare HMB-45 negative immunoprofile. Epithelioid variants (8% of all AMLs) tend to be associated with TSC and are characterized by aggressive and malignant behavior (1).

Therefore, renal AMLs may necessitate excision if the risk of malignancy or size-related complications is suspected; in this case, a classical AML (HMB-45 negative) was found despite its invasive characteristics. A significant proportion of AMLs are associated with TSC, and this should always be considered. Thorough cardiopulmonary investigation in preoperative planning is vital to optimizing overall outcomes; in this case, precipitating a concurrent CABG procedure.

Ethics

Informed Consent: Informed consent was obtained.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: K.L., T.S., A.T., Design: K.L., Data Collection or Processing: K.L., N.S., Analysis or Interpretation: K.L., N.S., T.S., A.T., Literature Search: K.L., N.S., Writing: K.L., N.S.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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CASE REPORT
General Urology

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Radical Surgical Treatment of A Large Seminal Vesicle Cyst Causing Acute Urinary Retention in A Patient with Zinner Syndrome: A Case Report and Review of Literature

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Abstract

Herein, we report a case of a large and complex seminal vesicle cyst causing urinary retention in a young patient with left renal agenesis, psychotic disorder, and deep venous thrombosis. Abdominal computed tomography showed left renal agenesis with associated incipient hydronephrosis of the right renal unit. Furthermore, the whole pelvis was occupied by a large, heterodense cyst (116×113×107 mm), with several adherent and small cystic lesions (39×70 mm), compressing the posterior bladder wall. Open surgical approach was performed, including bilateral vesiculectomy with resection of the vas deferentia, since these structures were closely adhering to the cystic wall, and there was no clear surgical plane between them. A brief review of the literature on the main surgical options and postoperative outcomes was also undertaken.
Keywords: Zinner syndrome, seminal vesicle cyst, surgical treatment

Introduction

Zinner syndrome is a congenital anomaly comprising renal agenesis, seminal vesicle cysts, and ejaculatory duct obstruction (1,2). In symptomatic cases, patients may complain of lower urinary tract symptoms, including epididymitis and post-ejaculation pain. These symptoms are reported in approximately 30% of patients and usually related to the mass effect of the cyst during sexual activities (1-4). Conservative treatment is usually feasible for most cases; however, minimally invasive procedures may be considered as well (5,6). In challenging cases, surgical resection of the cyst by laparoscopic or open surgery may be necessary. Open surgery has been the preferred approach for many decades since good postoperative results have been reported for the preservation of genital structures. Moreover, a lower abdominal midline incision provides excellent tissue exposure, and it remains the most suitable approach in patients with large seminal vesicle cysts (4). Despite its advantages, open excision may be associated with injuries to pelvic organs such as the rectum, bladder, and pelvic ureter or formation of urinoma (7).

The current literature presented only a few cases of complex cystic lesions with invasion of surrounding structures, impeding fertility after surgical treatment. Herein, we present the radical surgical treatment of a unique case of complex, large, and infiltrative seminal vesicle cyst in a patient with Zinner syndrome, describing an unusual approach in a young, sexually active patient.

Case Reports

A 34-year-old Caucasian man, without children, was referred to our clinic in October 2020 for urodynamic testing following an episode of acute urinary retention. Before referral to our institution, the report of his previous urologist was unremarkable, except for noting a distended bladder.

The patient complained of dysuria and perineal discomfort for 2 weeks, without fever or any other symptoms. His left renal agenesis was diagnosed many years ago by computed tomography (CT). He also had experienced a few episodes of acute paranoid reaction, although he was presently in remission. The

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physical examination was unremarkable, and the vas deferens was bilaterally palpable. During a digital rectal examination, an irregular, partially fluctuant and partially solid mass was palpated in the prostatic fossa, measuring approximately 10 cm in diameter; the mass was painless and had no clear borders to the surrounding structures.

Laboratory analyses of the mass showed high levels of D-dimer (>1000 µg/L) and creatinine (124 µmol/L). Urinalysis and other blood tests were unremarkable. On further investigation, Doppler ultrasonography of the lower extremity revealed old thrombotic masses within the common and superficial right femoral veins, with signs of recanalization. Abdominal CT confirmed left renal agenesis associated with incipient hydronephrosis of the right renal unit, with multiple ureteral "kinking" (Figure 1a). Furthermore, the whole pelvis was occupied by a large, heterodense cyst (116×113×107 mm), with several adherent and small cystic lesions (39×70 mm), which resembled a morphologically degenerated left seminal vesicle (Figure 1b). The cyst had compressed the posterior bladder wall, and its volume was reduced significantly (Figure 1c). The right seminal vesicle could not be clearly detected (confined within the cystic lesion), and the prostate appeared normal, as it was clearly defined and homogenous.

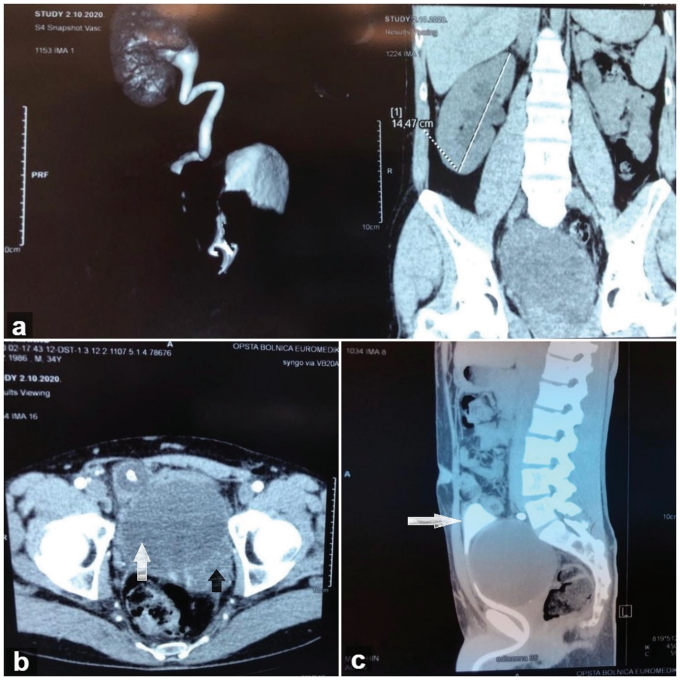

Figure 1. (a) Abdominal computed tomography with image reconstruction shows left renal agenesis and multiple right ureteral "kinkings" with incipient ureterohydronephrosis; (b) a large, heterodense (white arrow) and multifocal seminal vesicle cyst (black arrow), with anterior displacement of the bladder; (c) delayed phase CT urography reveals mass effect of seminal vesicle cysts with significant reduction of bladder capacity (white arrow). Contrast is seen within the bladder and urethral catheter

Surgical Treatment

An open surgical approach was initiated, as conservative treatment was not an option. The patient was positioned supine, and a lower midline incision was made to allow for an extraperitoneal approach. After separating the rectus muscle fibers, a large cystic mass was identified, bulging from the wound deep within the pelvis (Figure 2a). The cyst was multilocular in its distal part, with no clear plane of dissection to the left seminal vesicle. Moreover, the vas deferens was adherent to the cystic wall bilaterally, without a clear surgical plane between these structures (Figure 2b). Although the cyst was completely separated from the prostate, further dissection from the ipsilateral seminal vesicle and vas deferens was unsuccessful because of the close proximity of these structures to the cystic membrane. Therefore, bilateral vesiculectomy with resection of the vas deferentia was inevitable (Figure 2c). In the early postoperative period, the patient developed repeated urinary retention, which was treated with Foley catheterization. Cystoscopy revealed increased bladder capacity (>1500 mL), without voiding desire, even after instillation of 1500 mL of sterile saline. In the following month, urodynamic testing revealed normal detrusor function, with no involuntary voiding. The final pathology report confirmed the diagnosis of a complex cyst with nodular steatonecrosis, but no signs of malignancy.

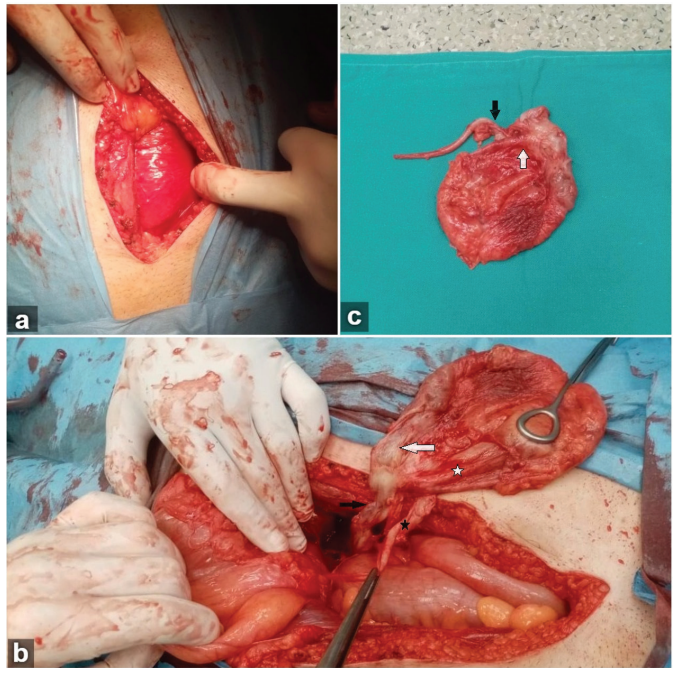

Figure 2. (a) A large cystic mass emerging from the deep pelvis; (b) a large cystic mass emerging from the left seminal vesicle (white arrow) with dilated vas deferens (black arrow); right seminal vesicle (white star) and distal vas (black star) adherent to the cystic wall; (c) resected specimen: left seminal vesicle and vas deferens (white arrow), together with right the vas deferens (black arrow). The right seminal vesicle is not seen on this image

Discussion

Herein, we present an unusual congenital anomaly, which in most instances, is difficult to detect. Only a few cases have been reported in the literature, and most cases presented during the sexually active period of life, usually in association with infertility (1,8). According to Tan et al. (2), seminal vesicle cysts can be categorized into four groups, ranging from simple cysts treated by a transrectal or transperineal approach to potentially malignant lesions, which are best treated by an open surgical resection. Our case report presents a complex cyst, which was larger than 10 cm, was multilocular and heterodense on CT, and required surgical treatment. In addition, the indication for surgery was compressive effect of the mass on the bladder (2).

Observation management may be implemented in asymptomatic or slightly symptomatic cases (8). Therefore, even symptomatic cases may benefit from conservative management with intense follow-up if the ejaculatory duct is unobstructed and the ipsilateral testis remains normal (9). Invasive treatment should be restricted to challenging cases or patients whose treatment fails using conservative measures (6). A conservative transrectal aspiration, although easy to perform, is associated with a high risk of recurrence and infection and should not be repeated if ineffective (1). Laparoscopic or robotic approaches are preferred, since they provide the best results in terms of blood loss and hospital stay (10,11).

However, in this case, we performed bilateral open vesiculectomy and resected the vas deferentia without prior clinical confirmation of infertility. However, this was the only treatment option available, as a large, multilocular cystic lesion had involved both seminal vesicles, and a clear dissection plane was not possible. Moreover, this patient had a history of psychiatric disorders, which presented as an additional risk factor for infertility in the preoperative setting. Thus, we determined that partial vesiculectomy or other conservative approaches should not be considered in patients with large infiltrative cysts and unproven fertility, especially if any concern exists regarding the oncological safety and completeness of cystic resection. Finally, assisted reproduction may be offered to the patient with preserved testicular function.

This case points out the necessity of radical surgery in young male patients with Zinner syndrome accompanied by a large, complex, infiltrative seminal vesicle cyst despite its detrimental effect on potential fertility.

Ethics

Informed Consent: Patient gave her consent prior to the creation of this case report.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: M.V., D.D., S.D., Concept: M.V., D.D., S.D., Design: M.V., D.D., S.D., Data Collection or Processing: M.V., D.D., S.D., Analysis or Interpretation: M.V., D.D., S.D., Literature Search: M.V., D.D., S.D., Writing: M.V., D.D., S.D.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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CASE REPORT
Endourology

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Journal of Urological Surgery, 2021;8(4):294-296

Video Endoscopic Inguinal Lymphadenectomy in Post Saphenous Vein Graft Harvest (Coronary Artery Bypass) Status

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Abstract

Video endoscopic inguinal lymphadenectomy (VEIL), either by the classical or robot-assisted approach, is performed to manage inguinal lymph nodes in penile carcinoma. Coronary artery bypass graft (CABG) is common in the age group affected by penile carcinoma. Saphenous vein graft harvesting (SVGH) is done for CABG and may be associated with scarred subcutaneous planes hindering VEIL. A 65-year-old male was diagnosed with T2 high-grade penile carcinoma. He had undergone CABG eight years ago. He underwent robot-assisted VEIL. The initial subcutaneous space beneath Camper's fascia was created by finger dissection and further developed by balloon inflation. A small space was made with difficulty to insert the ports. Monopolar shears were used to make a sharp dissection to develop the subcutaneous plane, and scarring was present close to Camper's fascia. Multiple small venules were visible and managed with bipolar diathermy. The rest of the procedure was performed as usual. The console time and estimated blood loss were higher in the SVGH limb. The drain output was higher on the SVGH side. Both sides had six negative lymph nodes. Minimal skin duskiness was noted on the ipsilateral side, which healed without any sequelae. This is the first documented report of robot-assisted VEIL, post saphenous vein harvest for CABG. It is associated with a slightly longer procedure time and more blood loss, but a satisfactory oncological outcome. This report highlights the feasibility and safety of robot-assisted VEIL in post-CABG saphenous vein harvest status.
Keywords: Penile carcinoma, video endoscopic inguinal lymphadenectomy, coronary artery bypass graft

Introduction

The prognosis of penile carcinoma is dependent to a fair extent on lymph node management. Open approach by either classical Dressler's or modified Catalona's inguinal lymphadenectomy is the standard treatment. However, inguinal lymphadenectomy is associated with considerable morbidity, especially skin loss and lymphedema (1). Video endoscopic inguinal lymphadenectomy (VEIL) helps to mitigate some complications (2). Saphenous vein graft harvest (SVGH) is usually done for coronary artery bypass graft (CABG) (3). This involves dissection in the subcutaneous space where we dissect for VEIL. With CABG being increasingly performed, a patient who had CABG presenting for VEIL is not uncommon. The potential problems caused by the previous SVGH in performing VEIL are unknown.

Case Report

A 65-year-old male was diagnosed with T2 high-grade penile carcinoma and underwent a partial penectomy. Magnetic resonance imaging did not reveal any significant lymphadenopathy. He had undergone CABG eight years ago with SVGH in his right lower limb (Figure 1). He was scheduled for an inguinal lymphadenectomy one month after penectomy. He underwent robot-assisted VEIL.

Under general anesthesia, he was placed in the supine position, with his lower limb abducted and externally rotated (frog-leg position). The landmarks were marked initially, and a 1.5 cm incision was made 3 cm distal to the apex of the femoral triangle. The initial subcutaneous space beneath Camper's fascia was created by finger dissection and further developed by balloon inflation (Figure 2a). A small space was made with difficulty, especially medially, to insert the four ports. The robot was docked from the left shoulder aspect.

Monopolar shears were used to make a sharp dissection to develop the plane below Camper's fascia. Multiple small venules were visible and managed with bipolar diathermy (Figure 2b). The dissection was extended until the predetermined lateral and medial borders of dissection as per Dressler's quadrilateral were

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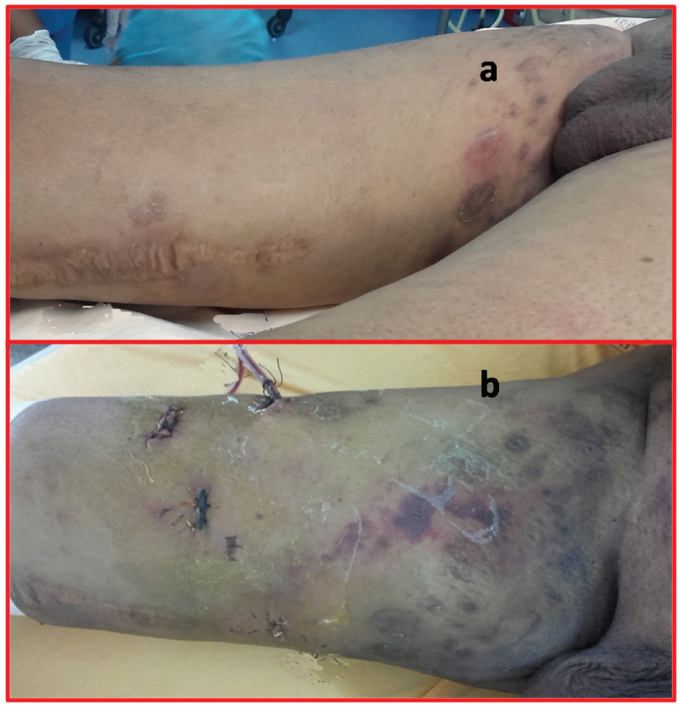

Figure 1. a) Preoperative image, b) Postoperative image

reached. Superiorly fascial dissection was done till the external oblique aponeurosis was visualized. The fibrofatty tissue was then dissected off the muscle fascia in a distal to proximal manner. This plane was relatively well preserved, as expected (Figure 2c). A small remnant of the saphenous vein of about 5 cm was identified and it was traced proximally until the femoral vein. Fibrofatty tissues around the femoral vessels were dissected out. The specimen was removed through the camera port after placing it in a retrieval bag. The procedure was repeated on the left side similarly, with the robot docked on the right side.

The console time and estimated blood loss were 140 minutes and 150 mL on the right (SVGH) side and 110 minutes and 50 mL on the left side. He was mobilized during the day with elastic compression stockings. His drain output was more on the SVH side and for a longer duration. His drain was removed on postoperative day (POD) 12 on the SVGH side compared with POD5 on the other side. Six lymph nodes were retrieved on both sides, and all were negative for the tumor. Minimal skin duskiness was noted on the SVGH side, which healed without any sequelae. Bilateral minimal lymphedema was noted at one-year follow-up.

Discussion

VEIL, either classical or robot-assisted, is preferred over open if expertise is available. Wound-related complications are decreased using this approach (2). An essential step in VEIL is the development of tissue planes. Similar to retroperitoneal

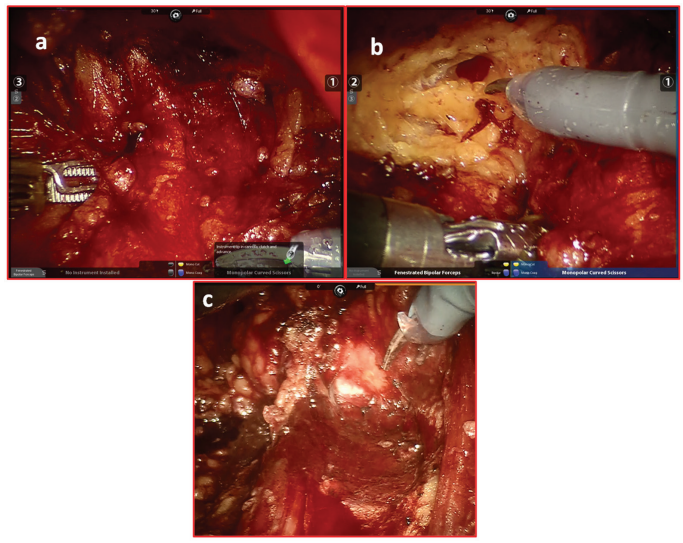

Figure 2. a) Initial view after balloon dilatation, b) Plane developed by sharp dissection with endoshears with coagulation of bleeders, c) Well preserved deep planes

planes during retroperitoneoscopy, previous surgeries in those areas and resultant scars might hinder tissue space development (4,5). SVGH is performed during CABG (3). Now, it is common to have patients who necessitate inguinal lymphadenectomy post-CABG. SVGH is done with either a single contiguous incision or multiple small incisions. There have been no previous reports on VEIL among those with previous SVH.

We experienced some difficulty in developing the tissue planes, especially on the medial aspect. After placing the initial ports and minimal dissection, additional tissue planes needed sharp dissections with monopolar shears. Usually, simple balloon dilatation will be sufficient to create tissue spaces. However, due to the fibrous scarring in these tissue spaces, sharp dissection was needed. Moreover, bleeding was comparatively more do the dilated small venules. Fibrotic tissue planes may cause flap thinning, resulting in later necrosis. The fascial planes near the muscles were relatively well preserved. The console time was more on the SVGH side due to more fibrous tissues and more bleeding encountered from small venules.

Saphenous vein preservation is one of the components of Catalona's modification to prevent lymphedema (1). However, we did not find increased lymphedema on the side of SVGH. Skin necrosis was also not seen.

Open inguinal lumphadenectomy is associated with high morbidity and complication rates of up to 50%. VEIL has a better complication profile, especially regarding skin flap necrosis. The operative time, lymph node yield, and blood loss were comparable to the open lymphadenectomy in a large series (6).

This is the first report of robot-assisted VEIL in a patient who has undergone previous SVGH. It emphasizes that it is oncologically

safe and technically feasible, though the procedure incurs more blood loss and increased console time.

Robot-assisted VEIL is a feasible and oncologically safe approach even in patients who have undergone SVGH for CABG.

Ethics

Informed Consent: This case report is presented after obtaining informed consent from the patient.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: A.M., R.C., Concept: A.M., Design: A.M., Data Collection or Processing: A.M., R.C., Analysis or Interpretation: A.M., Literature Search: A.M., R.C., Writing: A.M.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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CASE REPORT
Urooncology

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Journal of Urological Surgery, 2021;8(4):297-299

Penile Metastatic Disease Presenting as Malignant Priapism: A Case Report

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Abstract

Penile metastatic disease is an uncommon condition with a dismal prognosis. Reported herein is a case of metachronous penile metastasis from bladder urothelial carcinoma, which presents as malignant priapism without tumoral masses. The authors explain the imaging and pathologic findings that led to its diagnosis and staging.
Keywords: Penile metastasis, malignant priapism, bladder urothelial carcinoma, tumoral emboli

Introduction

Penile metastasis is a relatively rare condition, with only approximately 500 cases published since first reported in 1870 (1). The most common primary sites associated with metastatic penile disease include urogenital (70%) and gastrointestinal tumors (21%) (2), especially of pelvic origin.

Clinical manifestations vary widely, including penile nodules or masses, skin lesions, malignant priapism, and less commonly, hematuria or lower urinary tract symptoms. These lesions are often associated with disseminated disease and predict a poor prognosis (3).

Reported herein is a case of metachronous penile metastasis from bladder urothelial carcinoma, which presents as priapism.

Case Reports

Reported herein is a case of a 79-year-old male, who presented to the emergency department of our institution with persistent vomiting due to intestinal obstruction, secondary to adhesions. Additionally, the patient reported a 2-week history of painful and inconstant erection that did not respond to medical therapy.

The patient was diagnosed with prostatic adenocarcinoma (Gleason 6) 15 years ago. Three years before the admission, the simultaneous transurethral resection of the prostate and bladder showed not only prostate tumoral persistence but also a papillary urothelial carcinoma. Radical cystoprostatectomy was performed. The pathological evaluation of the specimen revealed a high-grade invasive bladder urothelial carcinoma-pT4aN2R0 and concomitant prostate acinar adenocarcinoma, Gleason 9 (5+4)-pT3aN0R1.

On physical examination, despite abdominal pain, a rigid penile shaft was found, with tenderness on palpation and no significant hypoesthesia. No palpable nodules and no overlying penile skin lesions were found.

The ultrasound revealed an edematous thickening of the overlying skin and a few areas of heterogeneous echotexture in both corpora cavernosa. Color Doppler evaluation was unremarkable.

The subsequent magnetic resonant evaluation revealed patchy ill-defined areas of decreased T2-signal intensity along with both corpora cavernosa, which lacked enhancement after gadolinium administration, thus suspicious for tumoral invasion/microthrombosis (Figure 1).

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The patient underwent a biopsy of the left corpus cavernosum that showed tumoral emboli from bladder urothelial carcinoma and thrombosis in the cavernosal spaces, which was contiguous with the neoplasia (Figure 2).

Multiple diffuse skeletal metastases were found on bone scintigraphy.

The case was presented to the multidisciplinary uro-oncology team of our institution that suggested palliative immunotherapy with pembrolizumab.

One month after the above-mentioned events, the patient died from tumor lysis syndrome.

Discussion

Penile metastatic cancer is an uncommon disease with a dismal prognosis.

Most cases arise from the genitourinary origin, with bladder cancer equaling prostate cancer (~30% of cases) according to Zhang et al. (2) comprehensive review.

Despite rich penile blood supply, the mechanism that can explain the rarity of this secondary involvement is unclearly known. A few mechanisms have been hypothesized, which include direct tumor extension, vascular spread, or iatrogenic implantation (4,5).

The most common scenario according to the literature on its clinical presentation is a tumoral mass appearance, usually in the shaft (6). Malignant priapism is reported in 20-53% of cases (4); therefore, the appearance of this sign in patients with a history of malignancy, especially of pelvic origin, should warrant the exclusion of a metastatic cause. However, unlike our case, priapism is rarely the first manifestation of disease with no accompanying tumoral mass. This phenomenon is mainly caused by tumoral invasion of the corpora cavernosa, vein occlusion, or interference with neural pathways, which predicts an even poorer prognosis (3).

To evaluate patients who are suspected of penile metastasis, a histopathologic examination is needed for a definitive diagnosis. Many imaging modalities play a role in the management and staging evaluation of these cases. Ultrasound is helpful in the early diagnosis of masses and Doppler ultrasonography in differentiating high-flow from low-flow priapism. Magnetic resonance imaging provides superior soft-tissue contrast and spatial resolution and therefore, can more accurately evaluate tumor size and anatomic structures invasion. Computed tomography (CT) and positron emission tomography/CT are relevant in the assessment of nodal and distant metastasis.

The differential diagnosis includes primary penile lesions (malignant, premalignant, or inflammatory) and in cases of priapism, other causes should be excluded, such as hematologic, trauma, iatrogenic, or drug-induced.

Treatment depends on the overall performance status but is frequently palliative, for symptom relief. Some patients may

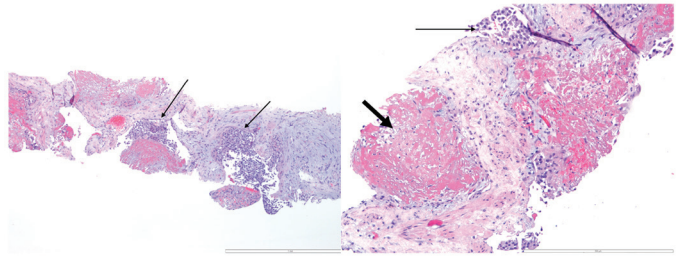

Figure 2. Corpus cavernosum biopsy with tumoral emboli from bladder urothelial carcinoma (thin arrows) and thrombosis in the cavernosal spaces that is contiguous with the neoplasia (thick arrow)

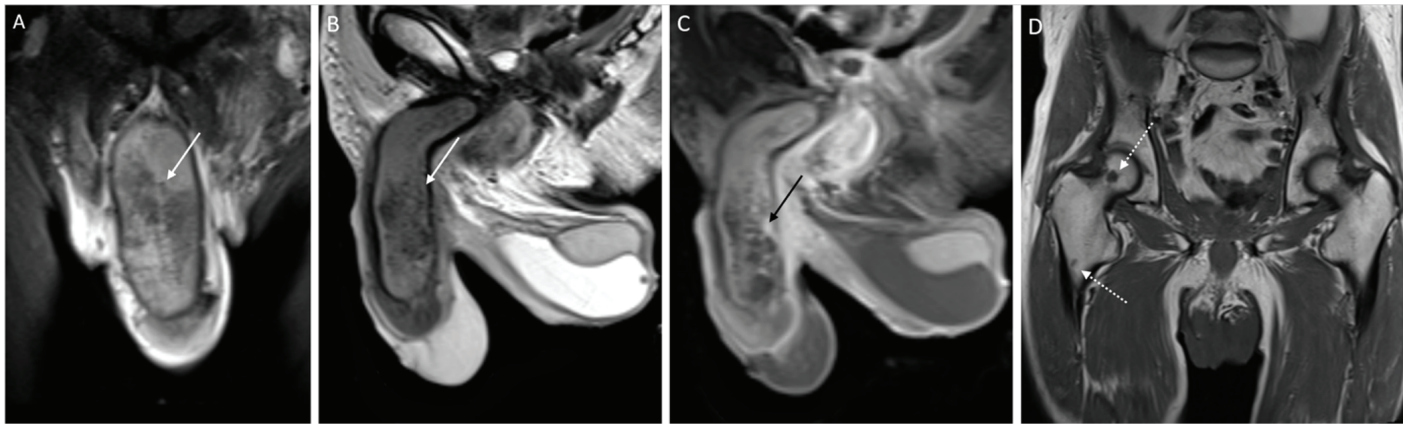

Figure 1. Penile magnetic resonance. Coronal and Sagittal T2-weighted images (A, B) showing patchy ill-defined areas of decreased signal intensity along both corpora cavernosa (white arrows). Diffuse thickening and increased signal intensity of the skin and the areolar tissue are also seen, which reflect edema. Sagittal T1-weighted image after the administration of gadolinium (C) revealing hypoenhancing areas in the mid and distal portions of the left corpus cavernosum (black arrow), consistent with hypovascularity due to tumoral invasion with associated microthrombosis. A moderate-size left hydrocele is also evident. (D) coronal T1-weighted image depicts two hypointense nodules in the right femur (dotted arrows), which is suspicious for bone metastases

benefit from trials of chemotherapy and if the tumor expresses programmed cell death ligand 1, as in this case report, the patient can be allocated to an ongoing multicentric clinical trial with pembrolizumab.

Secondary involvement of the penis typically indicates systemic dissemination and, consequently, a poor prognosis. A recent systematic review by Cocci et al. (3), based on published cases, found a mean survival time of 14.5 months for these patients.

Ethics

Informed Consent: Written informed patient consent for publication has been obtained.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: S.C.D., P.A.M., D.S., R.P., Concept: M.C.D.S., A.T.V., S.C.D., R.P., A.J.M., Design: M.C.D.S., A.T.V., D.S., A.J.M., Data Collection or Processing: M.C.D.S., S.C.D., R.P., Analysis or Interpretation: M.C.D.S., S.C.D., R.P., Literature Search: M.C.D.S., D.S., Writing: M.C.D.S., A.T.V., S.C.D., P.A.M., D.S., R.P., A.J.M.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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CASE REPORT
General Urology

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Journal of Urological Surgery, 2021;8(4):300-302

Stones in A Congenital Ureteric Diverticulum

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Abstract

True ureteral diverticula are rare, may be found incidentally, or form after urinary sepsis, stones, or obstruction. Stone formation is an uncommon complication because of urine stasis or recurrent infections. Radiological opacities suggestive of a stone in an extra-anatomical site of the ureter should raise the suspicion of a ureteric diverticulum. Although a congenital ureteric diverticulum is believed to be formed because of an abortive ureteric bud, its anatomy could be completely different from that of a duplex ureter. The presence of complications requires diverticulectomy with or without reconstruction of the ureteric defect.

Keywords: Ureteral diverticulum, calculi, ureteric duplication, urinary stones

Introduction

A true ureteral diverticulum is a rare condition. It may be an incidental finding on imaging or associated with symptoms such as hematuria, dysuria, and pain (1). Complications of ureteric diverticula include infection, stones, and obstruction (2,3). A case of a transitional cell carcinoma developing in a ureteral diverticulum has also been reported (4). Herein, we report a patient with a long pelvic ureteral diverticulum containing several calculi.

Case Reports

A 39-year-old otherwise healthy man attended the urology clinic for evaluation of persistent dysuria. He had been having dysuria for six months, without any other lower urinary tract symptoms, fever, or ureteric colic. His urine analysis showed pyuria, and urine cultures grew coliform bacteria on three occasions. He had been treated with antibiotics according to the sensitivity pattern. His urinary tract ultrasonography was normal, but X-ray kidney, ureter, and bladder (KUB) showed a hyperdense opacity in the pelvis medial to the normal pathway of the left ureter measuring 1 cm × 1.5 cm (Figure 1a). Computed tomography (CT) urogram showed a possible diverticulum arising from the left side of the distal ureter extending posteromedio-inferiorly and containing two calculi (Figures 1b-d). The patient underwent open surgery, and the left lower ureter was accessed extraperitoneally. The diverticulum was 10 cm long, and the origin was 2.5 cm proximal to the vesicoureteric junction. It was extending posteriorly in between the pelvic muscles toward the sacrum and lateral aspect of the mid-rectum. The diverticulum was mobilized fully and removed after ligation at the root (Figure 2a). His postoperative recovery was uneventful. The histopathological examination of the excised diverticulum showed flattened urothelium with atrophy of the muscularis propria of the wall (Figure 2b). Few foci were showing signs of inflammation. The infrared spectroscopic analysis revealed that the stone was composed of calcium oxalate monohydrate and calcium oxalate dihydrate crystals. After three months of follow-up, he was symptom-free, and his urinary tract ultrasonography showed normal upper urinary tracts. Informed written consent for publication of the text and accompanying images was obtained from the patient.

Discussion

Knowledge on ureteral diverticula is based on case reports and case series because of its rare occurrence. Ureteral diverticula are divided into two types (2). The congenital form usually represents the abortive duplication of the ureter, while the

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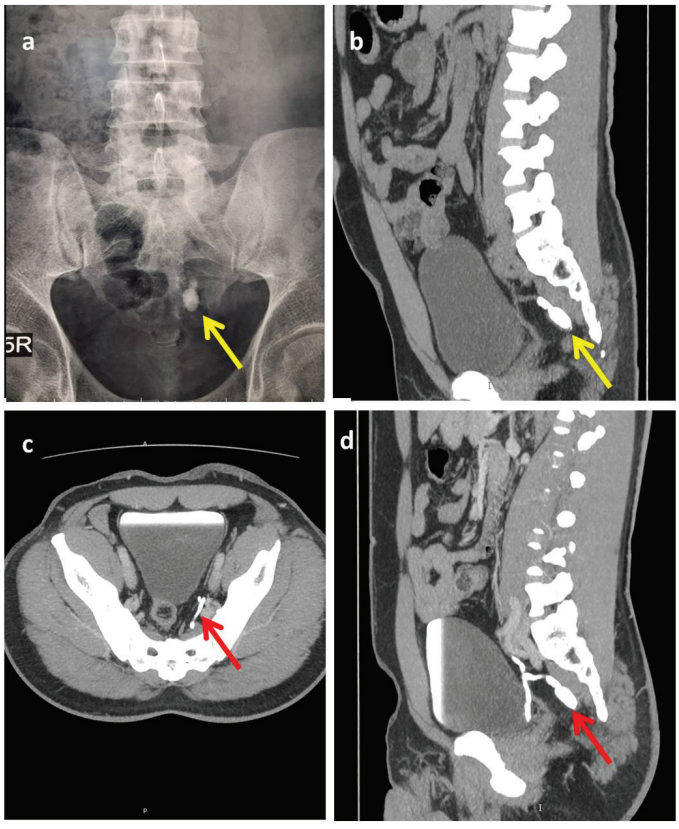

Figure 1. (a) X-ray kidney, ureter, and bladder (KUB), (b) non-contrast computed tomography (CT) KUB showing stones (yellow arrow), (c) CT urogram sagittal view, and (d) axial view showing the diverticulum (red arrow)

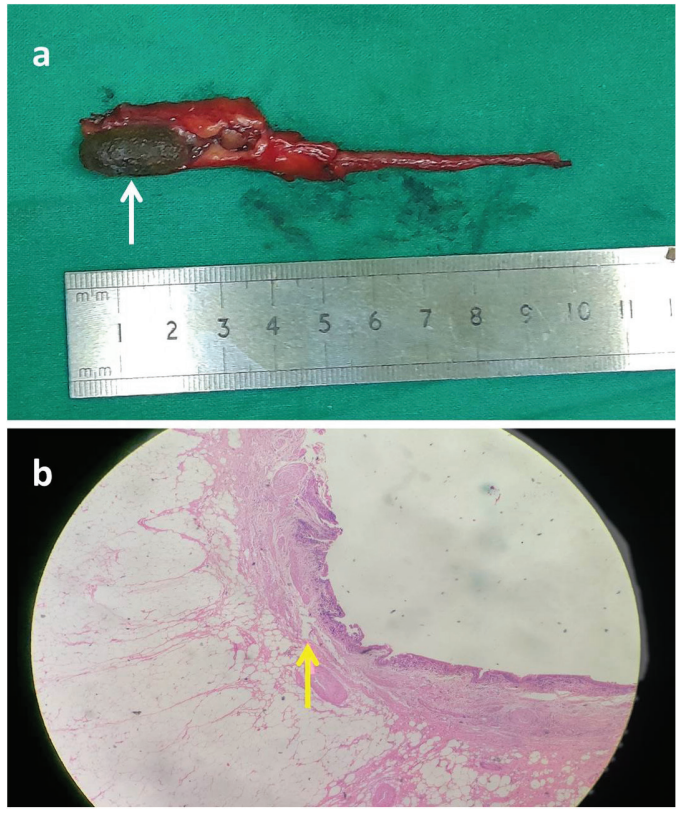

Figure 2. (a) Resected specimen with calculi (white arrow) and (b) microscopic view of the diverticular wall (hematoxylin and eosin staining, ×100)

acquired form can be subdivided into traction or pulsion types. The pulsing type is usually caused by a distal obstructing stone, and there is an associated proximal hydroureter (5). It may occur after the ureteric wall is weakened by stones, infections, shock wave lithotripsy, or ureteric surgery (5,6). Based on the histopathological findings by Kretschmer (7), the congenital type was described as a blind-ending duplication of ureteric buds. On histopathological evaluation, the diverticulum of this patient most likely represented an abortive ureteral duplication because of its long tubular nature, and all layers of the ureteric wall were preserved. Pulsion or traction types of diverticula are much shorter with a wide neck.

Few previous reports have described the formation of calculi inside the diverticulum (4,5). This may have been due to stasis of the refluxing urine inside the diverticulum or recurrent infections. In the present case, the postero-inferior direction of the distal part of the diverticulum may have led to dependency and urine stasis (Figures 2c and 2d). The stone formation can lead to both congenital and acquired diverticula. CT urogram can identify the exact anatomical relations of the diverticulum to avoid inadvertent damage to nearby vital structures and associated anomalies of the urinary tract. This is more relevant in diverticula with stones, as the anatomical direction of the diverticulum could be different from the expected normal course of a duplex ureter, leading to dependent segments at risk of stasis. The reasons for the unusual anatomy of congenital ureteric diverticula when compared with duplex ureters are unclear. The origin of the diverticulum at a lower level of the ureter, its length, and stone formation in the blind end of the diverticulum were unique features of the present case.

Diverticula are treated depending on the symptoms and associated complications. A conservative approach can be considered in asymptomatic cases and cases diagnosed incidentally on imaging (1). Depending on the configuration of the diverticulum and associated ureteric obstruction, diverticulectomy with or without reconstruction of the ureter has been used as treatment (2,6). This patient underwent ligation and resection of the diverticulum at its junction with the ureter, without the need for reconstruction as the neck was narrow. Resection of the diverticula can be performed laparoscopically if the anatomy of the diverticulum makes it feasible (8).

In conclusion, radiologically visible opacities suggestive of stones located away from the normal course of the ureter can be calculi located in a ureteric diverticulum. These calculi require diverticulectomy with or without ureteric reconstruction. Although congenital ureteric diverticula are formed following an abortive ureteric bud, its anatomy could be completely different

from that of a duplex ureter. This should be appreciated during surgery to avoid potential complications.

Ethics

Informed Consent: Informed written consent for publication of the text and accompanying images was obtained from the patient.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: O.B., A.A., Design: O.B., Data Collection or Processing: O.B., H.S., M.W., M.A., S.T., A.A., Literature Search: O.B., H.S., M.W., M.A., A.A., Writing: O.B., S.T.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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CASE REPORT
General Urology

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Journal of Urological Surgery, 2021;8(4):303-305

Masquerading as A Stone: An Unusual Cause of Chronic Ureteric Obstruction

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Abstract

Amyloidosis is a group of disorders characterized by the extracellular deposition of amorphous, misfolded proteins. Primary localized bladder amyloidosis is a rare form of the disease that usually presents with macroscopic hematuria, irritative lower urinary tract symptoms, or a bladder mass on imaging. Presented herein is a case of a 76-year-old female who presented with sepsis, distal ureteric calculus, and chronic ureteric obstruction without the classical symptoms of bladder amyloidosis. Cystoscopic resection of thickened bladder wall was positive for amyloid deposition with no signs of malignancy.

Keywords: Urinary bladder neoplasms, amyloid, ureteral obstruction

Introduction

Amyloidosis is a benign group of disorders, characterized by extracellular deposition of amorphous, misfolded proteins, known as amyloid fibrils that may have localized or systemic manifestations (1-3). Primary localized bladder amyloidosis (PLBA) is a rare form of the disease, with only a few hundred cases reported in the literature (4). PLBA most commonly presents with painless, macroscopic hematuria, or irritative lower urinary tract symptoms and may mimic bladder carcinoma radiologically and cystoscopically (2,4,5). Radiological findings are generally indeterminate, demonstrating bladder thickening or a discrete mass (2,6). The cystoscopic appearance includes ulcerated lesions, yellow plaques, or irregular thickening, which may suggest malignancy or cystitis (2,5,6). Therefore, PLBA diagnosis relies on histopathological analysis. Congo red stains deposit a salmon pink color, which shows apple-green birefringence on visualization under polarized light (2,5).

Case Report

Presented herein is a case of a 76-year-old female who presented with a 1-week history of generalized abdominal pain and distension. Her past medical history was significant for hypertension and the use of Chinese and herbal medicines. She was a non-smoker. The initial assessment noted rapid atrial fibrillation with a creatinine of 209 umol/L (45-90), leukocyte count of 17.4×10^9 (4-10), and a C-reactive protein of 516 mg/L (<5). A non-contrast computed tomography (CT) scan of the abdomen and pelvis demonstrated a grossly dilated left renal collecting system and ureter (Figure 1). Total cortical loss of the left kidney and a calcific density that measures 6×10 mm was noted in the region of the distal left ureter. The bladder wall was thickened. A left-sided percutaneous nephrostomy was inserted and purulent fluid was drained. Recovery was complicated by post-procedural *Escherichia coli* sepsis with rapid atrial fibrillation and hypotension, requiring admission to the intensive care unit for vasopressor support. Her inflammatory markers gradually normalized and creatinine decreased to 96

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umol/L. She was discharged after a short period of rehabilitation with the nephrostomy tube *in situ*.

A cystoscopy was performed approximately 3 weeks after discharge; the bladder mucosa was abnormal, thickened, and erythematous, suggesting possible high-grade malignancy; however, no papillary lesions or discrete masses were found. The ureteric orifice was not visible before resection. Histopathological analysis of resected mucosa demonstrated extensive, amorphous, and extracellular material, which was positively stained with crystal violet and congo red. On the latter stain, characteristic apple-green birefringence was detected with polarized light, consistent with amyloid deposition (Figure 2). No evidence of dysplasia or malignancy was found. A repeat cystoscopy was successfully performed following the biopsy results and laser lithotripsy of the left distal ureteric calculus. A retrograde ureteric stent was inserted, and then the nephrostomy tube was clamped and subsequently removed. A few months after the removal of the left ureteric stent, the patient was re-referred with worsening renal function. The repeat CT imaging demonstrated bilateral hydronephrosis without ureteric calculi or other causes of obstruction. A cystoscopy demonstrated a similar appearance. A left-sided ureteric stent was inserted; however, despite resection, the right ureteric orifice was not visible. A right-sided percutaneous nephrostomy was then inserted and subsequently removed following the antegrade stent placement. The patient will undergo monitoring and follow-up for ongoing cystoscopic surveillance and ureteric stent exchanges.

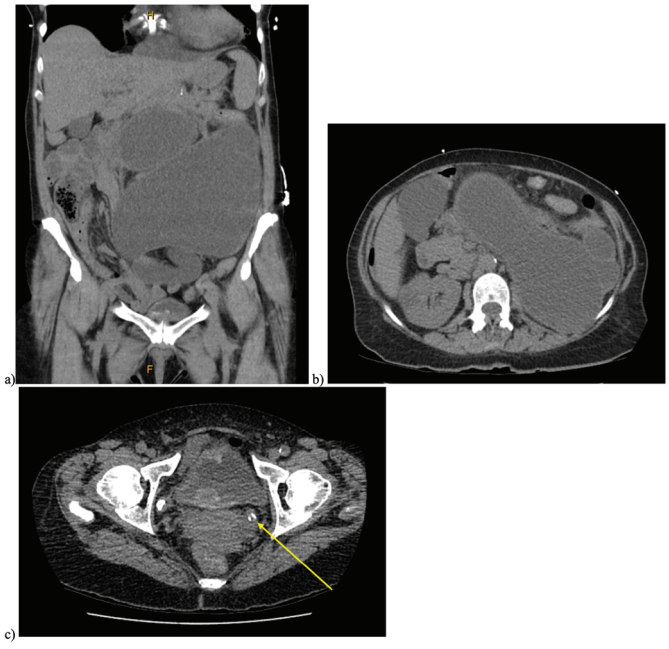

Figure 1. Coronal (a) and axial (b and c) computed tomography images demonstrating massive left-sided hydronephrosis with left renal cortical atrophy, distal left ureteric calculus (yellow arrow), and irregularly thickened bladder wall

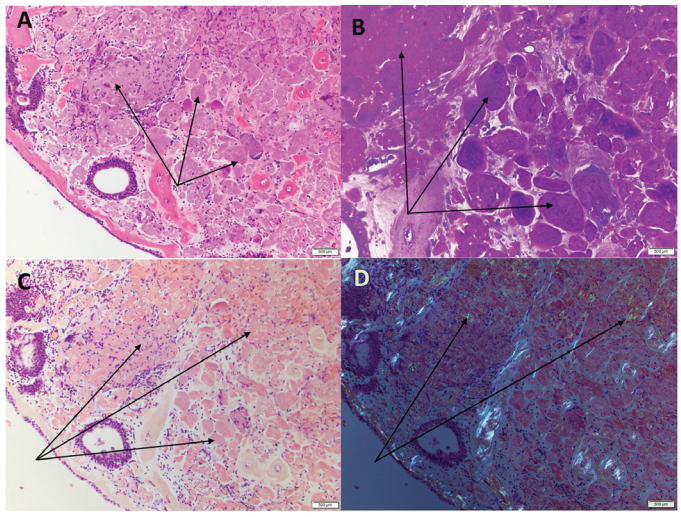

Figure 2. Microscopic bladder biopsy histopathological images at ×100 magnification. Extensive, extracellular, and homogenous amorphous deposits as seen on hematoxylin and eosin stain (A), which was positively stained with crystal violet (B) and confirmed as amyloid deposition with congo red stain (C) and apple-green birefringence under polarized light (D)

Discussion

The present case is unusual and interesting for several reasons. The patient did not present with the classical symptoms of lower urinary tract symptoms or macroscopic hematuria. She had no signs or symptoms suggestive of systemic amyloidosis. Our patient presented with sepsis due to obstructive uropathy. The PLBA possibly obstructed the left ureteric orifice gradually with subsequent development of hydronephrosis, renal cortical atrophy, and infection.

PLBA has an unknown etiology, but chronic inflammation is suggested to be responsible (2). The mechanism is thought to involve infiltration of the lymphoplasmacytic cells and secretion of abnormal light chain immunoglobulin, which lead to deposition of amyloid fibrils in the bladder mucosa (2,3). An underlying plasma cell neoplasm should be excluded. One possible mechanism of chronic inflammation is the development of a ureteric calculus with subsequent obstructive nephropathy, infection, and development of PLBA. However, this is considered less likely in our case due to the absence of previous renal colic and subsequent development of similar right ureteric obstruction without ureteric calculus.

The main treatment of PLBA is transurethral resection; however, cystectomy or medical therapy have also been used (3,5,7). Given that recurrence rates are as high as 50%, annual cystoscopic surveillance is recommended (3,7).

In conclusion, this is a very unusual case of PLBA, presenting with infection and chronic ureteric obstruction without lower urinary tract symptoms or macroscopic hematuria. PLBA often mimics bladder cancer but has a benign clinical course. Resection

with cystoscopic surveillance is the current recommended management.

Ethics

Informed Consent: Informed consent was obtained.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: M.H., F.M., P.M., Concept: M.H., P.M., Design: O.V.D.B.B., Data Collection or Processing: O.V.D.B.B., L.V., Analysis or Interpretation: O.V.D.B.B., L.V., M.H., F.M., Literature Search: O.V.D.B.B., L.V., Writing: O.V.D.B.B., L.V., M.H., F.M., P.M.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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CASE REPORT
Andrology

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Journal of Urological Surgery, 2021;8(4):306-309

The Impact of Coronavirus Disease-2019 on Men with Primary Infertility: Case Report

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Abstract

At present, the world is faced with the coronavirus disease-2019 (COVID-19) threat caused by another novel coronavirus, the severe acute respiratory syndrome coronavirus 2. A 29-year-old patient diagnosed with primary infertility had COVID-19. Temporary severe oligo-astheno-teratozoospermia was observed in the long term; however, permanent losses occurred in rapid progressive sperms. His total testosterone level and total motile sperm count were permanently reduced. Permanent reductions occurred in his testicular volumes. But semen analysis values before COVID-19 was observed again. Pregnancy with intra cytoplasmic sperm injection was achieved with a high fertilization rate.
Keywords: COVID-19, infertility, pregnancy

Introduction

Men are observed to be more affected by the highly contagious coronavirus disease-2019 (COVID-19) caused by severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) compared to women (male/ratio rate is 2.7:1) (1). In addition, a negative impact occurs in spermatogenesis and testes (2). The virus is not necessarily directly present to cause harm to the male reproductive system (3). This case provides a chronological presentation of COVID-19 following the diagnosis of primary infertility.

Case Report

A 29-year-old male patient, with no co-morbidities and who was married for 1.5 years, had been admitted to the emergency department due to a fever at 39 °C, which had persisted for 3 days. The result of the quantitative reverse transcriptase-polymerase chain reaction analysis performed on a pharyngeal swab sample was positive. Laboratory analyses resulted in mild leukopenia of 3.789/mm^3, hemoglobin of 14.3 g/dL, normal D-dimer of 0.2 mg/L, and ferritin of 65/µL. A urea of 24 mg/dL, creatinine of 1.08 mg/dL, sodium of 138 mg/dL, potassium of 4.01 mEq/L, aspartate aminotransferase of 22 U/L, alanine aminotransferase of 15 U/L, fibrinogen of 352.1 g/L, total bilirubin of 0.5 mg/dL, and sedimentation of 2 mm/h were at a normal level. The C-reactive protein (CRP) was 5.62 mg/L (normal 5-10 mg/L). Favipiravir and enoxaparin sodium were administered. The semen analyses were evaluated according to the World Health Organization 2010 reference values. The pain was assessed according to the Wong-Baker face pain rating scale. The testes were examined with scrotal ultrasound/Doppler. The patient had oligo-astheno-teratozoospermia before the onset of COVID-19 (Table 1). The patient came to our clinic on day 45 after COVID-19. The semen analysis performed in an external center revealed a severe oligo-astheno-teratozoospermia that has developed on day 22 of COVID-19. Mild pain began on day 22 and intensified on day 49 in both testicles (+). Left testicular volume was lower compared to that of the right testis under ultrasound. The volume reduction in right and left testes occurred as 16.3/mm^3 (29.9/23.3 mm^3, 25.41%) and 12.5/mm^3 (28.9/16.4 mm^3, 43.25%), respectively, on day 49 (Figure 1). Orchialgia, which woke up the patient and was suppressed with paracetamol, developed on days 60 and 75, but no typical

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Table 1. Chronological list evaluating the results before and after COVID-19

2020-2021 year	**22.01**	**23.01**	**01.06**	**19.09**	**11.10**	**14.10.2020**	**3.11**	**4.11**	**7.11**	**18.11/3.12**	**18.12**	**19-23/2021**	**4.1.2021**	**17.1.2021**
	Before	**Before**	**Before**	**Days 1,10,18**	**Day 22**	**Day 25**	**Day 45**	**Day 46**	**Day 49**	**Days 60,75**	**Day 90**	**Day 91-95**	**Day 108**	**Day 113**
FSH mIU/L		2.42						2.6			2.98		2.7	
LH mIU/L		5.46						4.04			3.74		3.93	
PRL mIU/L		15.77						8.53			14.22		9.66	
E2 pg/mL								48.2					33.49	
TT ng/dL		303.57						395.26			216.44		173.89	
Volume/mL	5		4		3.5		4				5.2		3.6	
Number/mL	$2.7x10^6$		$7x10^6$		$0.6x10^6$		$4x10^6$				$8x10^6$		$9x10^6$	
Total count	$13.5x10^6$		$28x10^6$		$2.1x10^6$		$16x10^6$				$41x10^6$		$32.4x10^6$	
Rapidly progressive %	24		32		0		0				0		0	
Slowly progressive %	0		12		0		0				13		33	
In situ motile %	10		56		4		7				0		0	
Immotile %	66		44		96		93				87		67	
Kruger normal %	1		1		0		1				1		1	
TMSC	$2.7x10^6$		$15.7x10^6$		$0.084x10^6$		$1.12x10^6$				$5.33x10^6$		$3.85x10^6$	
Rigth testis/ mm^3		29.9, echo N			29.9, echo N				23.3, echo↑, volume ↓	21.3, echo↑, volume↓			14, echo N, volume↓	
Left testis/ mm^3		28.9, echo N			28.9, echo N				16.4, echo↑, volume↓	15.7, echo↑, blood flow↑, volume↓			12.2, still high echo, volume↓	
Varicocele		2 mm, reflux (+)			2 mm reflux (+)					2 mm reflux (+)				
Rigth W-B	0	0	0	0	2 or 4	2 or 4	2 or 4	2 or 4	2 or 4	8	0		Absent	
Left W-B	0	0	0	0	4	4	4	4	4	10	0		2	
qRT-PCR for COVID-19				**Positive**		Negative				Negative				
CRP mg/L					5.62			9.77		37.9	2.9		0.1	
ORP/mV/10^6 sperm/mL			**0.98**		3.76		2.45				1.89		1.1	
SDFI (TUNEL)	8				22		26				11		8	
ICSI											**ICSI day**	Embryo transfer		
Time-lapse/h, division												42.9±27.88		**Pregnant**
Complete urine					N				**N**	N			N	
SPSS 27.0 program														

COVID-19: Coronavirus disease-2019, FSH: Follicle-stimulating hormone, LH: Luteinizing hormone, TT: Total testosterone, PRL: Prolactin, E2: Estradiol, LT: Liquefaction time, ICSI: Intracytoplasmic sperm injection, TMSC: Total motile sperm count, Wong-Baker (W-B) Face pain rating scale; 0 no hurt, 2 hurts little bit, 4 hurts little more, 6 hurts even more, 8 hurts whole lot, 10 hurts worst, qRT-PCR: Quantitative reverse transcriptase-polymerase chain reaction, CRP C-reactive protein, SDFI: Sperm DNA fragmentation, Time-lapse the system for monitoring early embryo morphokinetics development, ß HCG shows pregnancy value in blood. The embryo is checked on the 12th day following the transfer. It indicates pregnancy between 5-50 mIU/mL in the first three weeks. TUNEL: The terminal deoxynucleotidyl transferase-mediated deoxyuridine triphosphate-nick end labeling (TUNEL) assay, ORB: Oxidation-reduction potential (An ORB cut-off value of <1.42 mV/106 sperm/mL was regarded normal), N normal↓ decreased, ↑increased

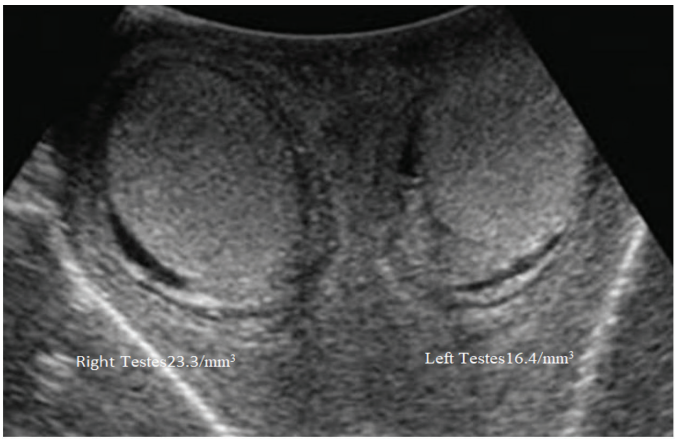

Figure 1. Testicles with elevated echogenicity on day 49 due to COVID-19
COVID-19: Coronavirus disease-2019

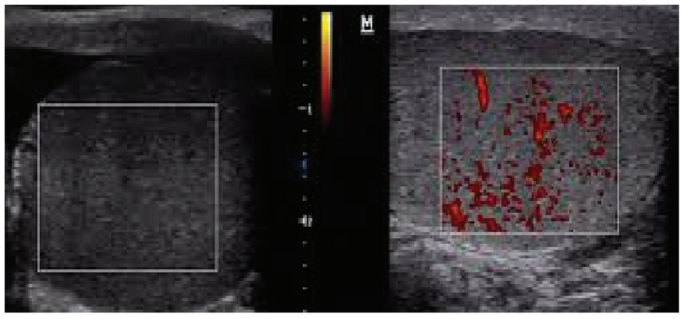

Figure 2. Elevated echogenicity in the right/left testes and elevated blood flow in the left testis under scrotal color Doppler on day 75 after COVID-19
COVID-19: Coronavirus disease-2019

epididymitis orchitis swelling was observed. The patient's white blood cell count was (12.600/μL) with lymphocytopenia (724/μL). A reduction in testicular volumes was noted in both testes and particularly in the left testis under Doppler. The echogenicity was elevated. The left testicular blood flow was observed to increase (Figure 2). The semen values were consistent with the levels before COVID-19 from days 45 to 108. No changes occurred in the gonadotropic and prolactin values on days 46 to 90 before and after COVID-19; however, a decrease was observed in the total testosterone (TT) hypogonadism level on days 90 to 108. The patient had no pain in his right testis on day 108 during his follow-up, but the pain in his left testis persisted. A decrease was observed in the testicular volumes under ultrasound. His left testicular echogenicity was still elevated. The volume reduction in the right and left testes occurred as 15.9/mm^3 (29.9/14 mm^3, 53.17%) and 16.5/mm^3 (28.7/12.2 mm^3, 57.78%), respectively from days 49 to 108. Permanent losses were noted in rapidly progressive and *in situ* motile sperms in the semen analyses on day 108 (Table 1). An intracytoplasmic sperm injection (ICSI) was performed on day 90. Embryo transfer was carried out on day 95 and pregnancy was detected in the blood on day 113. Ultrasonographic gestational sac and fetal pulses were observed on day 131 after COVID-19. A healthy pregnancy of 8 weeks is currently preserved. All chronological follow-up is presented in Table 1.

Discussion

It was claimed that SARS-CoV-2 causes spermatogonia and increases expression in Leydig and Sertoli cells with angiotensin-converting enzyme 2 receptors and triggers an autoimmune inflammatory response (4). Autoimmune orchitis disrupts the testicular-blood barrier (3,4). This disrupts the balance of reactive oxygen species. The oxidative stress disrupts sperm morphology and acrosome structure and leads to damage in sperm deoxyribonucleic acid (DNA). Simultaneous elevation of oxidative reduction potential (ORP), CRP, and sperm DNA fragmentation index (SDFI) seemed to support COVID-19 autoimmune orchitis. Interestingly, normalization was observed in all three values towards day 108. We saw high-quality sperms with acrosome and high motility and cytoplasmic integrity, in which we detected the nuclei in intracytoplasmic morphologically selected sperm injection (IMSI). We observed embryo formations of 2PN (pronucleus) quality in our morphokinetic follow-ups in time-lapse on day 5. CRP elevations may negatively impact testicular functions and spermatogenetic activity (4). CRP elevation, severe orchialgia, and increase in testicular echogenicity were observed on days 66 to 75, whereas a volume reduction was noted in the testes compared to day 49 (Figure 1, 2). Even if the body temperature increases by one degree, the regulation of the scrotal temperature is disrupted. Thus, sperm count and/or motility is/are reduced (5). This leads to a modification in the sperm DNA integrity (5). A minimum of 3 months may be required to normalize these parameters (6). Therefore, assisted reproductive approaches are recommended to be postponed for at least 3 months in men who have COVID-19 with fever (6). COVID-19 was reported to promote the negative impact of testosterone (7). Severe scrotal pain, elevation in testicular echogenicity, reduction in their volume, and a TT reduction signaling hypogonadism on days 90 through 108 were observed in our 3-month follow-up.

Despite being temporary, an elevation in CRP and ORP, high fever, and transiently rising SDFI levels were observed in the male patient with COVID-19. A severe reduction occurred in transient total sperm count, whereas a permanent reduction was noted in total motile sperm count levels. Testicular pain that developed after COVID-19 persisted for a long time. Most importantly, a permanent reduction occurred in testicular volumes. High-quality sperms were detected in IMSI. A high fertilization rate was achieved. Embryo morphokinetics was normal at time-lapse. Despite debated changes associated with COVID-19 in a male patient with primary infertility, ICSI that was performed 3 months after the disease resulted in pregnancy.

Ethics

Informed Consent: Consent was obtained from the patient to use the data.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: A.S., A.S.G., F.A., Design: A.S., Data Collection or Processing: A.S., F.A., Analysis or Interpretation: A.S., Literature Search: A.S., A.S.G., F.A., Writing: A.S.

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