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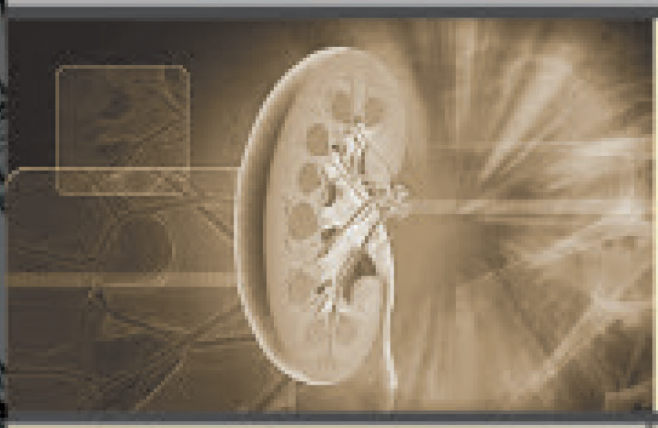

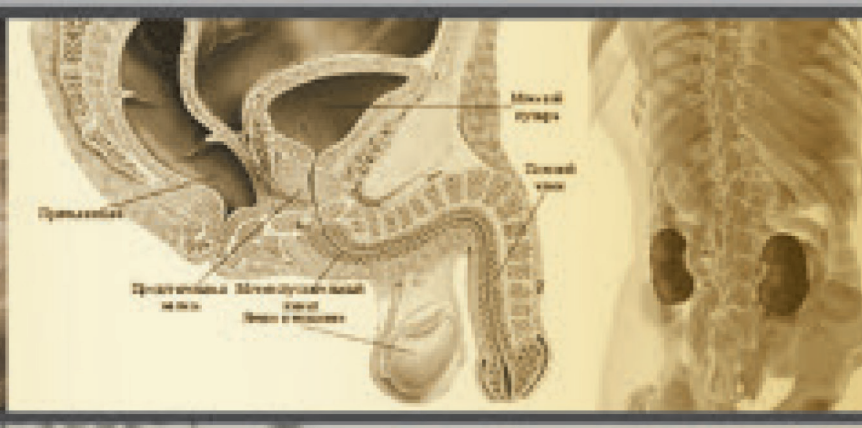

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CONTENTS

REVIEW
Andrology

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Genital Cosmetic Procedures in Urology

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Abstract

In recent years, genital cosmetic procedures have been increasing in the field of Andrology. The most common of these procedures are penis lengthening and girth enhancement. In this review, we have examined the studies conducted on penile reconstruction surgeries, including the details of surgical techniques as well as complications and methodological shortcomings with an emphasis on possible bias that might enormously affect the published literature. Although we have observed that these procedures have become increasingly popular in recent years due to the lack of sufficient studies on these surgeries, we believe that caution should be exercised and patient selection should be meticulous.

Keywords: Genital cosmetic, penile lengthening, penile girth enhancement, penile augmentation procedures

Introduction

Although aestheticism, has a long history that dates back to ancient times, aesthetic and plastic surgery's dominance as an independent branch is a matter of modern medicine (1). With advancements in medical approaches, aesthetic interventions have become more common and widely accepted and are creating a significant market in the medical field (2). Female genital aesthetics has established its role through well-documented procedures, demonstrating a significant positive impact on an individual's well-being following successful surgery (3,4). However, male genital aesthetics has faced significant opposition from authors and scientific associations due to low patient satisfaction rates and high complication rates. In this review, we aim to put together the available evidence and integrate it with the authors' experience, predict a possible outcome for the rising demand for male genital augmentation procedures, and bring the collective opinion of the Andrology Working Group of the Society of Urological Surgery in Türkiye (5).

Available Evidence, Classification, and Reporting

The evidence on male genital augmentation procedures remains limited in the medical literature, often highlighting complications from unlicensed and illegitimate interventions, with a scientific consensus yet to be established (6). Since its introduction to the literature in the 1980s, this subject has proven challenging for establishing strong evidence. Reflecting the tough nature of the proposed claims, cutting-edge literature consists of a significant number of reviews and society statements on male genital aesthetic surgery (7-9). In this review, we went through the available evidence based on the procedure and grouped it according to its evidence grade for each unique procedure or approach. Although the review has no aim of complete illustration of the surgical points, à là un atlas chirurgical, we also summarized the essential steps and possible devastating complications of the main surgical approaches that are often used in operative procedures of male genital aesthetic interventions.

Unique Situation of Penile Augmentation Surgery in Terms of Clinical Evidence

Despite worldwide recognition of modern digital libraries and numerous studies on a broad variety of conditions, penile augmentation still endures significant discrepancies between interventions performed in the healthcare sector and the reporting of their results. For most fields (i.e., oncology or stone disease), the evidence comes from the highest volume centres or

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individuals; however, for male genital aesthetics, there is a vast gap between the providers and the reporters. While preparing this review, we observed that many surgeons worldwide, known for performing high-volume cases in this field, have not reported their outcomes. We also identify another unique aspect of male genital aesthetics: many surgeons tend to abandon these interventions at some point in their careers, a trend that contrasts with other subspecialties such as paediatric urology, endourology, or urooncology.

Penile Lengthening Procedures

Penile Lengthening by Ligament Release and Dorsal Skin Advancement Techniques

The operation is usually performed under general anaesthesia; however, other options may also be available depending on the preferences of the anaesthesiologist and surgical candidate. An inverted V incision is carried out and anatomical layers are divided with control of the bleeders by cautery, until rectus fascia and periosteum of the pubic bone are distinguished. The dissection plane is further deepened under the pubic symphysis with extreme caution against possible harm to dorsal penile structures, especially arteries and nerves. A venous injury is generally more manageable, though it can still be significantly disruptive. After the complete visualization of the penile suspensory ligament complex, the main component is divided. Despite there being no consensus on foreseeing the possible benefit of length after this manoeuvre, magnetic resonance imaging seems a promising modality in predicting how much advancement would be possible with division of the ligament. After careful dissection of the main suspensory ligament of the penis and control of the bleeders, de-novo anatomical space under the pubic symphysis should be filled to avoid leaving a dead space in the surgical area. Either a native tissue, such as fat, spermatic cords, or a subcutaneous flap formed from excess skin, or a bio-compatible material, for instance a testis prosthesis or an acellular matrix sheet, can be used to fill the relevant space. Closure of the anatomical layers without tension is mandatory for a favourable result (Figures 1a to 1h).

The inverted V-Y plasty has long been the main option for penile lengthening and is well-described in plastic surgery literature (10,11). From an anatomical perspective, the procedure has potential benefits, namely increasing the visible proportion of the penis. However, the results appear to be underwhelming. Li et al. (12) reported an average of 1.3 cm of lengthening in the length of the stretched penis, with a risk of 1 cm of shortening in some patients. Deskoulidi and Caminer (13) reported enhanced self-esteem in all their subjects after V-Y plasty with suspensory ligament release, resulting in 2 to 4 cm of lengthening in the flaccid state. The authors suggested that the procedure has favorable results in experienced hands. Both studies hold significant importance, as they report results of men with normal penile length, which constitutes the main reason for penile enlargement procedures for aesthetic purposes (14).

The ligament release technique is also used in combination with penile prosthesis implantation, and the results are usually satisfactory (15). Given the remarkably high patient satisfaction reported in Borges' study (15), it is likely that the implant had a more significant influence on outcomes than the lengthening procedure alone. Some technical modifications of the suspensory ligament release, are also relevant for overcoming complications of the surgery. Cross-closing of the incision, filling the dead spaces with flaps, or insertion of biodegradable or biocompatible materials between the penis dorsum and pubic arch can be considered in this manner (16-19). All these variations aim to prevent tension during the skin closure and elimination of anatomical dead space, thereby preventing scar formation on the skin and/or re-attachment of the penis to the inferior side of the pubic bones, which are culprits of de novo penile shortening. The anatomy of the penile suspensory system has also attracted attention in accordance with the increasing demand for penile augmentation surgery. An unorthodox approach to suspensory ligament release is reported by Mertziotis et al. (20), who described a circumferential coronal incision resembling a circumcision. The incision prevented scarring, a common burden of the inverted V-Y plasty incision, and the results are quite satisfactory.

Contemporary anatomical studies also focused on the subject. Previously, Hoznek et al. (21) imaged the suspensory ligament complex of the penis using volunteers and further supported their findings with cadaveric dissections, and they clarified the role of the individual parts in the erection process. Currently, all contributors to the penile suspensory complex are better understood, and prediction of surgery outcomes is made possible using three-dimensional reconstruction (22-26). We think that the recent advancements in the penile suspensory ligament anatomy are quite fascinating as they reflect the increasing interest in male genital aesthetic surgery.

Complications of the procedure also draw attention and hold an important, albeit small, part of urological practice. Even though the loss of the anatomical leverage point, which results in a low-hanging penis and loss of acute angle during erection, is a well-known complication of suspensory ligament release; Ralph et al. (27) did not report any cases in their series that needed ligament repair after penile elongation surgery. However, suspensory ligament release is also known for high rates of complications that have necessitated admissions to tertiary healthcare centres and complex reconstructions (28,29). Overall, we can conclude that penile elongation with suspensory ligament release can be offered to candidates of surgery following the essential

ethical principles: setting realistic expectations, discussing potential complications, and aiming to benefit the patient and his well-being. We also want to indicate our opinion that the classical surgical approach should undergo improvements that account for special circumstances, such as short penile skin due to excessive circumcision. Moreover, concurrent interventions, such as prepubic liposuction and girth enhancement injections, should be better integrated into the surgical planning.

Penile Lengthening by Ventral Skin Adjustment and Correction of Scrotal Skin Web

The peno-scrotal corner portrays the inferior border of the penis. Thus, sharpening the angle of the corner and sliding the corner to a more caudal position resemble an extended penis. A wide scrotal skin web, which is usually a consequence of excessive removal of the ventral skin by circumcision, may also interfere with sexual mechanics. Correction can be achieved using Z-plasty, inverted V-Y plasty, skin removal, and primary closure (Figure 2a to 2e) (30-33). The procedure is also well-described as being performed in conjunction with penile prosthesis implantation (34,35). Satisfaction rates are noticeably high with all types of approaches for penoscrotal angle restoration. Candidates usually have anatomical condition at the time of admission, which is a major difference from those of penile lengthening surgery who have normal penile morphology (36,37). Based on this particularity of the candidates and high satisfaction rates, we hypothesize that the interventions may be less prone to medico-legal problems relative to suspensory ligament release. Considering all available evidence and our personal experience, we can conclude that penoscrotal reconstruction can be offered to patients who have an objective and documentable issue and are pursuing better cosmesis of the genitalia. The surgical approach should be determined by the surgeon based on the expectations of the patient and the feasibility of the patient's anatomy.

Complex Reconstruction Involving Massive Skin Removal, and Procedures Involving Graft or Flap Closure

Increased awareness of self-image, surge in obesity rates, rise in metabolic surgery, and advanced plastic surgery care, led to promising treatments for men including total abdominoplasty, panniculectomy, total grafting of the penile skin, as well as combined surgeries (11,38). It is not always possible to clearly distinguish between aesthetic and reconstructive procedures, as there are significant areas of overlap. On the other hand, we can propose that male genital surgery involving two distinct dissections, such as lower abdominal exposure via an inverted V, total penile degloving via a circumcision, implantation of foreign bodies, or any secondary and beyond procedures, can be considered complex interventions. For candidates who are

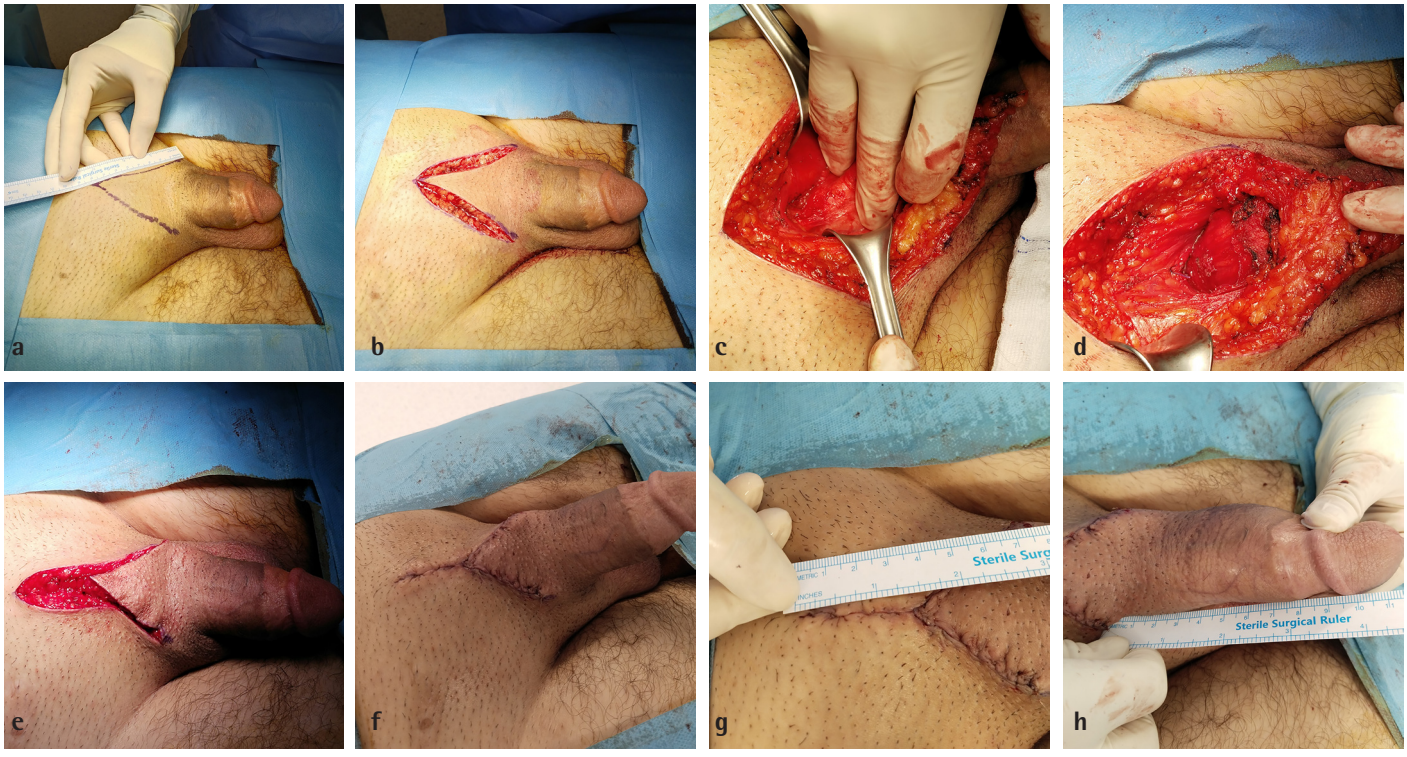

Figure 1a. Marking the skin where the inverted V incision will be made with a ruler and measuring its edges, **b.** Incising the skin and subcutaneous tissue, **c.** Release of the suspensory ligament, **d.** Appearance after cutting the suspensory ligament, **e.** Closing the inverted V incision in an inverted Y shape, **f.** Y-shaped skin suturing, **g.** Measurement of excess skin from the new incision, **h.** Measuring the length obtained from the penis skin

scheduled to undergo combined and extensive surgery, such as abdominoplasty, skin resection, or penile grafting or flap-based reconstruction, we suggest a multi-disciplinary evaluation, including a plastic surgery consultation and a precise pre-operative evaluation by an anaesthesiologist. Considering the condition of these candidates, the surgery can be regarded beyond the spectrum of pure aesthetic purposes; thus, we suggest that a decision process should aim to include the patient and the reconstructive surgery should be performed in experienced centres.

Penile Girth Enhancement Procedures

Penile Girth Enhancement Procedures Involving Dermal Grafts

Dermal and dermal-fat grafts are time-tested options for the reconstruction of tissue defects and have significant advantages since they are autologous grafts. Zhang et al. (39) implanted dermal grafts by first performing a suspensory ligament incision and then fixing the graft to the tunica albuginea after degloving of the penis. Their cohort was quite a young patient group; they reported an average of a 1.2 cm increase in penile girth during erection. Xu et al. (40) further confirmed these results with a similar mean girth benefit in two unique patient cohorts suffering from possible penile dysmorphophobia, and previous hypospadias surgery (41). Dermal grafts are also reported to be beneficial in reconstructive surgery for adults with a history of previous hypospadias surgery.

Considering the wide usage of dermal and dermal-fat grafts in plastic surgery for different kinds of tissue defects, one can clearly conclude that the procedure is safe, at least in the short term. Unfortunately, most studies lack long-term data. However, first-year satisfaction rates seem to be acceptable in the majority of papers. Most urologists are not familiar with the harvesting of dermal grafts. Thus, the procedure can be addressed through a multi-disciplinary approach. We can

Figure 2a. Marking of excess skin tissue in the anterior part of the penoscrotal region, **b.** Skin incision, **c.** Completion of excision of excess skin tissue, **d.** Anatomical closing of subcutaneous layers by sutures, **e.** Completion of the anterior phalloplasty procedure

Figure 3. Postoperative appearance just after a prepubic reduction, foreign material removal, penile skin excision and grafting on a young male who had undergone V-Y plasty penile lengthening and acellular matrix-based girth enhancement

conclude that dermal grafts are considered a time-tested option for penile girth enhancement procedures with an essential place in salvage surgery. Figure 3 shows a penile grafting procedure combined with pubic skin excision after a previous failed V-Y plasty and acellular matrix-involving girth enhancement. Based on the available case series, we can also conclude that dermal graft-based girth enhancement can be carried out in the same session with penile elongation procedures involving the penile suspensory ligament complex. Finally, we emphasize that dermal grafts are globally accepted for reconstructive surgery and endorsed by major sources in plastic surgery; thus, from a medicolegal point of view, as a material, dermal grafts seem to be one of the safest options, apart from the surgical procedure and its results.

Penile Girth Enhancement Procedures Involving Autologous Fat

Fat-injection based penile enhancement is extensively described in plastic surgery textbooks and, notwithstanding the alienation of urologists to the procedure, seems to have a solid place in common practice. The material is collected by liposuction through a sterile suction device. The gathered fat is thinned using a two-way syringe set and saline. The semi-viscose native jelly is injected just under the skin using a blunt tip cannula via a stab incision. The procedure can be a matter of a single, separate session, or can be carried out consequent to a lengthening procedure or cosmetic surgery that diminishes the belly fat (Figure 4a to 4e).

The intervention is quite popular due to its feasibility and recognition in aesthetic surgery practice. As we have stated, medicolegally, it is described in plastic surgery sources, thus, it can be accepted as a customary intervention. Despite its widespread use, the outcomes of penile enhancement procedures using autologous fat injections are not extensively reported in the literature. We suppose that the discordance is a result of the gap between the field practice, and contributions to the literature of the aesthetic surgery practitioners. Its complications, such as asymmetrical distribution of the fat deposits, are well-described and the cosmetic result may not be agreeable to the patients because of the loss of enhancement over time (28,42). Mortality is also reported because of systemic fat embolism (43).

Application of Dermal Fillers for Increasing the Penile Girth

Increased demand for minimally invasive options for cosmetic rejuvenation has led to outpatient injectable preparations comprising biocompatible materials. Hyaluronic acid (HA) has secured a solid place in clinical applications of cosmetology (44). Based on its wide usage, HA has been implemented in penile aesthetics mainly to add extra volume to the penile shaft (45). It is noteworthy that HA is a minimally invasive procedure that can be applied in an outpatient clinic setting compared to other penis thickening methods (Figure 5). HA based procedures provide a temporary enhancement, which can be considered both an advantage and a disadvantage.

It seems the scientific community has also accepted HA procedures quite well, which is evident in the number of published studies on using HA for penile augmentation. Kwak et al. (46) reported their feasibility study, which was performed on 50 patients, who underwent penile augmentation using HA dermal fillers because of subjective complaints of small penis size. Evaluating 41 out of 50 patients, they reported a mean of a 4 cm increase in girth that sustained over 18 months with an excellent safety profile. Further studies confirmed the safety and efficacy of penile girth enhancement by HA injections (47). HA injections are also used and reported to be successful in glans penis augmentation (48,49). Despite the tremendous market of penile girth enhancement, complications seem to be relatively low and manageable; however, dismal results are also possible, albeit rare (50,51).

The durability and mechanical behaviour of HA fillers in penile augmentation are strongly influenced by the type and concentration of the cross-linking agent used, 1,4-butanediol diglycidyl ether (BDDE). BDDE stabilizes the HA chains through covalent bonding, forming a three-dimensional network

Figure 4a. Measuring penis girth before the penile girth enhancement procedure, **b.** Removal of subcutaneous fat tissue from the belly with sterile liposuction device, **c.** Keeping the fat tissues obtained through liposuction in the syringe, **d.** Injecting diluted fatty tissues into the subcutaneous tissue of the penis using a syringe, **e.** Measuring penis girth after the penile girth enhancement procedure

that resists enzymatic breakdown. Fillers with higher BDDE concentrations demonstrate significantly greater durability with residence times extending up to 18-24 months. Therefore, the desired durability should be matched to the specific anatomical site and aesthetic goal. The BDDE cross-linking density of the filler should be selected accordingly. For instance, he penile shaft areas may benefit from moderately cross-linked fillers that balance pliability and longevity. Importantly, patients must be thoroughly informed about the expected duration, potential variability in outcomes, and the biodegradation profile of the selected filler material to ensure informed consent and optimize satisfaction (44,52,53).

Combining available scientific data, our personal experience, and observation of the male genital aesthetics market, we can conclude that dermal filler injections for penile girth enhancement are safe and effective options for candidates of penile aesthetic procedures. As providers, we think that urologists and plastic surgeons should carry out these interventions. Although the procedure is usually safe, proper informed consent, which includes the contemporary state of HA in the clinical guidelines, should be obtained.

Comparison of Different Dermal Fillers for Penile Augmentation Procedures

HA was compared to other fillers in well-conducted studies. Both Yang et al. (54) and Kim et al. (55) reported similar satisfaction rates of HA injections for penile augmentation when contrasted with polylactic acid injections. Kim et al. (55) also reported better augmentation by polymethyl methacrylate (PMA) compared to HA and PLA. Penile girth enhancement using PMA injections was also reported to be safe and successful by

Figure 5. Injection of hyaluronic acid under the skin of the penis with a syringe for penile girth enhancement procedures

Figure 6. Injection of hyaluronic acid into the glans penis with a syringe for glans penis augmentation

Casavantes et al. (56). Both studies agreed that dermal fillers for penile augmentation are safe, with extremely low adverse effects across all intervention arms.

Putting together the available evidence, we think that the choice of filler material should be based on the preference of the surgeon and approval of the local authorities.

Penile Augmentation Procedures Using Acellular Matrix Materials and Modifications

Biologically compatible acellular matrix scaffolds are available for clinical use with a wide variety of application areas. In terms of penile surgery, using acellular matrix grafts in Peyronie's Disease treatment is well-described and has become standard for most urologists. An effort to use acellular matrix scaffolds for penile girth enhancement also arose. Alei et al. (57) brought a proposed technique to the literature without any major complications and favourable psychosexual impacts. Tealab et al. (58) attempted a characteristic material for girth enhancement together with penile suspensory ligament division through dorsal inverted V incision and Y-plasty; unfortunately, their results were disappointing.

The clinical guidelines of the European Association of Urology classified acellular matrix scaffold-based penile augmentation procedures as experimental, which burdens the surgeon with a significant responsibility (59). As the authors, we think that acellular matrix procedures should not be considered as experimental, considering their time-tested usage in Peyronie's disease treatment and widely accepted benefits in wound care. On the other hand, we are unable to draw a conclusion about their role in penile girth enhancement surgery and think that associated procedures should be carefully carried out by a devoted clinical team experienced in penile reconstructive surgery. We also think that, regarding the safety profile and reversible nature of dermal fillers, acellular matrix-based enhancement procedures should not be offered as the first-line option for candidates of enhancement surgery.

Penile Augmentation Using Flaps

Notwithstanding their fundamental role in gender-reassignment phalloplasty, flap-based augmentation procedures did not become popular for cosmetic penile enhancement, likely because of their challenging nature. Virtually any muscle or musculocutaneous flap can be used for penile girth enhancement. A superficial circumflex artery and vein flap is reported to be successfully applied, and slightly more than 50% expansion of penile circumference is reported (60). From a surgical point of view, we propose vascularized flaps should provide substantial girth gain; however, the procedures are demanding and, unfortunately, most urologists lack such training. Therefore, flaps are not commonly considered primary options for cosmetic penile augmentation and are usually withheld for reconstructive tertiary interventions.

Penile Silicone Implants

Penile silicone sleeve implants, such as the Penuma® implant, have emerged as prominent options for penile augmentation. Additionally, other silicone-based devices, including the

Himplant® and similar sleeve-type implants, have expanded the range of available cosmetic solutions (61-64). These implants are intended primarily for aesthetic enhancement rather than functional correction, targeting men with normal erectile function who express dissatisfaction with flaccid penile dimensions. However, their rising popularity necessitates an evidence-based examination of their clinical outcomes and associated risks.

Silicone sleeve implants are typically inserted using either an infrapubic or lateral scrotal approach. Recent studies favoured the lateral scrotal approach due to lower revision and removal rates of the two approaches compared to the former method (65,66). Penile silicone implants are associated with consistent, measurable increases in penile dimensions. Multi-institutional studies indicate an average increase in flaccid penile length of approximately 4.1±1.5 cm (50% increase) and girth gains averaging 3.4±1.5 cm (37% increase). Retrospective studies report high patient satisfaction rates, often exceeding 70%, with significant enhancements in self-esteem and sexual confidence (67). Nevertheless, these outcomes must be interpreted cautiously, as most existing data are derived from retrospective analyses subject to selection and reporting biases, and it should be underlined that reported complications of Penuma® implant include seroma formation (2-12%), infection (1.3-3%), and implant displacement (up to 7%), de novo penile curvature, sexual dysfunction, and even disabling penile deformities (68,69).

Current guidelines from the Sexual Medicine Society of North America recommend deferring invasive cosmetic procedures in patients with unmanaged psychiatric conditions, highlighting the necessity for rigorous psychological screening. Furthermore, the European Association of Urology clinical guidelines caution against routine use of penile silicone implants, emphasizing the current limited evidence base and classifying these procedures as experimental due to inadequate long-term outcome data (59,70,71). Based on these cautions, we endorse the use of penile silicone implants, which should be offered to selected patients and preferably within clinical trial settings.

Glans Penis Augmentation Procedures

Augmentation of Glans Penis

The glans penis is a unique structure without any counterpart in the human body. It plays an essential role in sexual acts by possessing a large number of receptors and supporting erection through engorgement. Its role acting as a stream bed for the distal urethra is another peculiar function that is still not completely understood and revealed (72). Glans penis augmentation has become a matter of clinical practice due to its essential role and fundamental position. Glans augmentation in the treatment of premature ejaculation is also reported with satisfactory results; however, it is beyond the scope of our review (73).

There is considerable evidence on glans penis augmentation, including the techniques, clinical success, and complications. Although dermal fat grafts have also been proposed for glans augmentation, dermal fillers, with HA being quite common, seem to be used globally (74-76). The safety profile, clinical results, and availability of dermal fillers have already been discussed for penile augmentation, and the results are quite similar for glans augmentation. However, physicians should be aware that potential complications of glans augmentation, though rare, can be severe and may result in total loss of the organ (77).

Combining the available evidence, we can conclude that dermal fillers can be regarded as an option for glans penis augmentation for cosmetic purposes. We endorse using a minimal volume of fillers per session and dividing the total targeted amount of fillers into separate interventions to diminish the risk of necrosis as much as possible (Figure 6). We highly recommend early referral of the patient to a tertiary centre in case of glans necrosis.

A summary of outcomes and complications of representative studies from the available literature relevant to penile lengthening and/or girth enhancement surgery is given in Table 1.

Table 1. Summary of evidence among the reviewed literature with emphasis on representative studies for each penile augmentation procedure

Reference	No. of patients	Girth/ length	Technique	Mean gain in penile girth (cm)	Mean gain in penile length (cm)	Complications
Zhang et al. (39), 2016	17	Girth and length	Dermal free graft, ligamentolysis and V-Y advancement	1.5 (F) 1.2 (E)	2.7 (F) 0.8 (E)	Ischemic necrosis (n=1) 6%
Xu et al. (40), 2016	23	Girth and length	Dermal free graft ligamentolysis and V-Y advancement	1.6 (F)	2.2 (F) 3.1 (SP)	Scrotalization (n=5) Hypertrophic scar (n=2) n=7 of 23 (30%), Dermal fat shrinkage at 6 mo was <30%
Tealab et al. (58), 2013	24	Girth and length	Acellular dermal matrix, ligamentolysis and V-Y advancement	2.8 (F)	1.7 (F)	Ischemic ulcers (n=8) Implant loss (n=4) Decreased penile sensation (n=1) n=13 of 18 (72%)
Mertziotis et al. (20), 2013	35	Girth and length	Ligamentolysis and V-Y advancement, dermal fat graft	2.2 (SPL)	2 (SPL)	Penile retraction (n=4) Scar hypertrophy (n=18)
	47		Ligamentolysis via circumcision, dermal fat graft	1.9 (SPL)	2.1 (SPL)	Penile retraction (n=3) No scar hypertrophy
Elist et al. (61), 2018	400	Girth	Silicone implant	4.8 (F)	NS	Seroma 19 (4.8) Hypertrophic scar (n=18) Fibrosis of capsular tissue (n=14) Implant infection (n=9), 4 were removed Implant infection and breakage, (n=4), all were removed Implant breakage (n=1), implant was removed Temporary sensory loss (n=6) Detachment of sutures (n=6), 4 implants were removed Skin ulcer (n=5) Hematoma (n=4), 1 implant was removed n=86 of 400 (21.5%)
Shaeer (60), 2014	40	Girth and length	SCIAV flap	1.5 (F)	NS	Shaft ulcers (n=2) Penile length decrease (n=10) Scar revision (n=11) Debulking pedicle (n=6) Debulking shaft (n=4) Donor-site dehiscence (n=5) Donor-site infection (n=1) n=8 of 40 (20%)
Alei et al. (57), 2012	69	Girth	Porcine dermal acellular graft	3.2 (F)	NS	Fibrosis and retraction (n=9) Suture dehiscence (n=8) Seroma (n=2) n=19 of 69 (27%)
Casavantes et al. (56), 2016	203	Girth	PMMA injection	3.5 (F)	0.8 (F)	n=0 of 203 (0%)
Kwak et al. (46), 2011	41	Girth	Hyaluronic acid injection	3.8 (SP)	NS	n=0 of 41 (0%)

PMMA: Polymethyl methacrylate, SCIAV: Superficial circumflex iliac artery and vein, F: Flaccid penis, SP: Stretched penis, E: Erected penis, NS: Not specified

Conclusion

Medicine is a humanitarian craft. The demands of the people create the practice of medicine, while those demands are shaped by the prerequisites of the population. Male genital aesthetics is in demand and practiced. As a characteristic of this field, we have noted a strong dissociation between the clinical providers and reported literature on penile aesthetic procedures. For instance, Abecassis et al. (78) reported that they had performed about 2000 penile adipose grafting and suspensory ligament division surgeries between 1992 and 2010; unfortunately, we were unable to find any further papers by them. In 2009, Vardi and Gruenwald (79) pointed out that the lack of true methodological evaluation was the typical aspect, and from our point of view, the main shortcoming, of penile enhancement. As common practice, practitioners expect 90% or more of patients to be satisfied with the results, while a 5% or less occurrence of complications from the interventions endorsed to patients is anticipated. We believe that penoscrotal web corrections, moderate penile shaft thickening using dermal fillers, and buried penis corrections meet these criteria, supported by both literature evidence and our personal experience. However, V-Y plasty based lengthening, girth enhancement using acellular matrix-based procedures, or implants seem to have higher complication rates and are prone to result in devastating outcomes with low satisfaction rates (25). We also suppose that we may have to face complications from penile enhancement because of improper performance of penile enhancement procedures. The field also carries risks such as potential legal claims or, in rare cases, violent acts against surgeons, given its highly sensitive nature. On the other hand, practitioners will have to respond to rising demand, at least by directing the candidates to more appropriate interventions or management choices. Unfortunately, in most approaches for penile augmentation, the evidence is not conclusive enough between the clinical guidelines and practical implementations of urologists. It's clear that there has been significantly biased reporting of the results, which is discordant with the clinical experience of the authors as well as leading figures of the genital aesthetics worldwide. Apart from our distinctive endorsement of specific interventions that have been reviewed in this paper, we want to underline that male genital cosmetics, particularly penile enhancement and associated procedures, should initially follow the common sense of medical ethics and aim for the best interest of the patient, ensuring the patient is fully informed. The provider should be competent to overcome complications and manage the course, or refer when needed. The collection of accurate and appropriate data is the indispensable step in establishing scientific evidence, and unfortunately, it seems that it was the missing fundamental of penile enhancement surgery to date.

By this review, we underline that one of the main targets in this field should be recognizing the diversity of the surgical practice, making the outcomes of the practicing physicians available in a reliable fashion, preventing market-driven promotion of male genital enhancement surgery while acknowledging the availability of surgical options for candidates who would benefit from male genital aesthetic procedures. In the end, the metaphorical pendulum is still swinging.

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Footnotes

Authorship Contributions

Concept: Ö.U.Ç., A.Y., Ç.D., T.T., Design: Ö.U.Ç., A.Y., Ç.D., T.T., Data Collection or Processing: Ö.U.Ç., A.Y., Ç.D., T.T., Analysis or Interpretation: Ö.U.Ç., A.Y., Ç.D., T.T., Literature Search: Ö.U.Ç., A.Y., Ç.D., T.T., Writing: Ö.U.Ç., A.Y., Ç.D., T.T.

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References

1. Macionis V. History of plastic surgery: art, philosophy, and rhinoplasty. J Plast Reconstr Aesthet Surg. 2018;71:1086-1092. [Crossref]
2. Triana L, Palacios Huatuco RM, Campilgio G, Liscano E. Trends in surgical and nonsurgical aesthetic procedures: a 14-year analysis of the international society of aesthetic plastic surgery-ISAPS. Aesthetic Plast Surg. 2024;48:4217-4227. Erratum in: Aesthetic Plast Surg. 2024;48:4601. [Crossref]
3. Simonis M, O'Connell HE. Female genital cosmetic surgery: a social trend driving surgical practice. BJU Int. 2025;135(Suppl 3):12-13. [Crossref]
4. Alter GJ. Pubic contouring after massive weight loss in men and women: correction of hidden penis, mons ptosis, and labia majora enlargement. Plast Reconstr Surg. 2012;130:936-947. [Crossref]
5. Çeker G, Deliktaş H, Gül Ü, Turunç T, Turkiye TAWGotSoUSi. The Andrology Working Group of the Society of Urological Surgery in Turkiye: bridging academic gaps and advancing male reproductive or sexual health. J Urol Surg. 2025;12:101-107. [Crossref]
6. Christ JE, Askew JB Jr. Silicone granuloma of the penis. Plast Reconstr Surg. 1982;69:337-339. [Crossref]
7. Moore KT, Fu MZ, Lichtbroun BJ, Leitner DV. Penile enhancement surgery-the short and the long of it. Urology. 2025;197:226-231. [Crossref]
8. Roth BJ, Hammad MAM, Sultan MI, Abou Chawareb E, Banton J, Park SSH, Perito PE, Yafi FA, Raheem O. Hyaluronic acid and urology: a systematic review and meta-analysis. Sex Med Rev. 2025;13:52-61. [Crossref]
9. Falagario UG, Piramide F, Pang KH, Durukan E, Tzelves L, Ricapito A, Baekelandt L, Checcucci E, Carrion DM, Bettocchi C, Esperto F. Techniques

for penile augmentation surgery: a systematic review of surgical outcomes, complications, and quality of life. Medicina (Kaunas). 2024;60:758. [Crossref]

10. Alter GJ. Penile enlargement surgery. Tech Urol. 1998;4:70-76. [Crossref]
11. Alter GJ. Aesthetic Genital Surgery. IN: Neligan P and Rubin JP editors. Plastic Surgery. 4th Ed, Vol 2, Chapter 30. Elsevier Publishing. 2018 London. pp 742-764. [Crossref]
12. Li CY, Kayes O, Kell PD, Christopher N, Minhas S, Ralph DJ. Penile suspensory ligament division for penile augmentation: indications and results. Eur Urol. 2006;49:729-733. [Crossref]
13. Deskoulidi PI, Caminer D. Lengthening phalloplasty with division of the suspensory ligament and distally based fat flaps in penis enlargement operations. Plast Reconstr Surg. 2023;152:434e-437e. [Crossref]
14. Soubra A, Natale C, Brimley S, Hellstrom WJG. Revelations on men who seek penile augmentation surgery: a review. Sex Med Rev. 2022;10:460-467. [Crossref]
15. Borges F, Hakim L, Kline C. Surgical technique to maintain penile length after insertion of an inflatable penile prosthesis via infrapubic approach. J Sex Med. 2006;3:550-553. [Crossref]
16. Boiko MI, Notsek MS, Boiko OM, Chernokulskyi IS. Penis enlargement by penile suspensory ligament division with cross-plasty of the skin. Turk J Urol. 2022;48:91-97. [Crossref]
17. Danino MA, Benkahdra M, El Khatib A, Yafi N, Trouilloud P, Danino RP, Laurent R. Anatomical study of the penile suspensory system: a surgical application to micropenis. Plast Reconstr Surg Glob Open. 2023;11:e4728. [Crossref]
18. Zhang X, Huang Z, Xiao Y, Kuang L, Zhang M, Zhang G, Li Q, Bai W, Xu T. Suspensory ligament release combined with acellular dermal matrix filler in infrapubic space: a new method for penile length augmentation. Andrologia. 2019;51:e13351. [Crossref]
19. Shaeer O, Shaeer K, el-Sebaie A. Minimizing the losses in penile lengthening: "V-Y half-skin half-fat advancement flap" and "T-closure" combined with severing the suspensory ligament. J Sex Med. 2006;3:155-160. [Crossref]
20. Mertziotis N, Kozyrakis D, Bogris E. Is V-Y plasty necessary for penile lengthening? Girth enhancement and increased length solely through circumcision: description of a novel technique. Asian J Androl. 2013;15:819-823. Erratum in: Asian J Androl. 2013;15:854. [Crossref]
21. Hoznek A, Rahmouni A, Abbou C, Delmas V, Colombel M. The suspensory ligament of the penis: an anatomic and radiologic description. Surg Radiol Anat. 1998;20:413-417. [Crossref]
22. Filipoiu FM, Ion RT, Filipoiu ZF, Tulin AD, Enciu O, Enyedi M. Suspension of the penis - dissection, anatomical description and highlighting of anatomical risks in sectioning the suspensory ligaments. Basic Clin Androl. 2023;33:26. [Crossref]
23. Chen X, Wu Y, Tao L, Yan Y, Pang J, Zhang S, Li S. Visualization of penile suspensory ligamentous system based on visible human data sets. Med Sci Monit. 2017;23:2436-2444. [Crossref]
24. Liu W, Calopedos R, Blecher G, Love C. Penile suspensory ligament: anatomy, function, and clinical perspectives of its repair. J Sex Med. 2025;22:175-183. [Crossref]
25. Mariani UM, Fayman M, Nkomozepi P, Ihunwo AO, Mazengenya P. Topographic and structural anatomy of the suspensory ligament of the penis: implications for phalloplasty. Aesthet Surg J. 2024;44:516-526. [Crossref]
26. Wang R, Yang D, Li S. Three-dimensional virtual model and animation of penile lengthening surgery. J Plast Reconstr Aesthet Surg. 2012;65:e281-e285. [Crossref]
27. Ralph O, Shroff N, Anfosso M, Blecher G, Ralph D. Repair of the penile suspensory ligament for congenital and acquired pathology. BJU Int. 2019;124:687-692. [Crossref]
28. Alter GJ. Reconstruction of deformities resulting from penile enlargement surgery. J Urol. 1997;158:2153-2157. [Crossref]
29. Wessells H, Lue TF, McAninch JW. Complications of penile lengthening and augmentation seen at 1 referral center. J Urol. 1996;155:1617-1620. [Crossref]
30. Alter GJ, Salgado CJ, Chim H. Aesthetic surgery of the male genitalia. Semin Plast Surg. 2011;25:189-195. [Crossref]
31. Caso J, Keating M, Miranda-Sousa A, Carrion R. Ventral phalloplasty. Asian J Androl. 2008;10:155-157. [Crossref]
32. Schifano N, Castiglione F, Cakir OO, Montorsi F, Garaffa G. Reconstructive surgery of the scrotum: a systematic review. Int J Impot Res. 2022;34:359-368. [Crossref]
33. Alter GJ. Correction of penoscrotal web. J Sex Med. 2007;4:844-847. [Crossref]
34. Hakky TS, Rodriguez AR, Parker J, Lockhart JL, Honeymeyer Iii J, Carrion RE. Ventral phalloplasty. Int Braz J Urol. 2012;38:565-566. [Crossref]
35. Miranda-Sousa A, Keating M, Moreira S, Baker M, Carrion R. Concomitant ventral phalloplasty during penile implant surgery: a novel procedure that optimizes patient satisfaction and their perception of phallic length after penile implant surgery. J Sex Med. 2007;4:1494-1499. [Crossref]
36. Alter GJ. Augmentation phalloplasty. Urol Clin North Am. 1995;22:887-902. [Crossref]
37. Thomas C, Navia A. Aesthetic scrotoplasty: systematic review and a proposed treatment algorithm for the management of bothersome scrotum in adults. Aesthetic Plast Surg. 2021;45:769-776. [Crossref]
38. Croghan SM, Kelly C, Daniels AE, Fitzgibbon L, Daly PJ, Cullen IM. Reconstruction of the male external genitalia in diverse disease processes: our reconstructive algorithm, techniques, and experience. Curr Urol. 2022;16:185-190. [Crossref]
39. Zhang GX, Weng M, Wang MD, Bai WJ. Autologous dermal graft combined with a modified degloving procedure for penile augmentation in young adults: a preliminary study. Andrology. 2016;4:927-931. [Crossref]
40. Xu L, Zhao M, Chen W, Li Y, Yang Z, Ma N, Wang W, Feng J, Liu Q, Ma T. Augmentation phalloplasty with autologous dermal fat graft in the treatment of "small penis". Ann Plast Surg. 2016;77(Suppl 1):S60-S65. [Crossref]
41. Xu L, Zhao M, Yang Z, Chen W, Li Y, Ma N, Wang W, Feng J, Liu Q, Ma T. Modified penile augmentation by dermal-fat graft in post-hypospadias adults. Aesthetic Plast Surg. 2016;40:120-129. [Crossref]
42. Furr J, Hebert K, Wisenbaugh E, Gelman J. Complications of genital enlargement surgery. J Sex Med. 2018;15:1811-1817. [Crossref]
43. Zilg B, Råsten-Almqvist P. Fatal fat embolism after penis enlargement by autologous fat transfer: a case report and review of the literature. J Forensic Sci. 2017;62:1383-1385. [Crossref]
44. Bukhari SNA, Roswandi NL, Waqas M, Habib H, Hussain F, Khan S, Sohail M, Ramli NA, Thu HE, Hussain Z. Hyaluronic acid, a promising skin rejuvenating biomedicine: a review of recent updates and pre-clinical and clinical investigations on cosmetic and nutricosmetic effects. Int J Biol Macromol. 2018;120:1682-1695. [Crossref]
45. Schifano N, Capogrosso P, Antonini G, Baldini S, Scroppo F, Salonia A, Zerbinati N, Dehò F. The application of hyaluronic acid injections in functional and aesthetic andrology: a narrative review. Gels. 2023;9:118. [Crossref]
46. Kwak TI, Oh M, Kim JJ, Moon du G. The effects of penile girth enhancement using injectable hyaluronic acid gel, a filler. J Sex Med. 2011;8:3407-3413. [Crossref]
47. Zhang CL, Quan Y, Li H, Li Q, Bai WJ, Xu T, Zhang XW. Penile augmentation with injectable hyaluronic acid gel: an alternative choice for small penis syndrome. Asian J Androl. 2022;24:601-606. [Crossref]

48. Kim JJ, Kwak TI, Jeon BG, Cheon J, Moon DG. Human glans penis augmentation using injectable hyaluronic acid gel. Int J Impot Res. 2003;15:439-443. [Crossref]

49. Moon du G, Kwak TI, Kim JJ. Glans penis augmentation using hyaluronic acid gel as an injectable filler. World J Mens Health. 2015;33:50-61. [Crossref]

50. Quan Y, Gao ZR, Dai X, Kuang L, Zhang M, Li Q, Xu T, Zhang XW. Complications and management of penile augmentation with hyaluronic acid injection. Asian J Androl. 2021;23:392-395. [Crossref]

51. Wang HC, Long X. Filler-induced non-thrombotic pulmonary embolism after genital aesthetic injection. J Cosmet Laser Ther. 2022;24:66-72. [Crossref]

52. Kablik J, Monheit GD, Yu L, Chang G, Gershkovich J. Comparative physical properties of hyaluronic acid dermal fillers. Dermatol Surg. 2009;35(Suppl 1):302-312. [Crossref]

53. Flynn TC, Sarazin D, Bezzola A, Terrani C, Micheels P. Comparative histology of intradermal implantation of mono and biphasic hyaluronic acid fillers. Dermatol Surg. 2011;37:637-643. [Crossref]

54. Yang DY, Ko K, Lee SH, Lee WK. A comparison of the efficacy and safety between hyaluronic acid and polylactic acid filler injection in penile augmentation: a multicenter, patient/evaluator-blinded, randomized trial. J Sex Med. 2019;16:577-585. [Crossref]

55. Kim DW, Jeong HC, Ko K, Yang DY, Kim JK, Lee SH, Kim TH, Lee WK. Which dermal filler is better for penile augmentation for aesthetic purposes? A prospective, single-surgeon study based on real-world experience. World J Mens Health. 2025;43:428-436. [Crossref]

56. Casavantes L, Lemperle G, Morales P. Penile girth enhancement with polymethylmethacrylate-based soft tissue fillers. J Sex Med. 2016;13:1414-1422. [Crossref]

57. Alei G, Letizia P, Ricottilli F, Simone P, Alei L, Massoni F, Ricci S. Original technique for penile girth augmentation through porcine dermal acellular grafts: results in a 69-patient series. J Sex Med. 2012;9:1945-1953. [Crossref]

58. Tealab AA, Maarouf AM, Habous M, Ralph DJ, Abohashem S. The use of an acellular collagen matrix in penile augmentation: a pilot study in Saudi Arabia. Arab J Urol. 2013;11:169-173. [Crossref]

59. Minhas S, Boeri L, Capogrosso P, Cocci A, Corona G, Dinkelman-Smit M, Falcone M, Jensen CF, Gül M, Kalkanli A, Kadioğlu A, Martinez-Salamanca JI, Morgado LA, Russo GI, Serefoğlu EC, Verze P, Salonia A. European Association of Urology Guidelines on male sexual and reproductive health: 2025 update on male infertility. Eur Urol. 2025;87:601-616. [Crossref]

60. Shaeer O. Girth augmentation of the penis using flaps "Shaeer's augmentation phalloplasty": the superficial circumflex iliac flap. J Sex Med. 2014;11:1856-1862. [Crossref]

61. Elist JJ, Valenzuela R, Hillelsohn J, Feng T, Hosseini A. A single-surgeon retrospective and preliminary evaluation of the safety and effectiveness of the penuma silicone sleeve implant for elective cosmetic correction of the flaccid penis. J Sex Med. 2018;15:1216-1223. [Crossref]

62. Siegal AR, Celtik KE, Razdan S, Sljivich M, Kansas B, Shah B, Levine LA, Valenzuela RJ. A multi-institutional update on surgical outcomes after penile silicone sleeve implantation. Ther Adv Urol. 2024;16:17562872241241858. [Crossref]

63. Wilson SK, Picazo AL. Update on the Penuma® an FDA-cleared penile implant for aesthetic enhancement of the flaccid penis. Int J Impot Res. 2022;34:369-374. [Crossref]

64. Elist JJ, Baniqued M, Hosseini A, Wilson SK. Correction of retractile penis with subcutaneous soft silicone penile implant. Int J Impot Res. 2020;32:317-322. [Crossref]

65. Salkowski M, Levine LA. Outcomes and patient satisfaction after penuma silicone implant surgery via two surgical approaches. Ther Adv Urol. 2024;16:17562872241280021. [Crossref]

66. Siegal AR, Zisman A, Sljivich M, Razdan S, Valenzuela RJ. Outcomes of a single center's initial experience with the penuma® penile implant. Urology. 2023;171:236-243. [Crossref]

67. Salkowski M, Alter K, Levine L. Outcomes and satisfaction after penile silicone implant surgery. J Sex Med. 2022;19:S106. [Crossref]

68. Juwono T, Buscaino K, Fernandez-Crespo R, Carrion R. Infection of the penuma penile implant and associated post-operative complications: a case report. Urol Case Rep. 2021;39:101846. [Crossref]

69. Sökmen D, Albayrak AT, Başağa Y, Sertkaya Z. The first reported case of suprapubic migration of the Penuma penile implant as a post-operative complication: a case report. Urol Case Rep. 2025;59:102951. [Crossref]

70. Trost L, Watter DN, Carrier S, Khera M, Yafi FA, Bernie HL, Ziegelmann M, Köhler T. Cosmetic penile enhancement procedures: an SMSNA position statement. J Sex Med. 2024;21:573-578. [Crossref]

71. Penile size abnormalities and dysmorphophobia [Internet]. The European Association of Urology: Sexual and Reproductive Health Guidelines; 2025 [updated 2025]. [Crossref]

72. Özbey H, Arlı OT. "Fossa navicularis" and "septum glandis": a "flow-control chamber" for the male urethra? Med Hypotheses. 2020;140:109642. [Crossref]

73. Kim JJ, Kwak TI, Jeon BG, Cheon J, Moon DG. Effects of glans penis augmentation using hyaluronic acid gel for premature ejaculation. Int J Impot Res. 2004;16:547-551. [Crossref]

74. Shaeer O. Shaeer's glans augmentation technique: a pilot study. J Sex Med. 2012;9:3264-3269. [Crossref]

75. Moon DG, Kwak TI, Cho HY, Bae JH, Park HS, Kim JJ. Augmentation of glans penis using injectable hyaluronic acid gel. Int J Impot Res. 2003;15:456-460. [Crossref]

76. Yang DY, Ko K, Lee SH, Moon DG, Kim JW, Lee WK. Efficacy and safety of newly developed cross-linked dextran gel injection for glans penis augmentation with a novel technique. Asian J Androl. 2018;20:80-84. [Crossref]

77. Yamasaki Y, Asai A, Maruta S, Sakaguchi M, Tsurusaki T. [A case of glans penile necrosis due to hyaluronic acid into the penis for male genital augmentation]. Hinyokika Kiyo. 2021;67:399-401. Japanese. [Crossref]

78. Abecassis M, Berreby S, Boccara D. Chirurgie d'augmentation pénienne : lipopénosculpture d'épaississement et d'allongement [Penile enhancement surgery: widening and lengthening lipopenisculpture]. Ann Chir Plast Esthet. 2010;55:135-142. French. [Crossref]

79. Vardi Y, Gruenwald I. The lack of true methodological evaluation in penile enhancement. J Sex Med. 2009;6:623-624. [Crossref]

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A New Frontier in BPE Treatment: Intersection of Pelvic Floor Muscle Training & LUTS

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

This study highlights the emerging role of pelvic floor muscle training (PFMT) as an adjunct to medical therapy in managing lower urinary tract symptoms (LUTS) associated with benign prostatic enlargement (BPE). While alpha-blockers remain the cornerstone of treatment, their efficacy may be enhanced by targeting pelvic floor dysfunction, a factor often overlooked in LUTS management. The findings demonstrate that combining PFMT with Silodosin results in superior symptomatic relief, improved urinary flow, and better post-void residual reduction compared to medical therapy alone. Notably, these benefits were observed irrespective of constipation status, suggesting a broader therapeutic implication. Given the significant impact of LUTS on quality of life, this study paves the way for non-invasive, cost-effective strategies to optimise patient outcomes. The results warrant further large-scale trials to validate PFMT as a standard complementary approach in BPE management, potentially reshaping clinical practice and improving patient care.

Abstract

Objective: Lower urinary tract symptoms (LUTS) associated with benign prostatic enlargement (BPE) are common among ageing men. Emerging evidence suggests a strong interplay between pelvic floor dysfunction and LUTS, often exacerbated by underlying constipation, whether clinically apparent or subclinical. Pelvic floor muscle training (PFMT), a well-established intervention for constipation, may offer therapeutic benefits in BPE-related LUTS. However, limited literature exists on its efficacy in this context.

Materials and Methods: This multicentric, prospective, double-arm comparative observational study was conducted over six months at two institutions. Patients with BPE and LUTS were enrolled and divided into two groups. Group I received an alpha-blocker (Silodosin 8 mg) alone, while group II received Silodosin 8 mg plus PFMT. Baseline and post-treatment assessments at six weeks included International Prostate Symptom Score (IPSS), maximum urinary flow rate (Q_{max}), and post-void residual (PVR) volume.

Results: One hundred and ten patients were included (group I: 53, group II: 57). Both groups demonstrated significant improvements in LUTS after six weeks, but group II showed superior outcomes. IPSS reduction was significantly greater in group II (15±4 *vs.* 13±3 in group I, p=0.003). Q_{max} improved more in group II (12.4±1.5 mL/sec *vs.* 11.1±0.9 mL/sec, p=0.001), and PVR reduction was more pronounced in this group (71±22 mL *vs.*83±23 mL, p=0.006).

Conclusion: The addition of PFMT to standard medical therapy significantly improved LUTS in patients with BPE. This novel intervention, irrespective of constipation status, enhances urinary outcomes and warrants further investigation through larger clinical trials.

Keywords: BPE, LUTS, PFMT, constipation

Introduction

Up to half of men over 50 and as many as 80% of men over 80 experience lower urinary tract symptoms (LUTS) associated with benign prostatic enlargement (BPE) (1). A significant spectrum of these patients harbour an underlying constipation which many times remains clinically apparent or subclinical. Subclinical constipation refers to individuals who experience constipation symptoms but do not meet the full ROME III criteria for a clinical diagnosis. Studies have shown that managing coexisting constipation in such patients with LUTS may lead to a reduction in International Prostate Symptom Score (IPSS), improvement

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in uroflowmetry parameters, and enhancement of quality of life (QoL) (2).

Pelvic floor muscle training (PFMT) has been recognized as an effective intervention for managing constipation. The pelvic floor muscles play a crucial role in both bowel and bladder function, and improper coordination of these muscles can lead to difficulties in stool passage as well as urinary symptoms. There is a well-established crosstalk between the lower urinary tract and the bowel, where dysfunction in one system often influences the other. For example, constipation can exacerbate LUTS, and vice versa, as both the rectum and bladder share common neural pathways and are affected by pelvic floor muscle tone and coordination. A systematic review found that these interventions improved symptoms in individuals with inflammatory bowel disease experiencing constipation, further demonstrating the interconnected nature of pelvic floor dysfunction and the effectiveness of PFMT in managing these overlapping conditions (3).

What is known on the subject is that LUTS in men with BPE are influenced by multiple factors, including prostate volume, bladder function, and pelvic floor muscle activity. Most existing research focuses on pharmacological and surgical treatments for BPE, with limited emphasis on conservative, non-invasive approaches like PFMT. While PFMT has been extensively studied for post-prostatectomy incontinence and overactive bladder, there is a notable lack of structured clinical studies evaluating its role in BPE-associated LUTS. This gap is significant because a substantial proportion of men with BPE experience LUTS despite standard pharmacotherapy, necessitating adjunctive strategies to enhance treatment efficacy. Moreover, as PFMT is a low-cost, non-invasive therapy with minimal side effects, understanding its potential benefits in BPE management could offer an alternative or complementary approach to conventional medical treatments. Additionally, underlying constipation, whether overt or subclinical, can contribute to LUTS severity by exacerbating bladder dysfunction. Existing literature suggests that addressing constipation may improve LUTS, but limited evidence is available regarding the role of PFMT in this context (3,4).

All these associations suggest that PFMT might play a beneficial role in the management of BPE with LUTS irrespective of the presence or absence of clinically significant constipation. However, the literature has very few studies on this topic. To fill this gap, we conducted a comparative study to assess the role of PFMT in the management of BPE. This is the first prospective study ever conducted on this topic.

Materials and Methods

It was a multicentric, non-randomised, double-arm prospective comparative observational study that was conducted at two institutes over a period of 6 months. Ethics approval was obtained from the Institutional Ethics Committee of the KMC Medical College and Hospital (approval number: IEC/KMC/2025/0476, date: 08.01.2025) before commencement of the study. The study population included the patients with BPE with LUTS who visited the outpatient department. The study included men aged ≥50 years (with or without constipation) with moderate-to-severe LUTS (IPSS >7) and a prostate volume of ≥30 cc, as determined by transabdominal ultrasonography. Constipation was defined using the Rome IV criteria as having at least two of the following in over 25% of defecations: straining, hard/lumpy stools, incomplete evacuation, anorectal obstruction, or the need for manual assistance. Patients must have fewer than three spontaneous bowel movements per week, with symptoms lasting at least three months and starting at least six months prior. Exclusion criteria included patients with urethral stricture disease, active urinary tract infection, neurogenic bladder, the use of per-urethral catheter, and BPE patients who were planned for transurethral resection of the prostate. Proper informed consent was obtained from all the patients included in the study.

Patients meeting the inclusion criteria underwent a comprehensive history-taking and clinical examination, including IPSS scoring. Baseline investigations included uroflowmetry with post-void residual (PVR) volume measurement, ultrasonography of the kidneys, urinary bladder, and prostate, complete blood count, kidney function tests, serum prostate-specific antigen, and urine routine microscopy and culture. The patients were allocated into two groups based on their willingness to participate in PFMT or follow standard medical therapy. This systematic approach ensured that selection bias was minimized.

Group I: Treated with an alpha-blocker (Silodosin 8 mg) alone.

Group II: Treated with an alpha-blocker (Silodosin 8 mg) plus PFMT, irrespective of constipation status.

A formal power analysis was conducted to determine the appropriate sample size for this study, based on detecting a clinically significant difference in IPSS reduction between the alpha-blocker alone (group I) and alpha-blocker + PFMT, (group II) groups. Using G*Power software (Version 3.1.9.7), the calculation was performed with the following assumptions: effect size (Cohen's d) of 0.57 (derived from previous studies on PFMT in LUTS management) (1,2), significance level (α) of 0.05 (two-tailed), statistical power (1-β) of 80%, expected standard deviation of 5 points in IPSS, and a minimal clinically important difference of 2.5 points in IPSS. Based on these parameters, a minimum of 50 patients per group was required. To account for potential dropouts, a total of at least 53 patients per group was targeted.

PFMT was conducted in a structured manner to strengthen pelvic floor muscles and enhance control over urinary and

bowel function. Patients were first instructed to identify their pelvic floor muscles by contracting those used to stop urination midstream. Once identified, they practised contraction and relaxation cycles, initially holding contractions for 5 seconds, followed by 5-second relaxations. As their strength improved, contraction duration was increased to 10 seconds. Each set consisted of 10 repetitions, and patients were instructed to perform these sets in both sitting, lying, and standing positions, twice daily (morning and evening). This resulted in a total of 60 contraction cycles per day. Patients were followed up weekly for 3-4 weeks to ensure adherence and correct technique. Participants in the intervention group performed PFMT under supervision, incorporating biofeedback via an electromyographic (EMG) machine to ensure accurate technique and adherence. Via this machine, we were able to establish a baseline tone of the pelvic floor muscles. subsequently, every week, the patients were assessed to see the improvement in the tone of the muscles. Compliance was assessed both quantitatively (frequency and duration of exercises) and qualitatively (correct technique verification via biofeedback).

Follow-up and Outcome Measures

Patients in both groups were reassessed at six weeks using IPSS scores and uroflowmetry with PVR measurements. Baseline and follow-up values were compared to evaluate treatment efficacy. The study algorithm is summarised in Figure 1. The statistical analysis of continuous variables, including IPSS, maximum urinary flow rate (Q_{max}), and PVR, was conducted using paired t-tests within groups and independent t-tests for intergroup comparisons. Effect sizes (Cohen's d) were calculated to determine the magnitude of differences observed. The results demonstrated a statistically significant reduction in IPSS and PVR and a significant increase in Q_{max} in both groups. Additionally, the percentage change in these variables from baseline to six weeks was compared between groups to account for baseline variability, ensuring a more robust interpretation of treatment effects. The chi-square test was used to compare categorical variables.

Results

A total of 110 patients were recruited in the study out of which 53 were included in group I and 57 in group II. With respect to the baseline demographic parameters, there were no significant differences between the two groups in terms of age, IPSS scores, Q_{max}, prostate volume, or transitional zone index (TZI) and PVR values. The average age was 62±13 years in group I and 63±14 years in group II (p-value=0.70). Baseline IPSS scores were 17±6 in group I and 19±5 in group II (p-value=0.07). The mean maximum flow rate (Q_{max}) was 9.6±1.4 mL/sec in group I and 9.1±1.9 mL/sec in group II (p-value=0.12), while PVR was 97±34 mL in group I and 101±35 mL in group II (p-value=0.54). Prostate volume was 35±5 cc in group I and 36±4 cc in group II (p-value=0.34). The TZI was 0.15±0.05 in group I and 0.16±0.04 in group II (p-value=0.41). These results indicated that there were no statistically significant differences between the groups at the start of the study. Around 19 patients in group I and 22 patients in group II had constipation with no statistical difference between the 2 groups (p-value=0.92). The demographic parameters of the patients have been listed in Table 1.

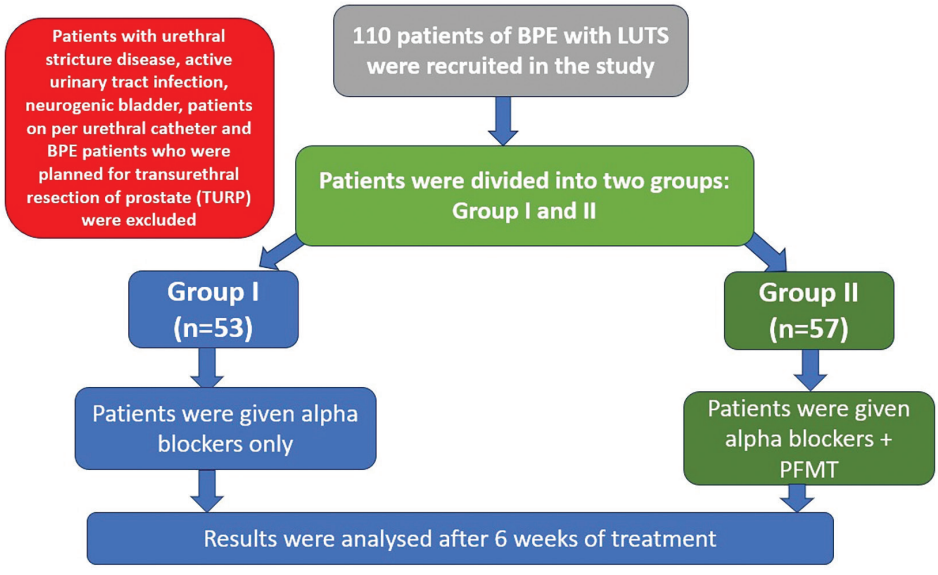

Figure 1. Study algorithm

BPE: Benign prostatic enlargement, LUTS: Lower urinary tract symptoms

Table 1. Showing baseline parameters			
Baseline parameters	**Group I (n=53)**	**Group II (n=57)**	**p-value**
Age	62±13 years	63±14 years	0.70
Constipation	19	22	0.92
IPSS	17±6	19±5	0.07
Q_{max}	9.6±1.4 mL/sec	9.1±1.9 mL/sec	0.12
PVR	97±34 mL	101±35 mL	0.54
IPSS: International Prostate Symptom Score, PVR: Post-void residual, Q_{max}: Maximum urinary flow rate			

After 6 weeks of treatment, significant improvements were observed in both groups across all measured parameters. The IPSS scores were reduced to 15±4 in group I and 13±3 in group II, with a p-value of 0.003, indicating a significant difference in the reduction of symptoms between the groups. In terms of Q_{max}, group I showed an increase to 11.1±0.9 mL/sec, while in group II, it increased to 12.4±1.5 mL/sec, with a p-value of 0.001, reflecting a greater improvement in group II. PVR values decreased to 83±23 mL in group I and 71±22 mL in group II (p-value=0.006), indicating a more significant reduction in group II. The percentage change in IPSS, Q_{max}, and PVR from baseline to six weeks was significantly greater in group II. The results have been summarised in Table 2.

Effect sizes (Cohen's d) were calculated to determine the magnitude of differences, revealing a moderate effect for IPSS reduction (d=0.57), a large effect for Q_{max} improvement (d=1.05), and a moderate effect for PVR reduction (d=0.53). The mean difference between groups was 2 points for IPSS (p=0.003), 1.3 mL/sec for Q_{max} (p=0.001), and 12 mL for PVR (p=0.006), all indicating statistically significant improvements in the PFMT group. Furthermore, percentage changes from baseline to six weeks were analyzed to account for baseline variability, ensuring a more comprehensive assessment of treatment effects.

To assess whether PFMT had a differential effect in constipated versus non-constipated patients, a subgroup analysis was performed. In constipated patients, those receiving PFMT (group II) showed greater improvement in IPSS (ΔIPSS: 6±2 *vs.* 4±1, p=0.01) and Q_{max} (ΔQ_{max}: 3.8±1.1 mL/sec *vs.* 2.9±1.0 mL/sec, p=0.03) compared to those in group I (Silodosin alone). Non-constipated patients in group II also experienced significant symptom improvement compared to group I, but the effect size was more pronounced in constipated patients, suggesting that PFMT may be particularly beneficial in patients with coexisting constipation.

Patients with constipation had lower baseline Q_{max} and higher IPSS scores. The PFMT group exhibited greater improvement in LUTS among non-constipated patients, however, constipated patients also showed a statistically significant reduction in symptoms following PFMT (p<0.05).

Discussion

BPE is a common condition in older men, frequently leading to LUTS such as urinary frequency, urgency, and nocturia. As the global population ages, the prevalence of BPE continues to increase, with up to 50% of men over 50 experiencing LUTS and up to 80% of those over 80 years old affected (1). Notably, the coexistence of constipation, often subclinical, can complicate the management of LUTS. Studies have shown that patients with BPE and LUTS who also experience constipation benefit from managing both conditions simultaneously (2). Constipation, even when subclinical, may exacerbate LUTS due to the shared neural pathways between the lower urinary tract and the bowel. This overlap in dysfunction suggests that addressing both conditions in tandem might improve patient outcomes.

PFMT has emerged as an effective intervention for managing constipation, and more recently, there has been growing interest in its potential role in improving BPE symptoms. The pelvic floor muscles play a crucial role in both bladder and bowel function, with improper coordination contributing to dysfunction in both systems (3). Our study aimed to investigate the role of PFMT in patients with BPE and LUTS, irrespective of the presence of clinically significant constipation, as a first-of-its-kind prospective investigation in this domain.

Table 2. Showing results after 6 weeks of treatment			
Parameters at 6 weeks	**Group I (n=53)**	**Group II (n=57)**	**p-value**
IPSS	15±4	13±3	0.003
Q_{max}	11.1±0.9 mL/sec	12.4±1.5 mL/sec	0.001
PVR	83±23 mL	71±22 mL	0.006
IPSS: International Prostate Symptom Score, PVR: Post-void residual volume, Q_{max}: Maximum urinary flow rate			

The results of our study demonstrate that combining PFMT with standard medical treatment (Silodosin) led to significantly improved outcomes when compared to medical treatment alone. The patients in group II, who received both Silodosin and PFMT, showed a reduction in IPSS scores, improvement in Q_{max}, and a reduction in PVR, compared to the control group, which only received Silodosin. These findings align with previous studies suggesting that PFMT can enhance the effectiveness of pharmacological interventions for LUTS (4,5).

Several studies have highlighted the interconnected nature of pelvic floor dysfunction in both bladder and bowel disorders. A systematic review by Khera et al. (3) demonstrated that PFMT could alleviate functional bowel symptoms in individuals with inflammatory bowel disease, emphasizing the potential of PFMT in managing overlapping dysfunctions between the bladder and bowel (6). This review supports the findings of our study, suggesting that PFMT not only improves bowel function but also positively affects urinary symptoms in patients with BPE.

In another study, Yonguç et al. (2) examined the impact of chronic constipation on LUTS and uroflowmetry parameters in men (7). They found that constipation exacerbates LUTS and negatively affects urodynamic parameters. Their research further supports the hypothesis that addressing constipation may lead to improvements in LUTS, even in the absence of overt constipation. Our study adds to this literature by demonstrating that PFMT, an intervention aimed at improving pelvic floor muscle coordination, can lead to significant improvements in both urinary and bowel function, regardless of the presence of clinically significant constipation.

The benefits of PFMT in the context of BPE may be due to its ability to strengthen the pelvic floor muscles, leading to improved bladder emptying and better control of urinary flow. Studies have shown that strengthening these muscles can increase bladder compliance, reduce detrusor overactivity, and enhance the bladder's ability to empty efficiently, all of which are essential for managing LUTS (8,9). Furthermore, PFMT can reduce the risk of urinary retention, a common complication in patients with BPE (10).

While our study provides valuable insights, it also has limitations that warrant further exploration. The relatively small sample size of 53 patients in group I and 57 in group II may limit the generalizability of the results. Additionally, the short follow-up period of 6 weeks is insufficient to assess the long-term benefits and sustainability of PFMT in managing BPE and LUTS. Larger multicentric studies with longer follow-up periods are needed to confirm our findings and establish PFMT as a standard adjunctive therapy for BPE. Future research should also explore the potential mechanisms through which PFMT improves bladder and bowel function, as well as its long-term effects on symptom relief and QoL (11,12).

Our study supports the hypothesis that PFMT can significantly improve the management of BPE with LUTS, enhancing the effectiveness of pharmacological treatments such as alpha-blockers. The findings suggest that PFMT should be considered as an adjunctive therapy in the management of BPE, particularly for patients with concomitant bowel dysfunction. This study provides compelling evidence that PFMT leads to early improvement in LUTS within six weeks. While long-term efficacy requires further assessment, short-term benefits were clear. A key strength of this study is the integration of EMG biofeedback, ensuring adherence and correct execution of PFMT. The findings indicate that constipation status influences PFMT outcomes, reinforcing the need for holistic management of LUTS.

This study demonstrates that PFMT is a promising adjunctive therapy in the management of BPE with LUTS. The significant improvements observed in the PFMT group, including reductions in IPSS, better uroflowmetry parameters, and lower PVR volumes, highlight the potential of PFMT to enhance the effectiveness of standard pharmacological treatments like alpha-blockers. The findings suggest that PFMT can be particularly beneficial for patients with concurrent bowel dysfunction, as it addresses the interconnectedness of bladder and bowel function. Despite the promising results, further research with larger sample sizes and longer follow-up periods is needed to confirm the long-term benefits and sustainability of PFMT in managing BPE and LUTS. Given its potential, PFMT should be considered as a viable addition to the treatment regimen for BPE, particularly in patients with overlapping bowel dysfunction.

Study Limitations

One key limitation of this study is selection bias due to the non-randomized study design. Patients self-selected into the PFMT group based on their willingness to participate in the intervention, which may have introduced motivational bias, as those more committed to symptom improvement were likely to adhere better to treatment. Additionally, because the study was conducted at two tertiary care centers, the patient population may not be fully representative of community-based or primary care settings, potentially affecting generalizability. Another limitation is the relatively short follow-up period of six weeks, which restricts our ability to assess the long-term sustainability of PFMT benefits. A longer follow-up period (at least six months) would be necessary to evaluate whether improvements in LUTS persist over time. Moreover, although adherence to PFMT was monitored using EMG biofeedback, real-world compliance outside of supervised sessions remains uncertain. Future studies

should incorporate objective long-term adherence monitoring to validate the feasibility of PFMT as a routine intervention.

Conclusion

What this study adds to the existing literature is that PFMT, when combined with alpha-blocker therapy, significantly improves LUTS in men with BPE, irrespective of constipation status. This study provides novel insights into the role of pelvic floor rehabilitation in BPE management and supports the integration of PFMT as an adjunctive therapy to pharmacological treatment.

Ethics

Ethics Committee Approval: The study was approved by the Institutional Ethics Committee of the KMC Medical College and Hospital (approval no: IEC/KMC/2025/0476, date: 08.01.2025).

Informed Consent: Proper informed and written consent had been taken from all the patients.

Footnotes

Authorship Contributions

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

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

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References

1. Lokeshwar SD, Harper BT, Webb E, Jordan A, Dykes TA, Neal DE Jr, Terris MK, Klaassen Z. Epidemiology and treatment modalities for the management of benign prostatic hyperplasia. Transl Androl Urol. 2019;8:529-539. [Crossref]
2. Yonguç T, Şen V, Bozkurt Hİ, Aydın ME, Polat S, Yarımoğlu S. Impact of chronic constipation on lower urinary tract symptoms and uroflowmetry parameters in men. J Urol Surg. 2019;6:308-313. [Crossref]
3. Khera AJ, Chase JW, Salzberg M, Thompson AJV, Kamm MA. Systematic review: pelvic floor muscle training for functional bowel symptoms in inflammatory bowel disease. JGH Open. 2019;3:494-507. [Crossref]
4. Lloyd GL, Marks JM, Ricke WA. Benign prostatic hyperplasia and lower urinary tract symptoms: what is the role and significance of inflammation? Curr Urol Rep. 2019;20:54. [Crossref]
5. Hagovska M, Svihra J Sr, Macko L, Breza J Jr, Svihra J Jr, Luptak J, Lachvac L. The effect of pelvic floor muscle training in men with benign prostatic hyperplasia and overactive bladder. World J Urol. 2024;42:287. [Crossref]
6. Okawa, Y. Effectiveness of pelvic floor muscle training for treating faecal incontinence. Gastrointest. Disord. 2024;6:774-783. [Crossref]
7. Vrolijks RO, Notenboom-Nas FJM, de Boer D, Schouten T, Timmerman A, Zijlstra A, Witte LPW, Knol-de Vries GE, Blanker MH. Exploring pelvic floor muscle activity in men with lower urinary tract symptoms. Neurourol Urodyn. 2020;39:732-737. [Crossref]
8. Woodley SJ, Boyle R, Cody JD, Mørkved S, Hay-Smith EJC. Pelvic floor muscle training for prevention and treatment of urinary and faecal incontinence in antenatal and postnatal women. Cochrane Database Syst Rev. 2017;12:CD007471. [Crossref]
9. Ali M, Hutchison DD, Ortiz NM, Smith RP, Rapp DE. A narrative review of pelvic floor muscle training in the management of incontinence following prostate treatment. Transl Androl Urol 2022;11:1200-1209. [Crossref]
10. Bearelly P, McVary KT. The role of benign prostatic hyperplasia treatments in ejaculatory dysfunction. Fertil Steril. 2021;116:611-617. [Crossref]
11. Docimo L, Gualtieri G, Gambardella C, Brusciano L. Role of pelvic floor rehabilitation: Patient selection and treatment. In: CTY - CHAP. 2022 Oct 10. p. 77-84. [Crossref]
12. Bø K, Kvarstein B, Nygaard I. Lower urinary tract symptoms and pelvic floor muscle exercise adherence after 15 years. Obstet Gynecol. 2005;105:999-1005. [Crossref]

ORIGINAL RESEARCH
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Optimizing Prostate Cancer Diagnosis: A Prospective, Randomized Comparison of 12-core vs. 20-core Biopsy for Detection Accuracy and Upgrading Risk

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

Transrectal ultrasound guided systematic prostate biopsy is widely regarded as the gold standard for diagnosing prostate cancer. Although the traditional 12-core biopsy protocol is extensively utilized, its capacity to detect clinically significant cancers is constrained due to the heterogeneous distribution of tumors. Multiparametric magnetic resonance imaging and targeted biopsies have emerged as significant components in the diagnostic process. However, their extensive use is impeded by high cost, limited accessibility, and technical challenges. Consequently, systematic biopsy techniques maintain their importance due to their cost-effectiveness and accessibility, despite the ongoing controversy regarding the efficacy of standard biopsy protocols and the potential benefit of extended biopsy schemes in improving diagnostic accuracy. The present study aims to compare the efficacy of 12 and 20 core biopsy protocols in the diagnosis of prostate cancer.

Abstract

Objective: This study compares the diagnostic efficacy of 12-core and 20-core transrectal ultrasound (TRUS)-guided prostate biopsy protocols in detecting prostate cancer (PCa) and evaluates the clinical significance of extended biopsy protocols.

Materials and Methods: A prospective, randomized, single-center study was conducted with 511 patients who underwent TRUS-guided prostate biopsy for suspected PCa. Patients were randomly assigned to either a 12-core biopsy group (n=248) or a 20-core biopsy group (n=263). The primary endpoint was the cancer detection rate, while secondary endpoints included clinically significant cancer detection [International Association of Urological Pathology (ISUP) grade ≥2], biopsy-pathology correlation, upgrade rates, and complication assessment.

Results: The 20-core biopsy group had a significantly higher cancer detection rate (39.2%) compared to the 12-core group (28.6%). However, clinically significant cancer detection rates were similar between the groups. The 20-core protocol reduced the likelihood of ISUP grade 1 cancer being upgraded after radical prostatectomy, improving diagnostic accuracy. A strong correlation was observed between tumor burden in biopsy and radical prostatectomy specimens. Prostate-specific antigen density analysis identified an optimal cutoff value of 0.1058, providing 66.1% diagnostic accuracy. Complication rates were comparable between the protocols [5.65% (n=14), 6.46% (n=17)].

Conclusion: The 20-core biopsy protocol enhances overall cancer detection and reduces unnecessary upgrading in low-risk PCa cases, improving diagnostic precision. While multiparametric magnetic resonance imaging (MRI)-guided fusion biopsy offers high accuracy, its limited availability makes extended biopsy protocols a viable alternative, particularly in centers without MRI-based targeting methods. Further multicenter studies are needed to refine biopsy strategies for clinical practice.

Keywords: Prostate biopsy, prostate cancer, PSA density, radical prostatectomy

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Introduction

Prostate cancer (PCa) is one of the most frequently diagnosed malignancies in men worldwide and ranks second in cancer-related mortality (1,2). While strategies aimed at early diagnosis of clinically significant cancer have been implemented, continuous improvements in diagnostic strategies remain necessary (3). Although biochemical markers and imaging techniques play a crucial role in PCa diagnosis, histopathological confirmation is still required for a definitive diagnosis (4).

Transrectal ultrasound (TRUS)-guided systematic prostate biopsy has long been considered the gold standard for diagnosing PCa (5). The traditional 12-core biopsy protocol is widely used; however, its limited sensitivity to the heterogeneous distribution of tumors has raised concerns about its ability to detect clinically significant cancers effectively (6). Consequently, expanded biopsy protocols with more cores have been proposed to improve diagnostic accuracy, particularly in high-risk cases.

In recent years, multiparametric magnetic resonance imaging (mpMRI) and targeted fusion biopsies have gained prominence in diagnostic workflows, enhancing detection rates for clinically significant PCa (7,8). mpMRI-guided biopsies have demonstrated superior sensitivity in identifying clinically relevant tumors compared to systematic biopsies (9). However, the high cost, limited accessibility, and technical challenges of advanced imaging techniques restrict their widespread application in all patients.

Given these constraints, traditional systematic biopsy techniques remain crucial due to their cost-effectiveness and widespread availability. Standard biopsy protocols continue to play a pivotal role, particularly in cases where imaging fails to identify suspicious lesions and biopsy remains necessary (10). However, there is ongoing debate regarding the effectiveness and necessity of standard biopsy protocols and whether more extended biopsy schemes provide superior diagnostic accuracy, and should be integrated into routine clinical practice (11,12).

This study aims to compare the diagnostic efficacy of 12-core and 20-core prostate biopsy protocols in detecting PCa. Specifically, the study evaluates cancer detection rates, identification of clinically significant cancers, upgrade rates after biopsy, and complication profiles. Furthermore, the potential impact of extended biopsy protocols on clinical practice will be discussed in the light of the current literature.

Materials and Methods

Study Design and Ethical Approval

This study is a prospective, randomized, single-center trial conducted between January 2011 and January 2014 to compare the diagnostic efficacy of 12-core and 20-core biopsy protocols in patients undergoing their first TRUS-guided prostate biopsy due to suspected PCa. The study was approved by the Clinical Research Ethics Committee of Düzce University Faculty of Medicine (decision no: 2010/101, date: 30.12.2010), and written informed consent was obtained from all participants prior to their inclusion in the study.

Study Population and Inclusion Criteria

The study included patients who presented to the urology outpatient clinic with lower urinary tract symptoms and required evaluation for suspected PCa. The inclusion criteria were a total prostate-specific antigen (tPSA) level between 2.5 and 10 ng/mL, suspicious digital rectal examination (DRE), and eligibility for the first TRUS-guided prostate biopsy. Patients were excluded if they had an active urinary tract infection, were had undergone urethral catheterization within the past two weeks, had a tPSA level exceeding 10 ng/mL, were using 5-alpha reductase inhibitors or phytotherapeutic agents, or had previously undergone transurethral prostate surgery.

Randomization and Study Groups

This study adheres to the CONSORT guidelines for randomized clinical trials. A total of 511 patients who met the inclusion criteria were randomly assigned to one of the two groups by computer-assisted block randomisation using the unequal allocation method with variable block sizes: the 12-core biopsy group (12PB, n=248) and the 20-core biopsy group (20PB, n=263). The randomisation process was performed using the Mersenne Twister algorithm, a high-quality pseudorandom number generator known for its long period and reliability in random sequence generation. Sample size determination was conducted through a power analysis to establish the minimum number of participants required for the study. Demographic characteristics, tPSA and free PSA (fPSA) levels, DRE findings, prostate volumes, and biopsy pathology results were evaluated for all patients. The CONSORT flow diagram for patient allocation and study progression is provided in Figure 1.

Biopsy Procedure

All biopsies were performed under local anesthesia (1% lidocaine) and with the prophylactic administration of 500 mg ciprofloxacin, using an 18-gauge biopsy needle and an automatic biopsy gun, via the transrectal route under TRUS guidance. The 12-core biopsy protocol was based on the standard sextant biopsy scheme. In this scheme, samples were obtained from the lower, middle, and upper regions of both prostate lobes, and these cores were symmetrically extended to obtain a total of 12 biopsy samples. In the extended 20-core biopsy protocol, additional samples were taken from the anterior and lateral prostate regions, expanding the biopsy coverage (13).

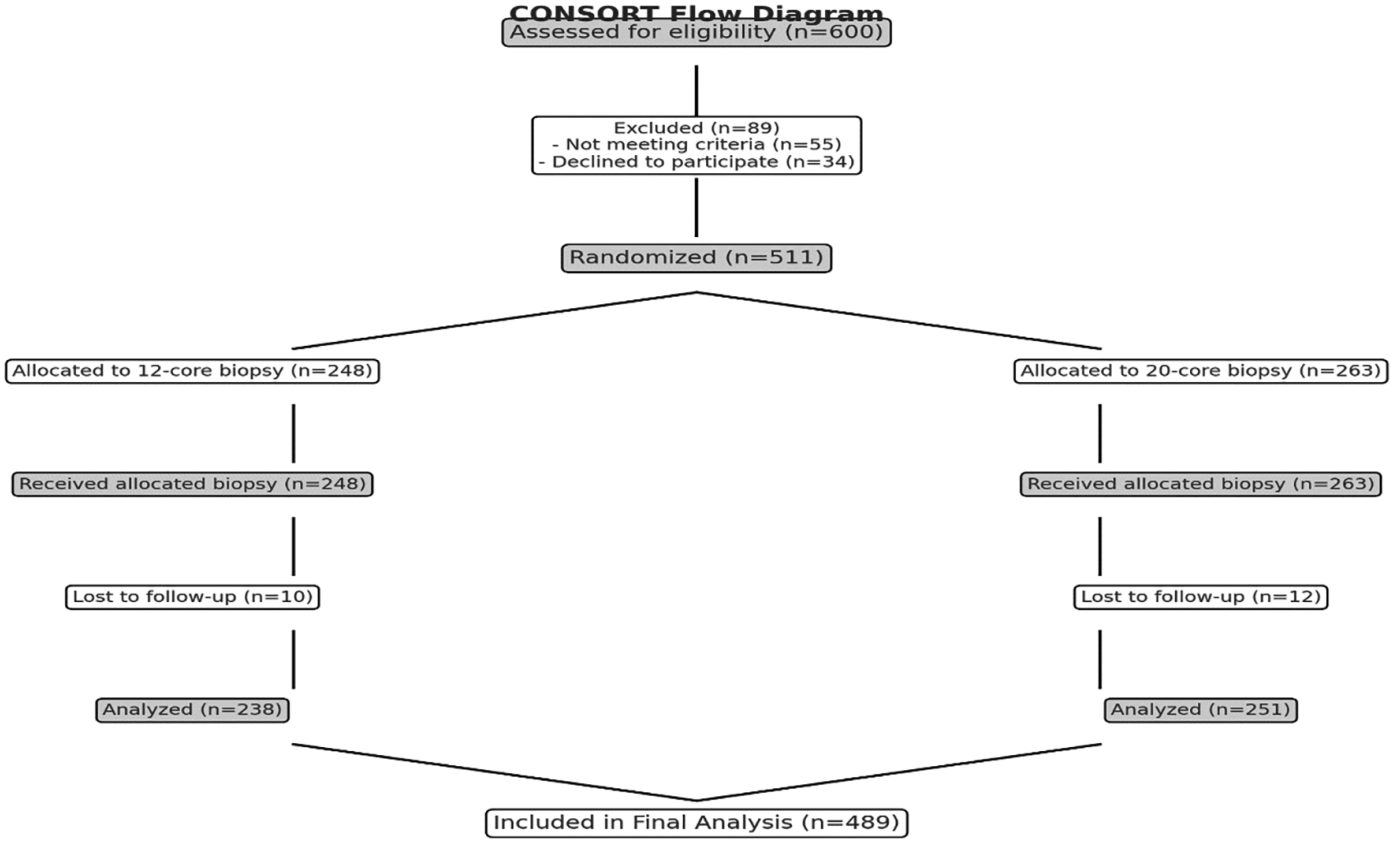

Figure 1. The flow diagram for patient allocation and study

Endpoints

The primary endpoint of the study was the cancer detection rate for each biopsy protocol. Secondary endpoints included the detection of clinically significant cancers [International Association of Urological Pathology (ISUP) grade ≥2], correlation between biopsy findings and radical prostatectomy specimens, staging discrepancies (upgrade and downgrade rates), and post-procedural complication rates.

Complication Monitoring

All patients were assessed before the procedure and again two weeks after the biopsy for potential complications, including urinary symptoms, fever, dysuria, hematuria, hematospermia, and rectal bleeding. Complications were classified using the Clavien-Dindo grading system, as recommended by the European Association of Urology, and statistical comparisons between the groups were performed.

Statistical Analysis

Data analysis was performed using the Statistical Package for the Social Sciences (SPSS). Descriptive statistics were presented as mean ± standard deviation, minimum-maximum values, and percentage distributions. The Fisher-Freeman-Halton exact test was used to analyze categorical variables, while independent t-tests and one-way analysis of variance (ANOVA) were applied for continuous variables. The relationship between the tumor proportion detected in biopsy specimens and that in radical prostatectomy specimens was assessed using Pearson's correlation analysis. The diagnostic value of PSA density was evaluated using receiver operating characteristic (ROC) curve analysis to determine the optimal cut-off value. A p-value of <0.05 was considered statistically significant.

Results

According to Table 1, a total of 511 patients were included in the study, with 248 undergoing a 12-core biopsy and 263 undergoing a 20-core biopsy. The mean age of patients in the 12-core biopsy group was 63.25±6.78 (44-78) years, while in the 20-core biopsy group, it was 62.14±7.56 (39-79) years (p=0.079). The mean PSA levels, ratio of free to total PSA levels and the prostate volumes were also similar, between the two groups. The rate of suspicious DRE was slightly higher in the 20-core biopsy group (31.78%) compared to the 12-core biopsy group (28.74%), but this difference was not statistically significant (p=0.518).

Table 1. Baseline characteristics and pathology results

Variable/pathology	12-core biopsy (mean ± SD)	12-core biopsy (minimum-maximum)	20-core biopsy (mean ± SD)	20-core biopsy (minimum-maximum)	p-value
Age (years)	63.25±6.78	44-78	62.14±7.56	39-79	0.079
PSA (ng/mL)	5.88±1.95	0.04-10.0	5.92±2.06	0.70-10.02	0.810
Free PSA (ng/mL)	1.33±0.945	0.03-6.90	1.23±0.798	0.07-5.60	0.387
PSA ratio	0.227±0.117	0.008-0.69	0.207±0.092	0.011-0.56	0.148
Prostate volume (mL)	60.09±31.94	13-184	60.55±34.12	11-243	0.882
Abnormal DRE (%)	28.74%	N/A	31.78%	N/A	0.518
BPH	166 (66.9%)	N/A	151 (57.4%)	N/A	N/A
Prostate cancer	71 (28.6%)	N/A	103 (39.2%)	N/A	0.024
ASAP	9 (3.6%)	N/A	4 (1.5%)	N/A	N/A
HGPIN	2 (0.8%)	N/A	5 (1.9%)	N/A	N/A

PSA: Prostate-specific antigen, DRE: Digital rectal examination, BPH: Benign prostatic hyperplasia, ASAP: Atypical small acinar proliferation, HGPIN: High-grade prostatic intraepithelial neoplasia, SD: Standard deviation

Histopathological evaluation demonstrated that the overall cancer detection rate was significantly higher in the 20-core biopsy group (39.2%) compared to the 12-core biopsy group (28.6%) (p=0.024). The rates of atypical small acinar proliferation and high-grade prostatic intraepithelial neoplasia were low and comparable between the two groups.

According to Table 2, the distributions of ISUP grade groups (BxISUPG) showed no statistically significant difference (p=0.503). However, when ISUP grades from radical prostatectomy specimens (RpISUPG) were analysed, significant differences were found: in the 12-core biopsy group, ISUP grade 2 biopsy cases comprised 45.83%, and in the 20-core biopsy group, 20.29% (p=0.0061).

According to Table 3, a significant positive correlation (r=0.510, p<0.001) was found between the tumor percentage detected in the biopsy samples and the tumor percentage observed in the radical prostatectomy specimens. Regarding staging discrepancies, the overall upgrade rate was 41.03%, while the downgrade rate was 7.69%. Although the upgrade rate was higher in the 12-core biopsy group (47.92%) compared to the 20-core biopsy group (36.23%) (p=0.089), this difference did not reach statistical significance. Similarly, the downgrade rates were comparable between the two groups (8.33% *vs.* 7.25%, p=0.729). Regarding radical prostatectomy outcomes, the overall prostatectomy rate was higher in the 20-core biopsy group (26.3%) compared to the 12-core biopsy group (19.4%), although this difference was not statistically significant.

However, the percentage of cases where ISUP grade group remained unchanged was slightly higher in the 20-core biopsy group (56.52%) compared to the 12-core biopsy group (43.75%), (p=0.585). These findings suggest that a higher biopsy core count may reduce the likelihood of upgrading but does not significantly affect downgrading rates.

As shown in Figure 2, biopsy tumor burden is strongly correlated with radical prostatectomy tumor burden, supporting the predictive value of biopsy-based assessments.

When patients who met the active surveillance criteria were analyzed, 47 patients were identified in the 12-core biopsy group and 74 patients were identified in the 20-core biopsy group. When the results of the radical prostatectomies performed on these patients were examined, the ISUP grade group 1 upgrade rate was significantly lower in the 20-core biopsy group (35.6%) compared to the 12-core biopsy group (62.5%), (p=0.020) (Table 4). This suggests that a higher biopsy core number increases the

Table 2. ISUP grade biopsy and radical prostatectomy

ISUP grade	12-core biopsy (n, %)	20-core biopsy (n, %)	p-value	RP (12-core)	RP (20-core)	p-value (RP)
1	47 (66.2%)	74 (71.84%)	0.503	29.17%	49.28%	0.047
2	14 (19.72%)	17 (16.5%)	0.688	45.83%	20.29%	0.006
3	8 (11.27%)	7 (6.8%)	0.411	10.42%	17.39%	0.431
4	1 (1.41%)	0 (0.0%)	0.408	6.25%	5.80%	0.874
5	1 (1.41%)	5 (4.85%)	0.403	8.33%	7.25%	1.000
2-5	24 (33.8%)	29 (28.16%)	0.503	70.83%	50.72%	0.0296

ISUP: International Society of Urological Pathology, RP: Radical prostatectomy, BxISUPG: Biopsy ISUP grade, RpISUPG: Radical prostatectomy ISUP grade

Table 3. Biopsy and radical prostatectomy correlation + staging errors			
Metric/category	**12-core biopsy (mean ± SD)**	**20-core biopsy (mean ± SD)**	**p-value**
Pearson correlation (r)	0.510	N/A	N/A
P-value	<0.0001	N/A	N/A
Sample size (N)	117	N/A	N/A
Upgraded	47.92%	36.23%	0.089
Downgraded	8.33%	7.25%	0.729
Unchanged	43.75%	56.52%	0.585
R. Prostatectomy performed	19.4%	26.3%	0.073
SD: Standard deviation			

Table 4. ISUP G1 upgrade rate and radical prostatectomy outcomes			
ISUP G1 patients Metric/radical prostatectomy outcome	**12-core biopsy (mean ± SD)**	**20-core biopsy (mean ± SD)**	**p-value**
Total	47	74	N/A
Radical prostatectomy performed	32	45	N/A
Count of ISUP G1 upgrades	22 (62.5%)	16 (35.6%)	0.020
ISUP G1: International Society of Urological Pathology grade 1, SD: Standard deviation			

accuracy of identifying clinically insignificant PCa and decreases the likelihood of upgrading after radical prostatectomy.

Since there was a significant difference between benign prostatic hyperplasia (BPH) and PCa groups in terms of PSA density, a cutoff value that could distinguish these two groups was determined. As a result of the ROC curve analysis, when PCA was diagnosed in patients with a PSA density of 0.1058 and above, the correct diagnosis rate was calculated as 66.1% (Figure 3).

Grade I complications according to the Clavien-Dindo classification were detected in a total of 31 patients. The most common complaints were hematuria and painful urination. 12-core biopsy group 5.65% (14) 20-core biopsy group 6.46% (17). No statistical difference was detected between the two groups (p=0.840).

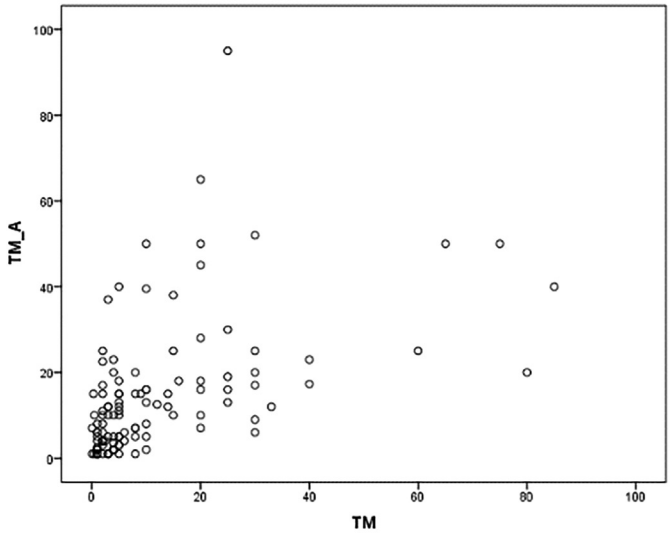

Figure 2. The relationship between the percentage of tumours in the biopsy (TM_A) and the percentage of tumours in the radical prostatectomy specimen (TM)

Discussion

This study evaluates the clinical relevance of extended biopsy protocols by comparing the diagnostic efficacy of 12-core and

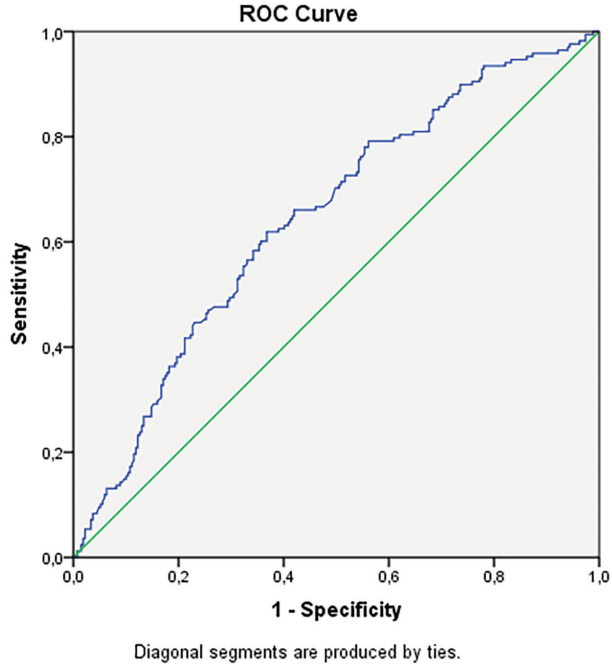

Figure 3. ROC curve analysis of PSA density 0.1058 and prostate ca diagnosis
ROC: Receiver operating characteristic, PSA: Prostate-specific antigen

20-core biopsy protocols in the detection of prostate cancer. The prospective and randomised design increased the reliability and generalisability of the findings. The results showed that the 20-core biopsy protocol increased the overall cancer detection rate and better identified PCa cases suitable for active surveillance when evaluated with radical prostatectomy outcomes. Consequently, the 20-core biopsy is considered a valid alternative for patients with no suspicious lesions detected on mpMRI or in centers where mpMRI is not available, thus contributing significantly to the clinical decision-making process.

The cancer detection rate of the 20-core biopsy protocol was significantly higher than that of the 12-core biopsy in our study (39.2% *vs.* 28.6%, p=0.024). Similarly, many previous studies have demonstrated that extended biopsy protocols improve the accuracy of PCa diagnosis (14-16). The standard 12-core biopsy protocol carries the risk of missing lesions in the lateral zones of the prostate, whereas extended biopsy protocols may better capture tumor heterogeneity, reducing the false-negative rate. However, some studies suggest that extended biopsy protocols may lead to overdiagnosis of clinically insignificant PCa (17-19). Our study demonstrates a lower upgrading rate in cancers detected by the 20-core biopsy, which is an important finding that may enhance diagnostic reliability in patients undergoing biopsy for active surveillance.

A significant proportion of PCa that are initially deemed clinically insignificant based on biopsy findings undergo upgrading after radical prostatectomy. Our findings show that patients undergoing 20-core biopsy in ISUP grade group 1 cases have a significantly lower upgrading rate after radical prostatectomy compared to those undergoing 12-core biopsy (35.6% *vs.* 62.5%). It is thought that 20-core prostate biopsy allows a more precise characterization of this group, especially in patients eligible for active surveillance, and that unnecessary overtreatment may be significantly reduced. In this context, it is anticipated that active surveillance can be implemented more safely and that the need for treatment in patients undergoing 20-core biopsy may be reduced. This suggests that the 20-core biopsy scheme provides a more accurate characterization of low-grade tumors, reducing overtreatment (20). Previous studies have also emphasized that accurate ISUP grading on biopsy is crucial in patients undergoing active surveillance, as misleadingly low biopsy grades may lead to underestimation of aggressive disease (21,22).

A significant positive correlation was found between the percentage of tumor detected in biopsy samples and the tumor percentage observed in radical prostatectomy specimens (r=0.510, p<0.001, Table 3, Figure 2) (23). This suggests that biopsy tumor burden is a strong predictor of tumor extent in surgical specimens. Literature supports that increasing biopsy sampling density strengthens this correlation, reinforcing the prognostic reliability of extended biopsy protocols (24). A high tumour percentage in biopsy samples can provide important information about the extent of cancer in the organ. Accordingly, this ratio can be considered a determining factor in the treatment planning of patients with a high tumour percentage in biopsy material.

Our analysis of the PSA density ROC curve indicated that a PSA density cutoff value of 0.1058 provides a diagnostic accuracy of 66.1% for PCa detection, consistent with the current literature (Figure 3). The diagnostic value of PSA density has been highlighted in previous studies, particularly in differentiating BPH from PCa (25,26). Studies have shown that threshold values for PSA density (e.g., ≥0.10 or ≥0.15) increase clinically significant cancer detection rates and are recommended to be included in clinical decision-making processes to prevent unnecessary biopsies (27). However, PSA density alone may not be sufficient, and it is recommended that it be used in combination with other biomarkers for optimal clinical decision-making (28).

MpMRI-guided targeted biopsies have become a gold-standard method in PCa diagnosis. Studies have demonstrated that mpMRI-guided biopsies have a higher clinically significant cancer detection rate compared to standard biopsy techniques (8,29). However, mpMRI is not universally accessible, and factors such as high costs, a steep learning curve, and technical requirements limit its widespread use. Our results indicate that since fusion biopsy is not available in every center, extended biopsy protocols remain a valuable alternative for clinical practice. In healthcare settings with limited MRI availability, the 20-core biopsy strategy has been shown to improve diagnostic accuracy compared to standard biopsy methods (30). Recently, the addition of perilesional sampling and standard biopsy to MRI fusion biopsy has also been recommended, while studies have suggested that 20-core biopsy should be performed in patients without suspicious lesions in MRI (14,31,32).

Study Limitations

This study has several limitations. First, it is a single-center study, which limits the generalizability of the findings to different patient populations. Variability in biopsy outcomes across different institutions must be considered when applying these results to broader clinical settings.

This study lacks long-term follow-up data. Specifically, in patients undergoing active surveillance, long-term tumor progression and false-negative biopsy outcomes were not assessed. Further prospective studies are needed to evaluate the long-term impact of extended biopsy protocols on disease progression and clinical outcomes.

The discrepancy between biopsy and radical prostatectomy findings is another important limitation. Biopsy may not fully capture tumor heterogeneity, and even with extended biopsy protocols, some tumor regions may remain unsampled, leading to false-negative results. Although our study demonstrated a significant correlation between biopsy and surgical pathology outcomes, discrepancies may still occur due to sampling errors and tumor heterogeneity.

None of the patients in our study underwent mpMRI, and the lack of fusion biopsy and mpMRI guidance is another limitation. The lack of fusion biopsy and mpMRI guidance in our study is another limitation. While mpMRI-guided biopsies have been shown to improve diagnostic accuracy, this technique is not widely available in all healthcare settings. Therefore, our findings suggest that extended biopsy protocols remain a viable alternative, particularly in centers without access to MRI or fusion biopsy technology.

Post-biopsy complications were not extensively analyzed in this study. While procedural complications were reported using the Clavien-Dindo classification, detailed evaluation of serious complications such as sepsis, hemorrhage, or urinary retention was not performed. Further large-scale studies are needed to assess whether extended biopsy protocols significantly increase procedural risks.

Cost-effectiveness analysis was not conducted. Increasing the number of biopsy cores may prolong the procedure, affect patient comfort, and increase the workload for pathology departments. Future studies should evaluate the financial impact of extended biopsy protocols and determine their cost-effectiveness in different clinical settings.

Conclusion

This study demonstrates that the 20-core biopsy protocol enhances overall cancer detection rates, reduces unnecessary upgrading in low-grade PCa, and strengthens the prognostic reliability of biopsy findings. The results suggest that the 20-core biopsy provides a more accurate risk stratification, particularly in patients undergoing active surveillance, potentially preventing overtreatment.

Although mpMRI-guided fusion biopsy offers high diagnostic accuracy, it is not widely available due to financial and logistical constraints. Our findings support that extended biopsy protocols remain a valuable diagnostic alternative, particularly in healthcare settings with limited MRI access.

Future multicenter, long-term follow-up studies are needed to further evaluate the clinical impact of extended biopsy protocols on patient outcomes. Additionally, cost-effectiveness analyses should be conducted to assess the financial feasibility of implementing extended biopsy strategies in routine clinical practice.

Ethics

Ethics Committee Approval: Approval was received from the Clinical Research Ethics Committee of Düzce University Faculty of Medicine (approval number: 2010/101, date: 30.12.2010).

Informed Consent: Informed consent forms were obtained from all patients.

Footnotes

Authorship Contributions

Surgical and Medical Practices: S.Ç., A.Ç., Y.Ş., A.T., Concept: A.T., Design: A.T., Data Collection or Processing: S.Ç., A.Ç., M.A.K., Analysis or Interpretation: D.B., Y.Ş., M.A.K., A.T., Literature Search: D.B., A.Ç., Writing: D.B., Y.Ş., A.T.

Conflict of Interest: Ali Tekin MD is section editor in Journal of Urological Surgery. He had no involvement in the peer-review of this article and had no access to information regarding its peer-review.

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References

1. Sekhoacha M, Riet K, Motloung P, Gumenku L, Adegoke A, Mashele S. Prostate cancer review: genetics, diagnosis, treatment options, and alternative approaches. Molecules. 2022;27:5730. [Crossref]
2. Naqvi SAA, Riaz IB, Bibi A, Khan MA, Imran M, Khakwani KZR, Raina A, Anjum MU, Cobran EK, Warner JL, Hussain SA, Singh P, Childs DS, Baca SC, Orme JJ, Mateo J, Agarwal N, Gillessen S, Murad MH, Sartor O, Bryce AH. Heterogeneity of the treatment effect with PARP inhibitors in metastatic castration-resistant prostate cancer: a living interactive systematic review and meta-analysis. Eur Urol. 2025:S0302-283802760-X. [Crossref]
3. James ND, Tannock I, N'Dow J, Feng F, Gillessen S, Ali SA, Trujillo B, Al-Lazikani B, Attard G, Bray F, Compérat E, Eeles R, Fatiregun O, Grist E, Halabi S, Haran Á, Herchenhorn D, Hofman MS, Jalloh M, Loeb S, MacNair A, Mahal B, Mendes L, Moghul M, Moore C, Morgans A, Morris M, Murphy D, Murthy V, Nguyen PL, Padhani A, Parker C, Rush H, Sculpher M, Soule H, Sydes MR, Tilki D, Tunariu N, Villanti P, Xie LP. The Lancet Commission on prostate cancer: planning for the surge in cases. Lancet. 2024;403:1683-1722. [Crossref]
4. Zhu M, Liang Z, Feng T, Mai Z, Jin S, Wu L, Zhou H, Chen Y, Yan W. Up-to-date imaging and diagnostic techniques for prostate cancer: a literature review. Diagnostics (Basel). 2023;13:2283. [Crossref]
5. Benelli A, Vaccaro C, Guzzo S, Nedbal C, Varca V, Gregori A. The role of MRI/TRUS fusion biopsy in the diagnosis of clinically significant prostate cancer. Ther Adv Urol. 2020;12:1756287220916613. [Crossref]
6. Serefoglu EC, Altinova S, Ugras NS, Akincioglu E, Asil E, Balbay MD. How reliable is 12-core prostate biopsy procedure in the detection of prostate cancer? Can Urol Assoc J. 2013;7:E293-E298. [Crossref]
7. Kim MM, Wu S, Lin SX, Crotty RK, Harisinghani M, Feldman AS, Wu CL, Dahl DM. Transperineal multiparametric magnetic resonance imaging-ultrasound fusion targeted prostate biopsy combined with standard template improves prostate cancer detection. J Urol. 2022;207:86-94. [Crossref]

8. Bjurlin MA, Mendhiratta N, Wysock JS, Taneja SS. Multiparametric MRI and targeted prostate biopsy: improvements in cancer detection, localization, and risk assessment. Cent European J Urol. 2016;69:9-18. [Crossref]
9. Giganti F, Moore CM. A critical comparison of techniques for MRI-targeted biopsy of the prostate. Transl Androl Urol. 2017;6:432-443. [Crossref]
10. Pahwa S, Schiltz NK, Ponsky LE, Lu Z, Griswold MA, Gulani V. Cost-effectiveness of MR imaging-guided strategies for detection of prostate cancer in biopsy-naive men. Radiology. 2017;285:157-166. [Crossref]
11. Chun FK, Epstein JI, Ficarra V, Freedland SJ, Montironi R, Montorsi F, Shariat SF, Schröder FH, Scattoni V. Optimizing performance and interpretation of prostate biopsy: a critical analysis of the literature. Eur Urol. 2010;58:851-864. [Crossref]
12. Deniffel D, Perlis N, Ghai S, Girgis S, Healy GM, Fleshner N, Hamilton R, Kulkarni G, Toi A, van der Kwast T, Zlotta A, Finelli A, Haider MA. Prostate biopsy in the era of MRI-targeting: towards a judicious use of additional systematic biopsy. Eur Radiol. 2022;32:7544-7554. [Crossref]
13. Leibovici D, Zisman A, Siegel YI, Sella A, Kleinmann J, Lindner A. Local anesthesia for prostate biopsy by periprostatic lidocaine injection: a double-blind placebo controlled study. J Urol. 2002;167:563-565. [Crossref]
14. Kwon HJ, Rhew SA, Yoon CE, Shin D, Bang S, Park YH, Cho HJ, Ha US, Hong SH, Lee JY, Kim SW, Moon HW. Comparing 12-core and 20-core biopsy for prostate cancer diagnosis with transperineal MR/US fusion biopsy: assessing the effective number of systemic cores using propensity score matching. Int Urol Nephrol. 2023;55:2465-2471. [Crossref]
15. Bjurlin MA, Carter HB, Schellhammer P, Cookson MS, Gomella LG, Troyer D, Wheeler TM, Schlossberg S, Penson DF, Taneja SS. Optimization of initial prostate biopsy in clinical practice: sampling, labeling and specimen processing. J Urol. 2013;189:2039-2046. [Crossref]
16. Taneja SS, Bjurlin MA, Carter HB, Cookson MS, Gomella LG, Penson DF, Schellhammer P, Schlossberg S, Troyer D, Wheeler T. Optimal techniques of prostate biopsy and specimen handling. Am. Urol. Assoc., White Paper: Optimal Techniques of prostate biopsy and specimen handling, AUA guideline 2013:1-29. [Crossref]
17. de la Rosette JJ, Wink MH, Mamoulakis C, Wondergem N, ten Kate FJ, Zwinderman K, de Reijke TM, Wijkstra H. Optimizing prostate cancer detection: 8 versus 12-core biopsy protocol. J Urol. 2009;182:1329-1336. [Crossref]
18. Ebtehaj B, Adhami M, Javadi A, Hajmanoochehri F. A Clinicopathologic study of 1598 ultrasound-guided needle prostate biopsies and trends in prostate cancer over a 14-year period. Clin Genitourin Cancer. 2025;23:102272. [Crossref]
19. Mensah JE, Akpakli E, Kyei M, Klufio K, Asiedu I, Asante K, Toboh B, Ashaley MD, Addo BM, Morton B, Quist EA. Prostate-specific antigen, digital rectal examination, and prostate cancer detection: a study based on more than 7000 transrectal ultrasound-guided prostate biopsies in Ghana. Transl Oncol. 2025;51:102163. [Crossref]
20. Özgür A, Özgür G, Şahin B, Filinte D, Tinay İ, Çam HK, Türkeri L. Risk factors of patients with prostate cancer upgrading for international society of urological pathology grade group i after radical prostatectomy. Bull Urooncol. 2022;21:10-13. [Crossref]
21. Srigley JR, Delahunt B, Egevad L, Samaratunga H, Yaxley J, Evans AJ. One is the new six: the International Society of Urological Pathology (ISUP) patient-focused approach to Gleason grading. Can Urol Assoc J. 2016;10:339-341. [Crossref]
22. Gandaglia G, Leni R, Plagakis S, Stabile A, Montorsi F, Briganti A. Active surveillance should not be routinely considered in ISUP grade group 2 prostate cancer. BMC Urol. 2023;23:153. [Crossref]
23. Sebo TJ, Bock BJ, Cheville JC, Lohse C, Wollan P, Zincke H. The percent of cores positive for cancer in prostate needle biopsy specimens is strongly predictive of tumor stage and volume at radical prostatectomy. J Urol. 2000;163:174-178. [Crossref]
24. Dawi L, Belkouchi Y, Lawrance L, Gautier O, Ammari S, Vasseur D, Wirth F, Hadchiti J, Morer S, David C, Bidault F, Balleyguier C, Kind M, Bayle A, Belcaid L, Aldea M, Nicotra C, Geraud A, Sakkal M, Blanc-Durand F, Moog S, Mosele MF, Tagliamento M, Bernard-Tessier A, Verret B, Smolenschi C, Auger N, Gazzah A, Micol JB, Caron O, Hollebecque A, Loriot Y, Besse B, Lacroix L, Rouleau E, Ponce S, André F, Soria JC, Barlesi F, Muller S, Cournede PH, Talbot H, Italiano A, Lassau N. Liquid biopsy versus CT: comparison of tumor burden quantification in 1065 patients with metastases. Radiology. 2024;313:e232674. [Crossref]
25. Saema A, Kochakarn W, Lertsithichai P. PSA density and prostate cancer detection. J Med Assoc Thai. 2012;95:661-666. [Crossref]
26. Aslanoğlu A, Saygın H, Öztürk A, Ergin İE, Asdemir A, Velibeyoğlu AF, Korgalı E. Correlation between PSA density and multiparametric prostate MRI in the diagnosis of prostate cancer. Bull Urooncol. 2024;23:29-35. [Crossref]
27. Cash H, Schostak M. The role of PSA density in the MRI pathway for prostate cancer diagnostics. Prostate Cancer Prostatic Dis. 2023;26:437-438. [Crossref]
28. McNally CJ, Ruddock MW, Moore T, McKenna DJ. Biomarkers that differentiate benign prostatic hyperplasia from prostate cancer: a literature review. Cancer Manag Res. 2020;12:5225-5241. [Crossref]
29. Nawfal G, Sarkis J, Assaf S, Mjaess G, Abi Chebel J, Semaan A, Alkassis M, Nemr E, Kamel G, Ayoub N, Sarkis P. Multiparametric MRI with in-bore targeted biopsy in the diagnostic pathway of prostate cancer: data from a single institution experience. Urol Oncol. 2021;39:781.e9-781.e15. [Crossref]
30. Kasabwala K, Patel N, Cricco-Lizza E, Shimpi AA, Weng S, Buchmann RM, Motanagh S, Wu Y, Banerjee S, Khani F, Margolis DJ, Robinson BD, Hu JC. The learning curve for magnetic resonance imaging/ultrasound fusion-guided prostate biopsy. Eur Urol Oncol. 2019;2:135-140. [Crossref]
31. Malewski W, Milecki T, Tayara O, Poletajew S, Kryst P, Tokarczyk A, Nyk Ł. Role of systematic biopsy in the era of targeted biopsy: a review. Curr Oncol. 2024;31:5171-5194. [Crossref]
32. Oderda M, Dematteis A, Calleris G, Diamand R, Gatti M, Marra G, Adans-Dester G, Al Salhi Y, Pastore A, Faletti R, Gontero P. MRI-targeted prostate fusion biopsy: what are we missing outside the target? Implications for treatment planning. Curr Oncol. 2024;31:4133-4140. [Crossref]

ORIGINAL RESEARCH
Basic Science

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Diagnostic Significance of Immunohistochemical Expression of E-26 Transformation-Specific (ETS)-Related Gene (ERG) and Golgi Membrane Protein 1 (GOLM1) in Prostatic Carcinoma

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

Many practical problems have been encountered in the accurate diagnosis of prostatic carcinoma and its differentiation from benign mimicker lesions, even when using the traditional panel of immunohistochemistry that fails to solve the problems. Thus, our research was motivated by the aim to reduce the undiagnosed cases of carcinoma, and our conclusion was encouraging. The combination of *ERG* and Golgi membrane protein 1 (*GOLM1*) as a diagnostic panel has not been discussed before. According to studies on both elements independently, their combination could be promising. We have found that the combination of *ERG* and *GOLM1* is a promising diagnostic panel for PCa, solving many practical diagnostic problems as traditionally encountered with the older panel, thereby leading to proper treatment and better survival outcomes.

Abstract

Objective: Diagnosis of prostatic adenocarcinoma (PAC) and differentiation from benign mimickers' lesions represent one of the most challenging problems. *ERG* and Golgi membrane protein 1 (*GOLM1*) have a role in PAC and may aid in solving this diagnostic dilemma for appropriate treatment, better prognosis, and survival. The aim of our study is to evaluate the diagnostic accuracy of *ERG* and *GOLM1* co-expression as a panel in PAC and the association between their expression and clinicopathological parameters.

Materials and Methods: This cross-sectional study was conducted on forty cases of PAC and twenty-four cases of benign prostatic lesions. Paraffin blocks of all studied cases were cut, and hematoxylin and eosin slides were examined. Immunohistochemical expressions of *ERG* and *GOLM1* were evaluated.

Results: Nuclear *ERG* and paranuclear *GOLM1* expression were observed in 55% and 92.5% of PAC cases, respectively. *ERG* showed 55% sensitivity, 100% specificity and 71.9% diagnostic accuracy, while *GOLM1* showed 92.5% sensitivity, 70.8% specificity and 87.5% diagnostic accuracy. The combined use of markers synchronously revealed 97.5% sensitivity, 70.8% specificity, and 87.5% accuracy. There was a statistically significant inverse association between *ERG* and prostate-specific antigen, Gleason grade groups, ki-67, and a direct association with metastasis. There was a statistically significant association between *GOLM1* and metastasis.

Conclusion: Our study recommends using both *ERG* and *GOLM1* as a panel for improving diagnostic validity of PAC. *ERG* expression could be a favorable prognostic marker, while *GOLM1* may also be a prognostic marker, albeit with limited value.

Keywords: Diagnosis, prostatic adenocarcinoma, *ERG*, *GOLM1*, immunohistochemistry

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Introduction

Prostate cancer (PC) is the second most common cancer (14.2%) and the fifth leading cause of death (7.3%) among men globally. About 1.5 million new cases have been diagnosed since 2022 (1).

One of the challenges in the diagnosis of PC using biopsy is the benign lesions that closely mimic prostatic adenocarcinoma (PAC) and differ in treatment from it. Although the light microscopic findings remain the gold standard for the diagnosis of PAC, difficult cases may benefit from immunohistochemical (IHC) studies (2). The most common diagnostic panel includes amethylacyl CoA racemase (AMACR) and high molecular weight cytokeratin (HMWCK) or p63, but multiple drawbacks have appeared in this panel (3). *ERG* and Golgi membrane protein 1 (*GOLM1*) are two potential IHC markers that are still under validation for use in PAC diagnosis.

ERG, *ETS*-related gene, is a member of the E-26 transformation-specific family of transcription factors. In 1987, ERG was first discovered in human colorectal carcinoma cells by Reddy et al. (4). In 2005, Tomlins et al. (5) identified gene fusions between the androgen receptor (AR)-regulated gene *TMPRSS2* and *ERG*. This fusion is caused by chromosomal translocation or interstitial deletion on chromosome 21. Nuclear expression of *ERG* by IHC correlates with the fusion. *ERG* plays a role in PC by disrupting the differentiation of the prostate epithelium, triggering tumor growth, progression, and angiogenesis through the activation of *MYC*, *AR*, and the nuclear factor-kappa B pathways (6,7).

GOLM1 is type II glycosylated protein residing on cis-Golgi cisternae. It was first isolated from viral hepatitis patients by Kladney et al. (8). It was reported that *GOLM1* acts as a key oncogene in PC by promoting tumor growth, invasion, migration, and metastasis through the Transforming growth factor-beta (TGF-β)/Smad, *AR* and *PIK3-AKT* signaling pathways (9-11).

To our knowledge, this is the first study to investigate the combination of *ERG* and *GOLM1* as a diagnostic panel in PAC. According to the studies on each of them, their combination could be useful in the accurate diagnosis of PAC and solving difficult cases to receive appropriate treatment and a better outcome (8-13).

Our study aimed to evaluate the diagnostic accuracy of *ERG* and *GOLM1* co-expression as a diagnostic panel for PAC and to accurately discriminate PAC from benign mimickers for proper management. Additionally, we sought to assess the association between the expression of *ERG* and *GOLM1* and clinicopathological parameters in PAC.

Materials and Methods

This cross-sectional study included 64 selected cases of prostatic lesions, comprising 40 cases of primary PAC and 24 cases of benign prostatic mimickers, collected between May 2023 and May 2024. Specimens were obtained through transrectal ultrasound-guided biopsy (TRUS), transurethral resection of the prostate (TURP), or radical prostatectomy. Clinicopathological data, including patient age, tumor size, lymph node involvement, metastasis, and preoperative prostate-specific antigen (PSA) serum levels, were retrieved from clinical reports accompanying the specimens. PAC slides were reviewed by two experienced pathologists to assess tumor characteristics. PAC cases were histologically classified according to the current World Health Organization Classification of Urinary and Male Genital Tumors (5th Edition) (14), graded using the Gleason grading system (15), and staged according to the 8th Edition of the The American Joint Committee on Cancer TNM staging system (16).

- The inclusion criteria were cases that were diagnosed as primary PAC or benign prostatic lesions and had clinical data.

- The exclusion criteria include cases with insufficient tissue for staining or a history of chemotherapy or radiotherapy.

Ethical Statement

All procedures were conducted in accordance with the ethical standards of the institutional research committee and the 1964 Helsinki Declaration, along with its later amendments or equivalent ethical guidelines. The study was approved by the Institutional Review Board of the Zagazig University Faculty of Medicine (IRB approval no: 10498, date: 26.02.2023). Written informed consent from participants was obtained.

Immunohistochemistry

IHC staining was performed using the EnVision system technique (DAKO, North America Inc., CA, USA). Tissue sections (3-5 µm) from formalin-fixed, paraffin-embedded tissue blocks were deparaffinized, rehydrated, and incubated for 10 minutes in an antigen retrieval solution (pH 6.0). Finally, the slides were incubated with *ERG* (DAKO, Rabbit Monoclonal, Code IR659, ready to use), *GOLM1* (Santa Cruz Biotechnology, sc-365817, 200 µg/mL, mouse monoclonal, dilution 1:500), and Ki-67 (DAKO, Monoclonal, Mouse, Anti-Human, ready to use).

Interpretation and Evaluation of Immunostaining

ERG immunoreactivity was recorded as nuclear staining in neoplastic cells. Staining intensity was classified as follows: 0 (no staining), +1 (mild), +2 (moderate), and +3 (strong). The H-score was calculated by multiplying the intensity score by the percentage of stained cells, resulting in a score ranging from 0 to 300. Cases were categorized as follows: ≤10 (no expression),

11-100 (low expression), 101-200 (intermediate expression), and >200 (high expression). *ERG* positivity was defined as an H-score ≥11. Endothelial cell reactivity served as an internal positive control (12).

GOLM1 immunoreactivity was observed as juxtanuclear staining located on the luminal side of neoplastic cells. A semiquantitative scoring system was used to evaluate both staining intensity (0=no staining, 1=mild, 2=moderate, 3=strong) and the percentage of stained cells (≤5%=0, 6%-25%=1, 26%-50%=2, 51%-75%=3, ≥75%=4). The total score, generating an immunoreactivity score (IRS) for each case, was calculated by multiplying the percentage score and the intensity score. *GOLM1* positivity was defined as IRS ≥4. Human gallbladder tissue was used as a positive control for *GOLM1* (10).

For ki-67 staining, only nuclear staining in tumor cell nuclei was considered positive. A 10% positivity threshold was used as the cut-off point to differentiate between low and high proliferation indices (12).

Statistical Analysis

All data were collected, tabulated, and analyzed using SPSS (Statistical Package for the Social Sciences, version 26, Chicago, Illinois, USA). Mean, standard deviation (SD), median, and range were calculated for quantitative variables, while frequency and percentage were used for qualitative variables. The chi-square test and Fisher's exact test were used to assess the association between two categorical variables. The t-test was used to compare the means of two normally distributed groups to determine whether there was a significant difference between them. The Mann-Whitney U test was used to compare two independent groups that were not normally distributed to assess whether there was a significant difference. The Spearman rank correlation test is used to measure the strength and direction of the relationship between two ordinal variables. Specificity [true negative/(true negative + false positive) × 100%), sensitivity (true positive/(true positive + false negative) × 100%), negative predictive value (NPV) (true negative/(true negative + false negative) × 100%), positive predictive value (PPV) (true positive/(true positive + false positive) × 100%), accuracy (true positive+ true negative)/(true positive + true negative + false positive + false negative) × 100%)], receiver operating characteristic curve, and area under the curve, along with their respective 95% confidence intervals, were calculated. A p-value <0.05 was considered statistically significant, while a p-value <0.001 was regarded as highly statistically significant.

Results

Patients' characteristics: The age of studied cases ranged from 49 to 86 years. All cases of prostatic carcinoma were of the adenocarcinoma type (PAC). Most of the PAC cases (29/40) (72.5%), were above 65 years with a high mean age (68.4), SD (±8), and interquartile range (11), while 14/24 (58.3%) of benign prostatic lesion cases were below 65 years with a lower mean age (60.6), SD (±8), and interquartile range (12). Regarding PSA, 38/40 (95%) of PAC cases were above 10 ng/mL, whereas all cases of benign prostatic lesions were below 10 ng/mL. Most PAC cases presented with had intermediate grades (group 2, 3) 17/40 (42.5%), low ki-67 expression 21/40 (52.5%), T2 19/40 (47.5%), absence of perineural invasion 21/40 (52.5%), and absent lympho-vascular invasion 35/40 (87.5%) Table 1.

Immunohistochemical Results

ERG: Nuclear *ERG* expression was observed in 22 out of 40 PAC cases (55%) with homogeneous staining in 20 PAC cases, and only two cases were heterogeneous. Strong and diffuse immunostaining of *ERG* (H-score above 200) was detected in 12 cases (30%). The remaining positive cases, eight cases with H-score 100-200, showed moderate staining, while two cases with H-score <100 showed mild staining. Eighteen out of 40 cases (45%) showed negative expression of *ERG* with an H-score of 0. All cases of benign prostatic lesions showed negative *ERG* expression (H-score=0). Highly statistically significant differences have been detected between malignant and benign prostatic tissue regarding *ERG* expression (p<0.001) Table 2/ Figure 1 (a-d), 3 (a, b).

GOLM1: Cytoplasmic granular *GOLM1* expression was observed in 37 out of 40 PAC cases (92.5%). A diffuse and strong *GOLM1* expression (IRS=12) was observed in 21 out of 40 cases (52.5%). Moderate intensity of *GOLM1* was detected in 16 out of 40 cases, in which 11 cases showed a diffuse pattern with IRS=7-9. While 5 cases showed less diffuse pattern expression with IRS=4-6. Mild intensity and diffuse *GOLM1* expression (IRS=3) were detected in 3 out of 40 PAC cases. Regarding benign prostatic lesions, positive *GOLM1* expression was detected in 7 out of 24 cases (29.2%). *GOLM1* expression was statistically significantly upregulated high in PAC compared with benign prostatic tissue (p<0.001): Table 2, Figure 2 (a-d), Figure 3 (c, d).

Statistical analysis of *ERG* and its diagnostic power in PAC at H-score ≥ 11 revealed 55% sensitivity, 100% specificity, 100% PPV, 57.1% NPV, and 71.9% accuracy. Statistical analysis of the diagnostic power of *GOLM1* at IRS ≥4 revealed 92.5% sensitivity, 70.8% specificity, 84.1% PPV, 85% NPV and 71.9% accuracy. Co-expression of *ERG*+ or *GOLM1*+ (positive expression was considered if either *ERG* or *GOLM1* was positive, whereas both needed to be negative to consider them negative) showed 97.5% sensitivity, 70.8% specificity, 84.8% PPV, 94.4% NPV, and 87.5% accuracy. The combined expressions of *ERG*+ and

Table 1. Clinico-pathological features of the studied cases		
Variables	**Prostatic adenocarcinoma n=40**	**Benign lesions n=24**
Age		
Mean ± SD	6 8.4±8	60.6±8
Median	6 8	60
Range	56-86	49-82
IQR	11	13
Age:	1	
<65	1 (27.5%)	14 (58.3%)
≥65	29 (72.5%)	10 (41.7%)
PSA		
Mean ± SD	74±39	4±2.5
Median	80	3
Range	9-180	1-9
PSA (ng/mL)		
<4	0	13 (54.2%)
4-10	2 (5%)	11 (45.8%)
>10	38 (95%)	0
Procedure used		
-TRUS	21 (52.5%)	4 (16.7%)
-TURP	5 (12.5%)	10 (41.7%)
-RP	14 (35%)	10 (41.7%)
Gleason grading group		
Group 1	8 (20%)	
Group 2,3	17 (42.5%)	
Group 4,5	15 (37.5%)	
Ki-67 expression		
Low	21 (52.5%)	
High	19 (47.5%)	
cT2	19 (47.5%)	
cT3	5 (12.5%)	
cT4	16 (40%)	
Nodal metastasis		
Nx	26 (65%)	
N0	10 (25%)	
N1	4 (10%)	
Metastasis		
Mx	21 (52.5%)	
M0	10 (25%)	
M1	9 (22.5%)	
PNI		
Absent	21 (52.5%)	
Present	19 (47.5%)	
LVI		
Absent	35 (87.5%)	
Present	5 (12.5%)	

IQR: Interquartile range, SD: Standard deviation, PSA: Prostate-specific antigen, TRUS: Transrectal ultrasound, TURP: Transurethral resection of the prostate, RP: Radical prostatectomy, PNI: Perineural invasion, LVI: Lymphovascular invasion

GOLM1+ (positivity of both *ERG* and *GOLM1* was required to consider positive, while negative expression was considered if either *ERG* or *GOLM1* was negative) showed 50% sensitivity, 100% specificity, 100% PPV, 54.5% NPV, and 68.8% accuracy. Table 3 and Figure 4.

Regarding the association between *ERG* expressions and clinico-pathological parameters, an inverse significant difference has been detected between positive and negative *ERG* expression cases, regarding PSA level, Gleason grade group, and ki-67 (p-value=0.019, 0.024, 0.005) respectively. Furthermore, a significant association was observed between *ERG* expression and metastasis (p=0.029) Table 4.

Statistical analysis of the association between *GOLM1* expressions and clinico-pathological parameters of PAC cases revealed a statistically significant association between *GOLM1* expression and metastasis (p=0.021). No association could be detected between other parameters and *GOLM1* expression. There was a highly significant association between *ERG* and *GOLM1* expression (p<0.001) Table 4.

Discussion

PC is a major health care challenge and one of the leading causes of mortality among men, often attributed to late diagnosis. Many practical problems have been encountered in the accurate diagnosis of PAC even when using the traditional panel of immunohistochemistry (AMACR and HMWCK or p63) (2,3). Multiple research projects have been documented for other immuno-histochemical markers that can overcome the drawbacks of the old panel and diminish the missing cases of PAC (11,12). *ERG* and *GOLM1* have shown potential roles in PAC diagnosis and prognosis (5-13). Both *ERG* and *GOLM1* as a diagnostic panel haven't been discussed before. According to studies conducted individually on both, their combination could be promising (9-13). In the present study, we evaluated *ERG* and *GOLM1* expression in all studied cases, their diagnostic validity in PAC as well as their potential prognostic role.

TMPRSS2-ERG gene fusion is responsible for *ERG* overexpression in PACs, leading to the activation of other subsequent oncogenes and the *PTEN/AKT/PIK3/mTOR* pathway. Moreover, *ERG* decreases the number of cells arrested at G0 and increases cells at G_1 (5).

In the current study, nuclear *ERG* expression was found in 55% of PAC cases, predominantly with a homogenous pattern; with negative expression in all benign lesion cases, showing a significant difference (p<0.001). Our results were in agreement with the previous studies using the same methods (12,13,17). However, other studies have demonstrated higher

Table 2. Immunohistochemical expression of *ERG*, *GOLM1* in benign prostatic lesions and prostatic adenocarcinoma

ERG expression					GOLM expression				
	Benign prostatic lesions=24	**Prostatic adenocarcinoma n=40**	**X^2**	**p-value**	**Benign prostatic lesions n=24**		**Prostatic adenocarcinoma n=40**	**X^2**	**p-value**
Negative	24 (100%)	18 (45%)			17 (70.8%)		3 (7.5%)		
Positive	0	22 (55%)			7 (29.2%)		37 (92.5%)		
H-score:					**IRS**				
0-10	24 (100%)	18 (45%)			**<4**	17 (70.8%)	3 (7.5%)		
					≥4:				
11-100	0	2 (5%)			4-6	7 (29.2%)	5 (12.5%)		
100-200	0	8 (20%)			7-9	0	11 (27.5%)		
>200	0	12 (30%)			**10-12**	0	21 (52.5%)		
Staining intensity			20.114	<0.001**				28.005	<0.001**
Negative	24 (100%)	18 (45%)			17 (70.8%)		0		
Mild	**0**	2 (5%)			5 (20.8%)		3 (7.5%)		
Moderate	0	8 (20%)			2 (8.3%)		16 (40%)		
Strong	0	12 (30%)			0		21 (52.5%)		
% of positivity									
Mean ± SD	0	77.9±15			34±40		80.7±12		
Median	**0**	80			0		80		
Range	0	50-100			0-100		60-100		

x^2: Chi-square test, **: Highly significant, TRUS: Transrectal ultrasound, TURP: Transurethral resection of the prostate, RP: Radical prostatectomy, PNI: Perineural invasion, LVI: Lympho-vascular invasion, PSA: Prostatic specific antigen. IQR: Interquartile range, GOLM: Golgi membrane protein, SD: Standard deviation, IRS: Immunoreactivity score

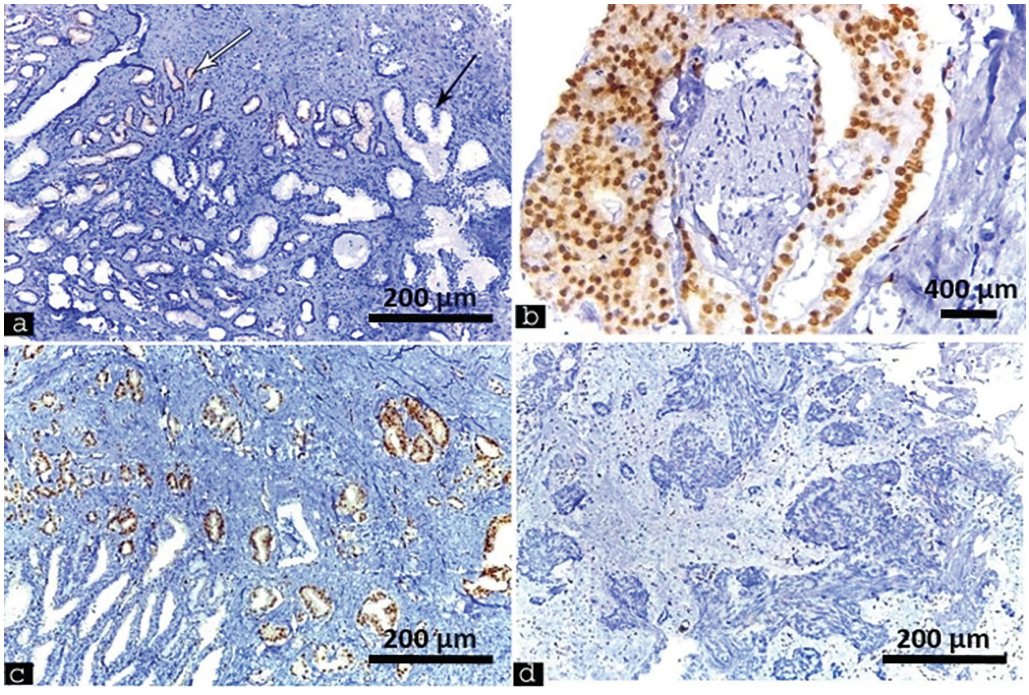

Figure 1. Immunohistochemical expression of *ERG*: **(a):** Mild nuclear expression of PAC (White arrow) and negative staining in adjacent benign glands (Black arrow) (x100) **(b):** Moderate nuclear expression of malignancy (pattern 4) with perineural invasion (x400) **(c):** Strong nuclear expression of malignancy (pattern 3) invading seminal vesicles, T3, with internal control positive) (x100) **(d):** Negative nuclear expression of malignancy (pattern 5) invading bladder wall T4, with positive internal control (X100)

PAC: Prostatic adenocarcinoma

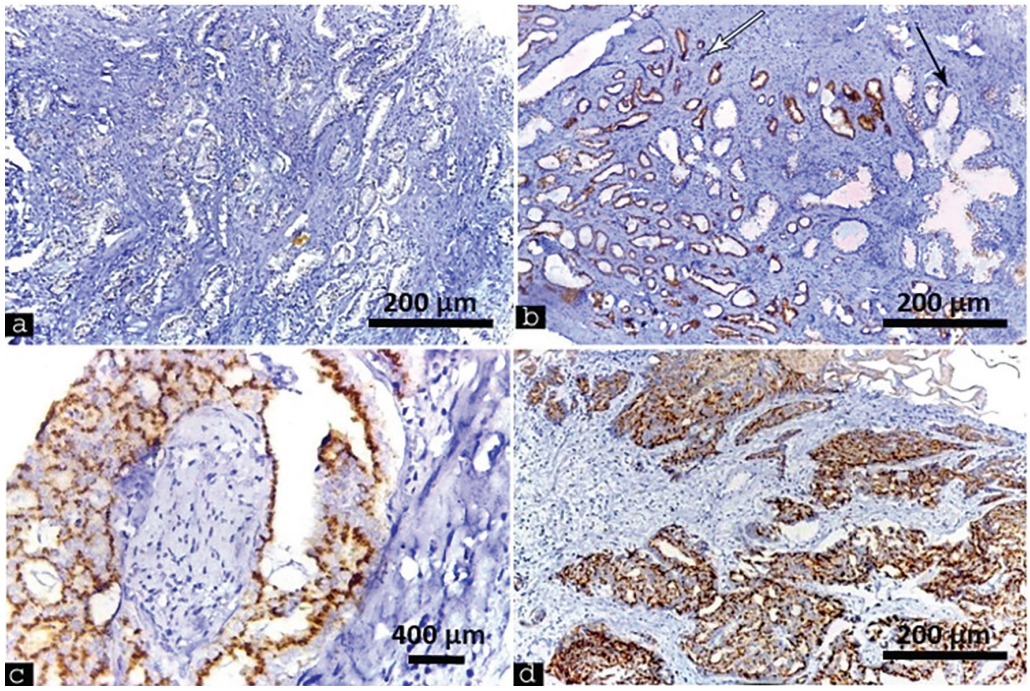

Figure 2. Immunohistochemical expression of *GOLM1*: **(a):** Mild paranuclear expression of malignancy (pattern 3, foamy), (x100) **(b):** Moderate paranuclear expression of malignancy (Pattern 3) (White arrow), and mild expression in adjacent benign glands (Black arrow), (x100) **(c)** Moderate expression of malignancy (pattern 4) with perineural invasion (x400) **(d):** Strong expression of malignancy (pattern 5) with bladder invasion T4 (x100)

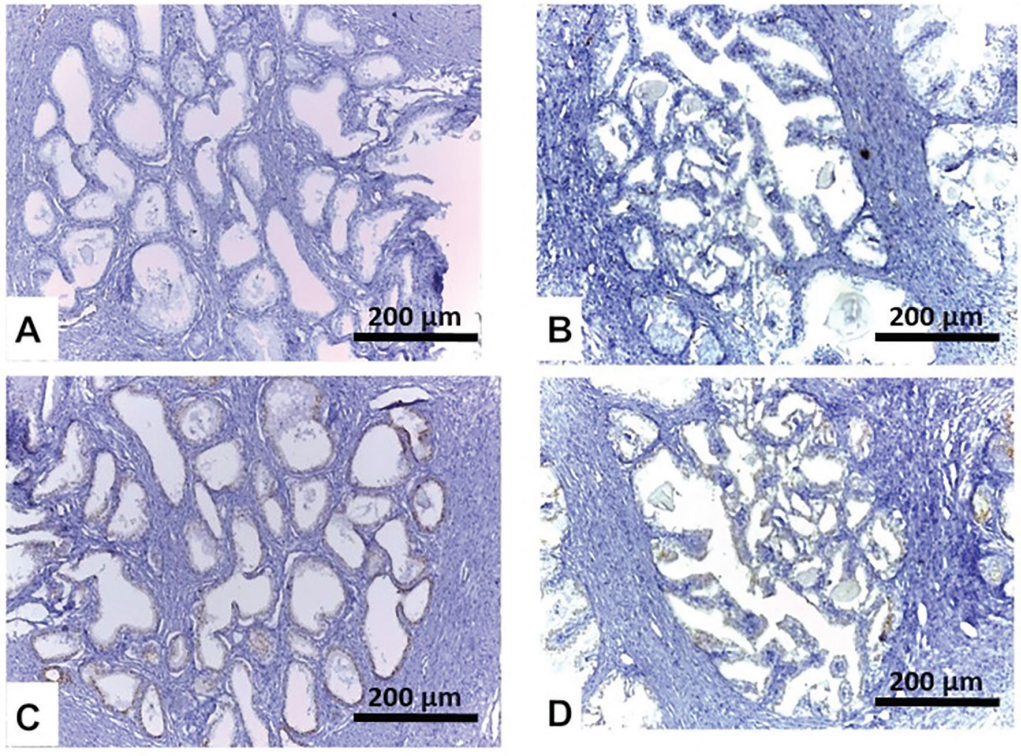

Figure 3. Immunohistochemical expression of benign prostatic lesion: **(a):** Negative nuclear *ERG* expression in adenosis with positive internal control (x100). **(b):** Negative nuclear *ERG* expression in clear cell cribriform hyperplasia (x100). **(c):** moderate granular *GOLM1* expression in adenosis (x100). **(d):** Mild fine granular *GOLM1* expression in clear cell cribriform hyperplasia (x100)

Table 3. The diagnostic validity of *ERG* and *GOLM1* expression in the diagnosis of prostatic adenocarcinoma				
	ERG	**GOLM1**	**Combination (*ERG*⁺ or *GOLM1*⁺)**	**Combination (*ERG*⁺ and *GOLM1*⁺)**
Sensitivity	55%	92.5%	97.5%	50%
Specificity	100%	70.8%	70.8%	100%
PPV	100%	84.1%	84.8%	100%
NPV	57.1%	85%	94.4%	54.5%
Accuracy	71.9%	84.4%	87.5%	68.8%
AUC	0.775	0.817	0.842	0.750
P-value	<0.001**	<0.001**	<0.001**	0.001*
Confidence interval	0.663-0.887	0.696-0.937	0.725-0.958	0.633-0.867

IRS: Immunoreactivity score, **: Highly significant, PPV: Positive predictive value, NPV: Negative predictive value, AUC: Area under the ROC curve, *GOLM1*: Golgi membrane protein 1, ROC: Receiver operating characteristic

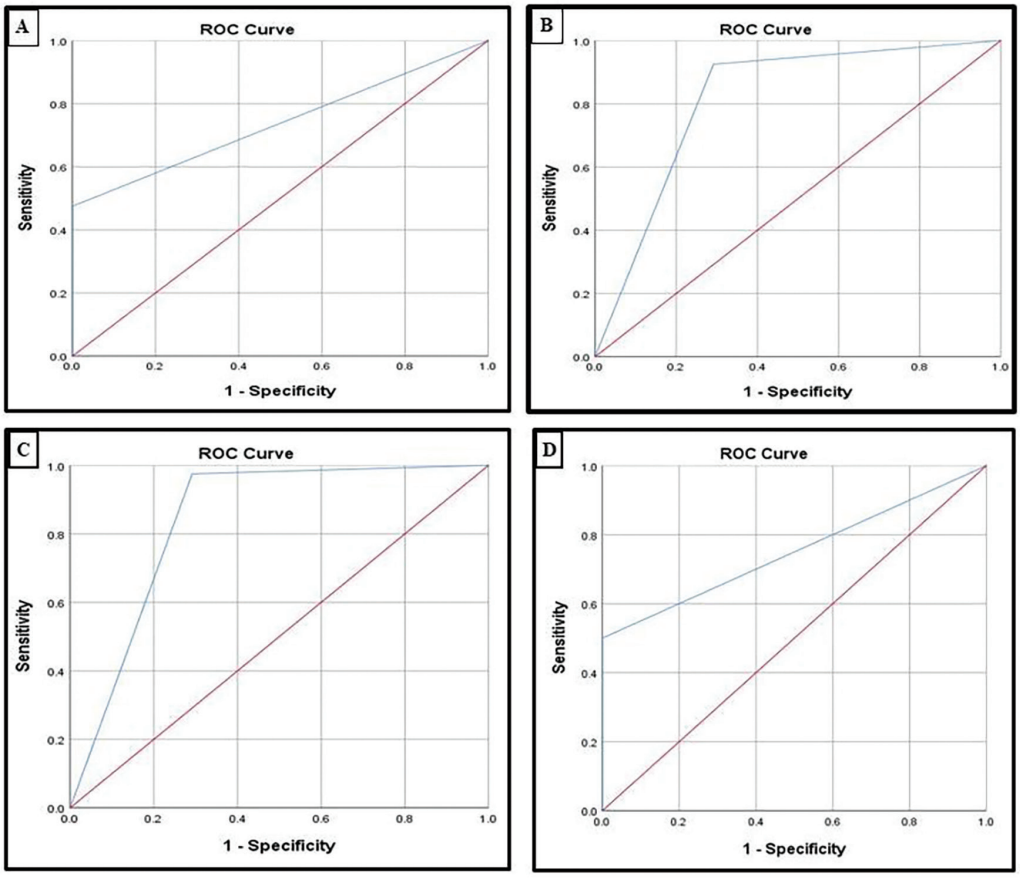

Figure 4. A) ROC curve of *ERG*, **B)** ROC curve of *GOLM1*, **C)** ROC curve of combination (*ERG*⁺ or *GOLM1*⁺). **D)** ROC curve of combination (*ERG*⁺ and *GOLM1*⁺)
ROC: Receiver operating characteristic

percentages of *ERG* expressions (18-20), while others have observed a lower percentage in PAC cases (21-23). Based on types of biopsies, tumor site, methods of assessment, race, and genetic variation, *ERG* expression differs between studies (6,7). The highest ERG expression was observed in cases analyzed using polymerase chain reaction (PCR) and IHC compared to those analyzed using fluorescence *in situ* hybridization, and was higher among Caucasians than among Americans and Asians. It was also higher in prostatectomy cases than in TURP cases (6,7,17). In our study, we used IHC as one of the two most effective methods, alongside PCR, for detecting *ERG* expression. Additionally, Caucasians were more susceptible to ERG expression than other racial groups. Moreover, utilizing different types of biopsy procedures expanded the scope of the results.

Table 4. Association between *ERG*, *GOLM1* and clinicopathological parameters of prostatic adenocarcinoma cases

Variables	Total	*ERG* n=40		p	*GOLM1* n=40		p
		Negative 18 (45%)	Positive 22 (55%)		Negative 3 (7.5%)	Positive 37 (92.5%)	
Age Mean ± SD		70.2±8	66.3±7	0.11ℓ	60.7±5	69±8	0.06 ℓ
Less than 65	11 (27.5%)	4 (36.4%)	7 (63.6%)	0.583 ϰ	2 (18.2%)	9 (81.8%)	0.178 ℱ
More than 65	29 (72.5%)	14 (48.3%)	15 (51.7%)		1 (3.4%)	28 (96.6%)	
PSA Mean ± SD		87.4±44	58.1±24	0.019* ℓ	76.7±25	74.5±40	0.661 ¶
Procedure used							
TRUS	21 (52.5%)	11 (52.4%)	10 (47.6%)	0.053 ℱ	2 (9.5%)	19 (90.5%)	0.702 ℱ
TURP	5 (12.5%)	4 (80%)	1 (20%)		0	5 (100%)	
RP	14 (35%)	3 (21.4%)	11 (78.6%)		1 (7.1%)	13 (92.9%)	
Gleason group							
Group 1	8 (20%)	2 (25%)	6 (75%)	0.024* ℱ	0	8 (100%)	0.587 ℱ
Group 2, 3	17 (42.5%)	5 (29.4%)	12 (70.5%)		1 (5.9%)	16 (94.1%)	
Group 4, 5	15 (37.5%)	11 (73.3%)	4 (26.7%)		2 (13.3%)	13 (86.7%)	
Ki-67 expression							
Low	21 (52.5%)	5 (23.8%)	16 (76.2%)	0.005* ϰ	3 (14.3%)	18 (85.7%)	0.233 ℱ
High	19 (47.5%)	13 (68.4%)	6 (31.6%)		0	19 (100%)	
Tumor size							
cT2	19 (47.5%)	6 (31.6%)	13 (68.4%)	.304 ℱ	3 (15.8%)	16 (84.2%)	0.338 ℱ
cT3	5 (12.5%)	3 (60%)	2 (40%)		0	5 (100%)	
cT4	16 (40%)	9 (56.3%)	7 (43.7%)		0	16 (100%)	
Nodal metastasis							
Nx	26 (65%)	14 (53.8%)	12 (46.2%)	0.340 ℱ	3 (11.5%)	23 (88.5%)	0.671 ℱ
N0	10 (25%)	3 (30%)	7 (70%)		0	10 (100%)	
N1	4 (10%)	1 (25%)	3 (75%)		0	4 (100%)	
Metastasis							
Mx	21 (52.5%)	8 (38.1%)	13 (61.9%)	0.029* ℱ	0	21 (100%)	0.021* ℱ
M0	10 (25%)	8 (80%)	2 (20%)		3 (30%)	7 (70%)	
M1	9 (22.5%)	2 (22.2%)	7 (77.8%)		0	9 (100%)	
PNI							
Absent	21 (52.5%)	11 (52.4%)	10 (47.6%)	0.360 ϰ	2 (9.5%)	19 (90.5)	1 ℱ
Present	19 (47.5%)	**7 (36.8%)**	12 (63.2%)		1 (5.3%)	18 (94.7%)	
LVI							
Absent	35 (87.5%)	16 (45.7%)	19 (54.3%)	1 ℱ	3 (8.6%)	32 (91.4%)	1 ℱ
Present	5 (12.5%)	2 (40%)	3 (60%)		0	5 (100%)	
ERG expression							
Negative	18 (45%)				1 (5.6%)	17 (94.4%)	<0.001** r
Positive	22 (55%)				2 (9.1%)	20 (90.9%)	

f: t-test, ¶: Mann-Whitney U test, x^2: Chi-square test, *ƒ*: Fisher's exact test, r: Correlation coefficient. *: Significant. **: Highly significant, TRUS: Transrectal ultrasound, TURP: Transurethral resection of the prostate, RP: Radical prostatectomy, PNI: Perineural invasion, LVI: Lympho-vascular invasion, PSA: Prostatic specific antigen, *GOLM1*: Golgi membrane protein 1, SD: Standard deviation

GOLM1 is a Golgi-specific transmembrane protein that functions as an oncogene, activating the PI3K-AKT-mTOR pathway and is characterized by para-nuclear granular expression. The granules are much coarser and stain deeply brown in malignancy compared to benign glands (8).

In the current study, *GOLM1* expression was homogeneously positive in 92.5% of PAC cases and 29.2% of benign lesion cases, showing a significant difference (p<0.001). These results were similar to the observations from several previous studies (9,10,24,25). Kristiansen et al. (25), reported the upregulation of *GOLM1* in PAC (92.3%) compared to benign lesions (20%) using both PCR and IHC staining on tissue. On the other hand, Varambally et al. (26) detected lower *GOLM1* expression, observing it in 75% of PAC and 28% of benign lesions using the cytological urine sample. Li et al. (27) found a higher percentage of *GOLM1* expression in benign lesions (50%), using different methods of assessment. In IHC, the assessment depends only on the color score to compare between benign and malignant lesions. The difference in results may be due to differences in genetic backgrounds or techniques of assessment (PCR, Western blot, Immunofluorescence). *GOLM1* expression can be more effectively demonstrated using IHC or PCR on tissue samples rather than through cytology. Although cytology is a non-invasive diagnostic method, its results, as reported by Varambally et al. (26), were not encouraging due to low sensitivity. Additionally, *GOLM1* expression has been observed to be higher in Asian and Caucasian populations compared to American populations (10,11,24-27). However, it has been reported that African Americans exhibit higher *GOLM1* upregulation than European Americans (24).

In our study, positive *ERG* can predict PAC with a sensitivity of 55%, specificity 100%, PPV 100%, NPV 57.1%, and accuracy 79.1%. *ERG*-IHC is a reliable diagnostic test for PAC. These findings align with several studies conducted by the same assessment methods (12,17,28,29). In contrast to our findings, Sayed et al. (21) and Navaei et al. (30) reported lower sensitivity (22%, 27.8%, respectively), but observed the same specificity (100%). Similarly, Positive *GOLM1* can predict PAC with sensitivity of 92.5%, specificity of 70.8%, PPV of 84.1%, NPV of 85% and accuracy of 84.4%. *GOLM1*-IHC is a good diagnostic test for PCa. We found that the optimal cutoff value for *GOLM1* expression in our study was IRS=5, where the sensitivity reached 92.5%, specificity 100%, PPV 100%, NPV 88.9%, and accuracy 95.3%. Based on this, we recommend using IRS=5 to achieve better diagnostic accuracy. Our results are consistent with the study done by Kristiansen et al. (25) and Li et al. (27). However, Varambally et al. (26), and Wei et al. (31) reported lower sensitivity and specificity.

Our study concluded that positive *ERG* expression is defined as at least mild staining in more than 10% of tumor cells; this can confirm PAC. However, negative ERG expression does not exclude malignancy, as some PAC cases lack ERG expression. Additionally, since PC is the only tumor with *ERG* rearrangement, *ERG* expression in a metastatic lesion of unknown origin strongly suggests PC. Similarly, positive *GOLM1* expression is defined as at least moderate intensity in more than 50% of tumor cells and can confirm PAC. However, negative or mild *GOLM1* expression in malignant cases does not exclude the diagnosis of PAC.

Owing to the low sensitivity but high specificity of *ERG*, and high sensitivity but lower specificity of *GOLM1*, along with their cost-effectiveness as IHC tools, it was motivating to test the combination of both markers for PAC diagnosis. Here, 17 out of 18 *ERG*-negative cases (94.4%) were identified by *GOLM1*, demonstrating its complementary role in detection. Two out of 3 cases (66.7%) without *GOLM1* upregulation were *ERG*-positive, highlighting the benefit of dual-marker assessment. One case was negative for both markers, a finding that was associated with a high Gleason grade. Twenty cases showed positivity for both markers, reinforcing their combined diagnostic potential. The combined expression of *ERG*+ or *GOLM1*+ (positivity for either marker) showed 97.5% sensitivity, 70.8% specificity, 84.8% PPV, 94.4% NPV, and 87.5% accuracy.

Thus, the combined use of *ERG* and *GOLM1* significantly improves diagnostic accuracy, making it a valuable approach for PAC diagnosis.

Statistical analysis of *ERG* in the present study revealed a significant association between *ERG* positivity and low PSA, low ki-67, and low and intermediate Gleason grade groups (p=0.019, 0.005, 0.024, respectively). These findings agree with several studies (12,13,17,32,33). Notably, a study done by Dawoud et al. (12), reported a significant association between *ERG* expression and low Gleason grading group and ki-67, where most cases of low and intermediate Gleason grading groups were *ERG*-positive expression (93%). However, Hashmi et al. (34) found that 64.5% positive cases were more related to high grades with significant association with aggressive disease. Our findings support the role of *ERG* in early prostatic carcinogenesis, as *ERG* expression is commonly detected in early-stage or lower-grade tumors. The variation in *ERG* expression across different tumor grades might be explained by the number of gene fusions. Lower copy fusion is linked to low-grade tumors. Higher-grade tumors may exhibit an increased number of fusion copies, leading to more aggressive disease (7).

Regarding surgical biopsy procedures, our study found that most radical prostatectomy cases were *ERG*-positive, although the association was not statistically significant (p=0.053). This finding is consistent with previous studies by Kong et al. (35)

and Xu et al. (36), but inconsistent with Mosquera et al. (29). A key factor influencing *ERG* positivity in TRUS and TURP samples may be tumor heterogeneity and multifocality, leading to lower *ERG* detection rates. Additionally, it is well established that *TMPRSS2-ERG* fusion is less frequent in transition zone tumors, which may explain the lower *ERG* positivity observed in TURP and TRUS biopsy specimens (37).

In our study of tumor staging and metastasis, we found a statistically significant association between distant metastasis and *ERG* expression, where 77.8% of metastatic cases were *ERG*-positive (p=0.029). These findings agree with previous studies (37-39), supporting the role of *ERG* in tumor progression and metastasis. However, our results are inconsistent with the study by Tabriz et al. (40), in which all cases were obtained via radical prostatectomy, potentially influencing the findings. It has been suggested that PAC harboring *ERG* gene fusions caused by deletion has a worse prognosis than those resulting from translocation (38). Additionally, aberrant *ERG* expression plays a key role in epithelial-mesenchymal transition by reducing E-cadherin expression, leading to increased tumor invasiveness. Furthermore, *ERG* upregulates CXCR4 expression in about 80% of primary PAC cases, which enhances bone metastasis (7).

For the prognostic significance of *GOLM1*, our study found no significant association between *GOLM1* expression and clinico-pathological parameters except metastasis. These results are consistent with the previous studies done by Kristiansen et al. (25), and Yan et al. (10), suggesting that *GOLM1* plays a role in the initiation and persistence of PAC tumor proliferation and migration (27). In the current study, *GOLM1* expression is significantly associated with metastasis (p=0.021). A similar observation was reported by Qin et al. (9), who detected the relation between *GOLM1* and E-cadherin, metastasis, and poor survival via the TGF-β1/Smad2 signaling pathway. There is a significant association between *ERG* and *GOLM1* in PAC cases. This suggests that *ERG* and *GOLM1* intersect in key oncogenic pathways, contributing to PAC progression (7,10).

Study Limitations

- Other types of PC (transitional, squamous, basal cell carcinomas) were not available.
- The sample size was relatively small and should be further evaluated on a larger scale. The sample size was determined based on the number of cases received at the institution during the study period. A small sample size may introduce a risk of error due to false negatives, making it difficult to detect significant differences.

Conclusion

Our study is the first to discuss the combination of *ERG* and *GOLM1* as a diagnostic panel in PAC. We concluded that the co-expression of *ERG* and *GOLM1* is a useful diagnostic panel and represents an important aid in solving the diagnostic difficulties associated with PAC and prostatic benign mimickers' lesions for proper management and better prognosis. *ERG* is a potential prognostic marker in PAC and is associated with favorable clinicopathological features. *GOLM1* may be a prognostic marker with limitations.

Ethics

Ethics Committee Approval: All procedures were conducted in accordance with the ethical standards of the institutional research committee and the 1964 Helsinki Declaration, along with its later amendments or equivalent ethical guidelines. The study was approved by the Institutional Review Board of the Zagazig University Faculty of Medicine (IRB approval no: 10498, date: 26.02.2023).

Informed Consent: Written informed consent from participants was obtained.

Footnotes

Authorship Contributions

Concept: S.A.A., M.M.O., H.A.A., M.A., A.E.A., Design S.A.A., M.M.O., H.A.A., A.E.A., Data Collection or Processing: S.A.A., M.A., Analysis or Interpretation: M.M.O., H.A.A., A.E.A., Literature Search: S.A.A., Writing: S.A.A., M.M.O., H.A.A., M.A., A.E.A.

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References

1. Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I, Jemal A. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2024;74:229-263. [Crossref]
2. Netto GJ, Amin MB, Berney DM, Compérat EM, Gill AJ, Hartmann A, Menon S, Raspollini MR, Rubin MA, Srigley JR, Tan PH. The 2022 World Health Organization classification of tumors of the urinary system and male genital organs—part B: prostate and urinary tract tumors. Eur Urol, 2022;82:469-482. [Crossref]
3. Rubin MA, Zhou M, Dhanasekaran SM, Varambally S, Barrette TR, Sanda MG, Pienta KJ, Ghosh D, Chinnaiyan AM. α-methylacyl coenzyme a racemase as a tissue biomarker for prostate cancer. Jama. 2002;287:1662-1670. [Crossref]
4. Reddy ES, Rao VN, Papas TS. The erg gene: a human gene related to the ets oncogene. Proc Natl Acad Sci. 1987;84:6131-6135. [Crossref]

5. Tomlins SA, Rhodes DR, Perner S, Dhanasekaran SM, Mehra R, Sun XW, Varambally S, Cao X, Tchinda J, Kuefer R, Lee C. Recurrent fusion of TMPRSS2 and ETS transcription factor genes in prostate cancer. Science. 2005;310:644-648. [Crossref]
6. Lorenzin F, Demichelis F. Past, current, and future strategies to target ERG fusion-positive prostate cancer. Cancers. 2022;14:1118. [Crossref]
7. Adamo P, Ladomery MR. Oncogene ERG: a key factor in prostate cancer. Oncogene. 2016;35:403-414. [Crossref]
8. Kladney RD, Bulla GA, Guo L, Mason AL, Tollefson AE, Simon DJ, Koutoubi Z, Fimmel CJ. GP73, a novel Golgi-localized protein upregulated by viral infection. Gene. 2000;249:53-65. [Crossref]
9. Qin X, Liu L, Li Y, Luo H, Chen H, Weng X. GOLM1 promotes epithelial-mesenchymal transition by activating TGFβ1/Smad2 signaling in prostate cancer. Technol Cancer Res Treat. 2023;22:15330338231153618. [Crossref]
10. Yan G, Ru Y, Wu K, Yan F, Wang Q, Wang J, Pan T, Zhang M, Han H, Li X, Zou L. GOLM1 promotes prostate cancer progression through activating PI3K-AKT-mTOR signaling. The Prostate. 2018;78:166-177. [Crossref]
11. Laxman B, Morris DS, Yu J, Siddiqui J, Cao J, Mehra R, Lonigro RJ, Tsodikov A, Wei JT, Tomlins SA, Chinnaiyan AM. A first-generation multiplex biomarker analysis of urine for the early detection of prostate cancer. Cancer Res. 2008;68:645-649. [Crossref]
12. Dawoud MM, Aiad HA, Bahbah AM, Shaban MI. Comparative study of immunohistochemical expression of ERG and MAGI2 in prostatic carcinoma. Ann. Diagn. Pathol. 2021;52:151727. [Crossref]
13. Abdel-Rahman MA, Habashy HO. ERG expression in prostate cancer: diagnostic significance and histopathological correlations. Egypt J Pathol. 2020;40:212-216. [Crossref]
14. Netto GJ, Amin MB. The lower urinary tract and male genital system. in: Robbins basic pathology e-book. Kumar V, Abbas AK, Aster JC, (eds). 10th ed. Elsevier Health Sciences; 2021:975-982. [Crossref]
15. Epstein JI, Amin MB, Fine SW, Algaba F, Aron M, Baydar DE, Beltran AL, Brimo F, Cheville JC, Colecchia M, Comperat E. The 2019 genitourinary pathology society (GUPS) white paper on contemporary grading of prostate cancer. Arch Pathol Lab Med. 2021;145:461-493. [Crossref]
16. Buyyounouski MK, Choyke PL, McKenney JK, Sartor O, Sandler HM, Amin MB, Kattan MW, Lin DW. Prostate cancer–major changes in the American Joint Committee on Cancer eighth edition cancer staging manual. CA: Cancer J. 2017;67:245-253. [Crossref]
17. Lu Z, Williamson SR, Carskadon S, Arachchige PD, Dhamdhere G, Schultz DS, Stricker H, Peabody JO, Jeong W, Chitale DA, Bismar TA. Clonal evaluation of early onset prostate cancer by expression profiling of ERG, SPINK1, ETV1, and ETV4 on whole-mount radical prostatectomy tissue. The Prostate. 2020 ;80:38-50. [Crossref]
18. Al Bashir S, Alorjani MS, Kheirallah K, Al Hamad M, Haddad HK, Al-Dwairy A, Bani-Fawwaz BA, Aldaoud N, Halalsheh O, Amawi S, Matalka II. PTEN, ERG, SPINK1, and TFF3 Status and relationship in a prostate cancer cohort from Jordanian Arab population. Medicina. 2024;60:174. [Crossref]
19. Mitala Y, Ssenkumba B, Birungi A, Kiconco R, Mutakooha MM, Atwine R. A cross-sectional study of ERG expression and the relationship with clinicopathological features of Prostate cancer in Southwestern Uganda. Diagn Pathol. 2024;19:67. [Crossref]
20. Gouda MH, Eloseily GM. Differential immunohistochemical expression of AMACR and ERG in prostatic lesions. Egypt J Pathol. 2019;39:452-461. [Crossref]
21. Sayed RM, El Shorbagy G, Shibel PE. Immunohistochemical expression of alpha-methyl-coa (AMACR) and ERG in prostatic adenocarcinoma and prostatic hyperplasia: a comparative study. APJCP. 2023;24:2861. [Crossref]
22. Nie L, Pan X, Zhang M, Yin X, Gong J, Chen X, Xu M, Zhou Q, Chen N. The expression profile and heterogeneity analysis of ERG in 633 consecutive prostate cancers from a single center. The Prostate. 2019;79:819-825. [Crossref]
23. Bismar TA, Hegazy S, Feng Z, Yu D, Donnelly B, Palanisamy N, Trock BJ. Clinical utility of assessing PTEN and ERG protein expression in prostate cancer patients: a proposed method for risk stratification. J Cancer Res Clin Oncol. 2018;144:2117-2125. [Crossref]
24. Yamoah K, Johnson MH, Choeurng V, Faisal FA, Yousefi K, Haddad Z, Ross AE, Alshalafa M, Den R, Lal P, Feldman M. Novel biomarker signature that may predict aggressive disease in African American men with prostate cancer. J Clin Oncol. 2015;33:2789-2796. [Crossref]
25. Kristiansen G, Fritzsche FR, Wassermann K, Jäger C, Tölle A, Lein M, Stephan C, Jung K, Pilarsky C, Dietel M, Moch H. GOLPH2 protein expression as a novel tissue biomarker for prostate cancer: implications for tissue-based diagnostics. Br. J. Cancer. 2008;99:939-948. [Crossref]
26. Varambally S, Laxman B, Mehra R, Cao Q, Dhanasekaran SM, Tomlins SA, Granger J, Vellaichamy A, Sreekumar A, Yu J, Gu W. Golgi protein GOLM1 is a tissue and urine biomarker of prostate cancer. Neoplasia. 2008;10:1285-1294. [Crossref]
27. Li W, Wang X, Li B, Lu J, Chen G. Diagnostic significance of overexpression of Golgi membrane protein 1 in prostate cancer. Urol J. 2012;80:952-e1. [Crossref]
28. Birol IE, Bahadir B, Ozdamar SO, Kaymaz E, Girgin R. Immunohistochemical expression of the ERG gene in prostatic adenocarcinoma and its relationship with clinicopathological parameters. Malays J Pathol. 2021;43:381-388. [Crossref]
29. Mosquera JM, Mehra R, Regan MM, Perner S, Genega EM, Bueti G, Shah RB, Gaston S, Tomlins SA, Wei JT, Kearney MC. Prevalence of TMPRSS2-ERG fusion prostate cancer among men undergoing prostate biopsy in the United States. Clin Cancer Res. 2009;15:4706-4711. [Crossref]
30. Navaei AH, Walter BA, Moreno V, Pack SD, Pinto P, Merino MJ. Correlation between ERG fusion protein and androgen receptor expression by immunohistochemistry in prostate, possible role in diagnosis and therapy. J. Cancer. 2017;8:2604. [Crossref]
31. Wei S, Dunn TA, Isaacs WB, De Marzo AM, Luo J. GOLPH2 and MYO6: putative prostate cancer markers localized to the Golgi apparatus. The Prostate. 2008;68:1387-1395. [Crossref]
32. Stephen N, Badhe BA. Diagnostic utility of immunohistochemical markers alpha methyl acyl coA racemase (AMACR) and Ets related gene (ERG) in prostate cancer. Int J Clin Exp Pathol. 2022;15:364. [Crossref]
33. Qi M, Yang X, Zhang F, Lin T, Sun X, Li Y, Yuan H, Ren Y, Zhang J, Qin X, Han B. ERG rearrangement is associated with prostate cancer-related death in Chinese prostate cancer patients. PloS One. 2014;9:e84959. [Crossref]
34. Hashmi AA, Khan EY, Irfan M, Ali R, Asif H, Naeem M, Nisar L, Faridi N, Khan A, Edhi MM. ERG oncoprotein expression in prostatic acinar adenocarcinoma; clinicopathologic significance BMC Res Notes. 2019;12:1-5. [Crossref]
35. Kong DP, Chen R, Zhang CL, Zhang W, Xiao GA, Wang FB, Ta N, Gao X, Sun YH. Prevalence and clinical application of TMPRSS2-ERG fusion in Asian prostate cancer patients: a large-sample study in Chinese people and a systematic review. Asian J. Androl. 2020;22:200-207. [Crossref]
36. Xu B, Chevarie-Davis M, Chevalier S, Scarlata E, Zeizafoun N, Dragomir A, Tanguay S, Kassouf W, Aprikian A, Brimo F. The prognostic role of ERG immunopositivity in prostatic acinar adenocarcinoma: a study including 454 cases and review of the literature. Hum. Pathol. 2014;45:488-497. [Crossref]
37. Pettersson A, Graff RE, Bauer SR, Pitt MJ, Lis RT, Stack EC, Martin NE, Kunz L, Penney KL, Ligon AH, Suppan C. TMPRSS2: ERG rearrangement, ERG expression, and prostate cancer outcomes: a cohort study and meta-analysis. Cancer Epidemiol Biomarkers Prev. 2012;21:1497-1509. [Crossref]
38. Spencer ES, Johnston RB, Gordon RR, Lucas JM, Ussakli CH, Hurtado-Coll A, Srivastava S, Nelson PS, Porter CR. Prognostic value of ERG oncoprotein

in prostate cancer recurrence and cause-specific mortality. The Prostate. 2013;73:905-912. [Crossref]

39. Furusato B, van Leenders GJ, Trapman J, Kimura T, Egawa S, Takahashi H, Furusato M, Visakorpi T, Hano H. Immunohistochemical ETS-related gene detection in a Japanese prostate cancer cohort: diagnostic use in Japanese prostate cancer patients. Pathol Int. 2011;61:409-414. [Crossref]

40. Tabriz HM, Sabaghi LA, Nabighadim A, Elham E, Aghamir SM. Evaluation of ERG expression in prostate adenocarcinoma and its prognostic impact in patients' survival rate. Iran J Pathol. 2021;16:411. [Crossref]

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Is the Autologous Testicular Tunica Vaginalis Graft Effective in Persistent Urethrocutaneous Fistulas After Hypospadias Surgery? A Comparative Study

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

Urethrocutaneous fistula is one of the most common postoperative complications associated with hypospadias repair. Despite the various techniques described in the literature for urethrocutaneous fistula repair, success rates remain relatively low, especially in recurrent cases. The fundamental principles of successful fistula repair include the use of appropriate tissue, tension-free closure, and the incorporation of a secondary protective layer. Ensuring that the suture line is covered with well-vascularized tissue is essential in preventing fistula recurrence. Autologous tunica vaginalis graft is a readily available, flexible, cost-effective material that is resistant to infection and traction, preserves erectile function, and has low morbidity. Based on our findings, the treatment has proven to be effective in the repair of persistent urethrocutaneous fistula.

Abstract

Objective: This comparative study aims to evaluate the effectiveness of an autologous tunica vaginalis graft (TVOG) as an intermediate protective layer in the repair of persistent urethrocutaneous fistulas (UCFs) following hypospadias surgery.

Materials and Methods: A total of 39 patients who underwent surgery for persistent UCF between 2013 and 2021 were evaluated. An intermediate protective layer was applied using a local penile dartos flap (LPDF) in 17 patients and an autologous TVOG in 22 patients. The study included cases with a history of at least one failed UCF repair and a fistula size of ≥4 mm. Patients with a single failed repair were treated using the LPDF method, while those with at least two previous failures underwent the TVOG technique. Surgical repair was performed at least six months after the most recent unsuccessful fistula repair. All patients were followed up intermittently for two years. During the follow-up period, medical history was taken for each patient, and the repair site and voiding function were assessed. Urine analysis, including culture and sensitivity testing when necessary, was conducted. Successful repair was defined as the absence of recurrence and the presence of a urine stream with adequate force and caliber.

Results: The mean age of patients who underwent LPDF was 6.1 years (range: 3-9), with an average operative time of 43.2 minutes (range: 35-50). For patients who received TVOG, the mean age was 6.3 years (range: 3-9), and the average operative time was 44.8 minutes (range: 34-53). The mean postoperative hospital stay was 5.9 days in the LPDF group and 5.8 days in the TVOG group. When the two techniques were compared in terms of fistula location, scrotal complications, operative time, and hospital stay duration, no statistically significant differences were observed ($p>0.05$). However, a statistically significant difference was found in the recurrence rates between the two techniques ($p<0.05$). During follow-ups, recurrent fistulas were detected in nine patients, all of whom underwent successful repair using TVOG.

Conclusion: Compared to the LPDF method, the TVOG technique represents a simple, rapid, cost-effective, and reliable approach for the repair of recurrent UCFs. By providing a highly effective secondary protective layer, TVOG has demonstrated satisfactory clinical outcomes.

Keywords: Urethrocutaneous fistula, tunica vaginalis graft, dartos flap, autologous

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Introduction

Urethrocutaneous fistula (UCF) repair is associated with one of the most common postoperative complications in hypospadias cases (1,2). Its incidence varies depending on the surgical technique and the surgeon's experience, with an average rate of approximately 7.5% (3). This rate increases with the severity of the initial anomaly and the presence of chordee, reaching up to 25% in proximal hypospadias cases (4). Several factors are known to contribute to the development of UCF, including overlapping sutures between the neourethra and skin, secondary distal obstruction due to meatal stenosis or urethral stricture, turbulent urine flow (particularly when associated with diverticula), and impaired local vascularization (5).

Fistulas are typically detected within the first few months postoperatively, although they may also develop years later. While some may close spontaneously, the majority require surgical correction. Despite the various techniques described in the literature for UCF repair, success rates remain relatively low, especially in recurrent cases (6). The fundamental principles of successful UCF repair include tension-free closure, the use of well-vascularized tissue flaps, avoidance of overlapping sutures, and correction of distal obstruction (5). Additionally, incorporating vascularized tissue between the penile skin and the fistula closure suture line is essential (7).

Studies have clearly demonstrated that a soft tissue covering over the neo-urethra yields favorable functional outcomes and contributes to a reduced incidence of UCF (8). The existing literature describes various tissues that can be used to protect the neo-urethra, including epithelialized skin flaps, dartos fascia, corpus spongiosum, and tunica vaginalis (TV) (9-13). The use of an intermediate protective layer has been shown to play a role in decreasing the incidence of UCF (14). Each of these tissues offers distinct advantages and disadvantages.

This study aims to compare and evaluate the effectiveness of an autologous tunica vaginalis graft (TVOG) in the repair of persistent UCF following hypospadias surgery.

Materials and Methods

Patients

A total of 39 patients who underwent surgery for persistent UCF between 2013 and 2021 were evaluated. The medical records of these cases were reviewed. This study was retrospective and conducted in accordance with the Declaration of Helsinki. Patients were informed that their data would be used for scientific purposes, and written consent was obtained from all participants.

Patients with an initial fistula after hypospadias surgery, a fistula diameter of ≤4 mm, or associated chordee were excluded from the study. Data from 39 patients who met these criteria were evaluated. Patients who had undergone a single failed fistula repair were treated using the LPDF method, whereas those with at least two previous failed repairs received the TVOG method. Data collected included patient age, operative time, number of previous fistula repair attempts, fistula location, hospital stay duration, postoperative recurrence, and scrotal complications. All surgical procedures were performed by the same surgeon.

Surgical Technique

General anesthesia was administered in all cases. As prophylaxis, a third-generation cephalosporin antibiotic (50-100 mg/kg) was given to each patient. A preoperative examination was conducted under anesthesia. The location and number of fistulas were confirmed by injecting diluted povidone-iodine into the urethra through a Nelaton catheter inserted via the urethral meatus. Subsequently, to rule out meatal stenosis or distal urethral stricture, intraoperative urethral calibration was conducted using an 8F (or a larger size as appropriate for patient age) Nelaton catheter, and the fistula diameter was measured (Figure 1a). A circumferential incision was made around the fistula. Using meticulous dissection, the fistula edges were excised, and the fistula tract was sharply dissected down to the urethral mucosa and then completely removed. The urethra was then closed using a continuous subcuticular inverting suture with 6-0 polyglactin sutures (Figure 1b). A scrotal incision was made to harvest the TVOG (Figure 1c). The graft was placed over the suture line with its scrotal surface facing the urethra as quickly as possible (Figure 1d). The TVOG was secured in place using 6-0 polyglactin sutures (Figure 1e). Hemostasis was ensured in the scrotum, and the testis was repositioned within the scrotal sac. The remaining TV edges were sutured to the scrotal dartos layer with 4-0 polyglactin sutures, and the scrotal incision was closed in two layers. Finally, the penile skin was closed using 4-0 polyglactin sutures (Figure 1f).

In both the TVOG and LPDF groups, a compressive dressing with an elastic bandage was applied postoperatively. A transurethral catheter (8F or a larger size depending on the patient's age) was left in place for 10-12 days. Most patients were discharged between postoperative days 5 and 7. The first follow-up was conducted two weeks after catheter removal, and all patients were monitored intermittently for two years. During follow-up, patient history was reviewed, and the repair site and voiding function were assessed. Urine analysis, along with culture and sensitivity tests when necessary, was performed. Successful repair was defined as the absence of recurrence and the presence of a urine stream with adequate force and caliber.

Ethics Approval

The study was approved by the Non-Interventional Clinical Research Ethics Committee of Tokat Gaziosmanpaşa University

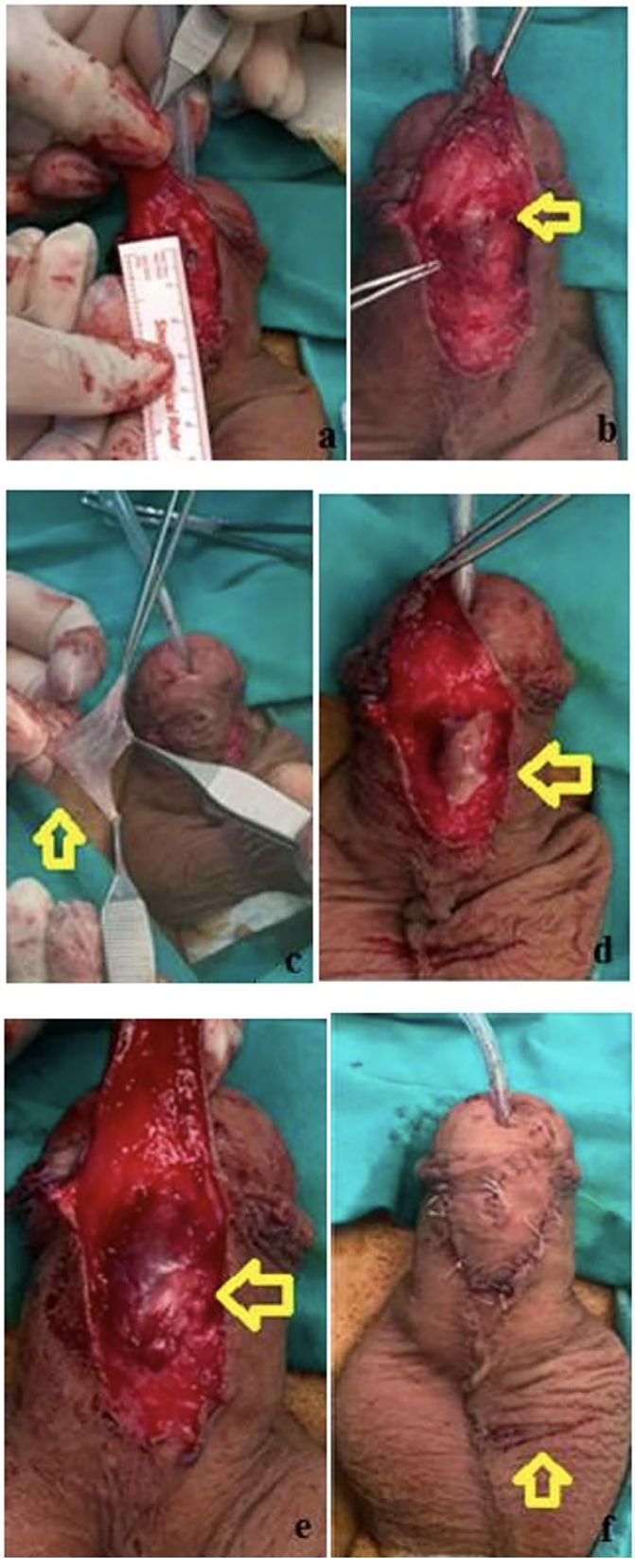

Figure 1. Intraoperative stages of autologous tunica vaginalis graft application in urethrocutaneous fistula repair

Faculty of Medicine (approval no: 25-MOBAEK-052, date: 20.02.2025).

Statistical analysis

Statistical analyses were performed using MedCalc (version 20.009; Ostend, Belgium) statistical software. Descriptive statistics were presented as counts, percentages, means, and standard deviations. For numerical data, the Shapiro-Wilk test was used to assess whether the groups conformed to a normal distribution. Comparisons of numerical variables between groups were conducted using the independent samples t-test, while categorical variables were analyzed using the chi-square test. Groups were presented as stacked percentage bar charts. A p-value of <0.05 was considered statistically significant for result interpretation.

Results

The mean age of patients who underwent LPDF as an intermediate protective layer was 6.1 years (range: 3-9), with an average operative time of 43.2 minutes (range: 35-50). Similarly, the mean age of patients who underwent TVOG as an intermediate protective layer was 6.3 years (range: 3-9), with an average operative time of 44.8 minutes (range: 34-53). The mean postoperative hospital stay duration was 5.9 days in the LPDF group and 5.8 days in the TVOG group. The most common fistula location in both groups was the coronal level, with an incidence of 41.2% in the LPDF group and 36.4% in the TVOG group. Regarding scrotal complications, one patient (5.9%) in the LPDF group developed a hematoma, and another had a wound infection. In the TVOG group, one patient (4.5%) experienced hematoma, while two patients (9.1%) had a wound infection. No statistically significant differences were observed between the two techniques in terms of fistula location, scrotal complications, operative time, or hospital stay duration (p>0.05). However, recurrence rates differed significantly between the groups. Recurrence was observed in seven patients (41.2%) in the LPDF group, while only two patients (9.1%) in the TVOG group experienced recurrence. However, postoperative fistula recurrence showed a statistically significant difference between the two techniques (p<0.05) (Table 1).

Scrotal complications were completely resolved with cold application and antibiotic therapy. None of the 39 patients experienced testicular morbidity. Fistula recurrence was observed in seven patients (41.2%) in the LPDF group and two patients (9.1%) in the TVOG group. The recurrent fistulas were visibly smaller than the preoperative ones, which facilitated subsequent repairs. All recurrences in both groups were successfully repaired using TVOG six months after surgery. The cosmetic appearance of the penis was deemed satisfactory in all patients, with no cases of torsion or ventral chordee.

Table 1. Demographic characteristics and operation data of groups								
n		LPDF			TVOG			p-value
		Mean	SD	n	Mean	SD		
Age (years)		17	6.1	1.56	22	6.3	1.67	0.62
Operative time (min)		17	43.2	4.16	22	44.8	4.97	0.28
Hospital stay duration (days)		17	5.9	0.8	22	5.8	0.7	0.64
		n	%		n	%		p-value
Site of fistula	Coronal	7	41.2		8	36.4		0.99
	Distal penile	3	17.6		4	18.2		
	Middle penile	5	29.4		7	31.8		
	Proximal penile	2	11.8		3	13.6		
Recurrence after surgery	No	10	58.8		20	90.9		0.02*
	Yes	7	41.2		2	9.1		
Scrotal complications	None	15	88.2		19	86.4		0.92
	Hematoma	1	5.9		1	4.5		
	Wound infection	1	5.9		2	9.1		

*: Significant difference at <0.05 level according to chi-square test, n (%) presented, SD: Standard deviation, TVOG: Tunica vaginalis graft, LPDF: Local penile dartos flap

Discussion

UCF is one of the most challenging complications encountered by surgeons performing hypospadias repair. Several key factors influence the outcomes of fistula repair, including the size, location, and condition of the surrounding tissue. To allow for the resolution of local inflammation, tissue healing, and revascularization, fistula repair should be performed at least six months after the previous procedure (15). The presence of distal stricture or urethral diverticulum is a significant factor contributing to fistula formation and recurrence. If distal obstruction is present, it should be corrected during fistula repair to prevent further complications (2,16). In our study, no patients had meatal stenosis or distal urethral stricture. Additionally, all patients underwent intraoperative urethral calibration prior to fistula repair to ensure optimal surgical outcomes.

The fundamental principles of successful fistula repair include the use of appropriate tissue, tension-free closure, and the incorporation of a secondary protective layer. Ensuring that the suture line is covered with well-vascularized tissue is essential in preventing fistula recurrence. Various tissue types can serve as a second protective layer, including adjacent local tissues, de-epithelialized skin, dartos flaps, and tunica vaginalis flaps and grafts (4). Despite ongoing research efforts to identify the most effective strategies and treatment algorithms, an optimal approach for UCF repair remains uncertain. Researchers face several limitations, such as variations in fistula characteristics (size, location, and local tissue condition), the small sample sizes in studies, and the diversity of surgical techniques applied in clinical practice.

In 1986, Snow (13) introduced the use of a pedicled tunica vaginalis flap (TVF) in hypospadias surgery, a technique that was originally described by Hösli (17) in 1970. Later, in 1995, Snow et al. (18) applied TVF following hypospadias repair to prevent UCF formation. Several histological advantages make TVF a suitable protective layer in recurrent UCF repair: it is highly vascularized, thin, flexible, expandable, and easy to harvest (19). According to published data, TVF has demonstrated excellent outcomes, with a reported success rate of 85-100% in cases involving recurrent fistulas and no reported penile curvature (4,19,20). However, Pattaras and Rushton (21) reported two cases in which patients experienced exaggerated penile torque due to cremasteric reflex stimulation following hypospadias repair with TVF as a protective layer. In both cases, the fibrous band of the TV was later divided to correct the penile torque. Routh et al. (20) emphasized that strict adherence to technical principles-particularly ensuring adequate TVF dissection without including cremasteric fibers-could help prevent complications associated with TVF, such as penile curvature.

Perlmutter et al. (22) and Kajbafzadeh et al. (23) successfully corrected severe chordee associated with hypospadias using TVOG, which was sutured into a defect created in the tunica albuginea through a transverse incision at the point of maximum curvature. Additionally, TVOG has been utilized in the surgical management of Peyronie's disease following plaque excision (24-27). One of the disadvantages of TVF is the potential risk of anterior curvature and the additional surgical time required for dissection and tunneling beneath the penile skin. Moreover, in cases of recurrent UCF where local adjacent tissue is depleted, extragenital tissue, such as buccal mucosal grafts (BMG), is widely used. This has led to the adoption of TVOG as a protective layer in recurrent UCF repair (28,29). To compensate for graft contraction, the graft dimensions should be at least 20% larger than the recipient site. In the study conducted by

Hafez et al. (30), TVOG exhibited an average contraction of 22%. In our study, TVOG was used as a protective layer with a size 20% greater than the suture line, and no significant effect of anticipated contraction on urethral lumen caliber was observed. The harvesting of TVOG is technically simple, though it may prolong operative time by approximately 15-20 minutes. In our study, the average operative times were comparable between the groups. We believe that surgical experience played a key role in preventing a significant increase in operative duration.

In the literature, most small UCFs (≤4 mm) can be successfully corrected with simple excision and closure using a secondary protective layer. For larger fistulas that cannot be closed directly, skin flaps may be used if local skin is sufficient and flexible. When previous surgeries have resulted in scar formation and a lack of surrounding tissue, LPDF or tunneled TVF can be utilized as a protective layer (20). As a genital graft, TVOG has been effectively used for UCF repair, yielding favorable outcomes (31,32). In cases where prior surgeries have led to local tissue deficiency and inadequate blood supply, extragenital grafts may be required. BMG is commonly employed for UCF repair and has demonstrated successful results (33). In our study, LPDF and TVOG were selected based on our clinical experience in UCF repair.

According to published data, small fistulas with healthy local tissues can be successfully repaired with simple closure, achieving a success rate of 71-92%. In cases where the fistula is large or recurrent, or when local adjacent tissues are insufficient, extragenital grafts such as BMG have demonstrated success rates of 78-85% (28,29,33). Several authors have reported success rates ranging from 85% to 100% in UCF repair using TVF, including cases of recurrent fistulas (4,34). In our study, the success rate was 90.9%, which is considered high compared to previously published studies. Based on this high success rate, we suggest, that defending the use of a TV pedicle in cases with potential penile curvature risk may not be necessary. We believe that placing a protective TVOG during UCF repair is a safe and easily performed procedure.

There are a limited number of studies in the literature regarding the use of TVOG in UCF repair, with most research focusing on TVF applications. In a study conducted by Aldaqadossi et al. (32), where TVOG was used in 45 patients, a success rate of 95.6% was reported. UCF recurrence was observed in two patients (4.4%), both of whom underwent successful repair six months later. No cases of ventral chordee or testicular morbidity were reported. Similarly, Voges et al. (31) evaluated 32 patients who underwent TVOG application, reporting a success rate of 93.7%. Recurrence was observed in two patients (6.25%), both of whom were repaired successfully six months postoperatively. In our study, involving 22 patients who received TVOG, we observed a success rate of 90.9%. Among the LPDF group, recurrence occurred in seven patients (41.2%), whereas only two patients (9.1%) in the TVOG group experienced recurrence. These recurrences were successfully repaired using the same TVOG method six months later. We consider it significant that TVOG has demonstrated effectiveness even in cases of multiple recurrent fistulas, reinforcing its reliability in UCF repair.

LPDF can be easily obtained without the need for a secondary incision, although it requires meticulous dissection. The major disadvantage of the dartos flap is that dartos dissection may lead to penile skin devascularization, which can increase the incidence of UCF formation (35). This factor may explain the 41.2% recurrence rate observed in the LPDF group in our study. Reported complications of TVF include ipsilateral testicular retraction, testicular torsion, scrotal hematoma, and even scrotal abscess (8,21). However, none of our patients experienced testicular morbidity.

Most UCFs are localized in the distal penile and coronal regions. This finding is consistent with the reports of Yassin et al. (15), Sunay et al. (36), and Santangelo et al. (37), who documented incidence rates of 59.7%, 43.2%, and 37%, respectively. In our study, UCF recurrence in the coronal region was observed in five cases in the LPDF group and two cases in the TVOG group. Additionally, two cases of recurrence occurred in the distal penile region. Recurrence was observed in two cases in the distal penile region. The high incidence of UCF localization and recurrence in the distal penile region may be attributed to the increased prevalence of distal penile hypospadias. The coronal sulcus is one of the most challenging areas for healing after reconstructive procedures, as it is poorly vascularized due to its anatomical location between the glans penis and the corpora cavernosa. Additionally, during hypospadias surgery, penile skin dissection may further disrupt coronal vascularization. In the postoperative period, erections can exacerbate coronal ischemia, increasing the risk of fistula formation and recurrence 2. We believe that the recurrence of UCF in seven patients within the coronal region in our study may be explained by this mechanism.

There is ongoing debate in the literature regarding the necessity of urethral or suprapubic diversion following fistula repair. Redman (38) did not recommend the use of a urethral or suprapubic catheter in the repair of small fistulas. Conversely, Eardley and Whitaker (39) suggested the use of a urethral or suprapubic catheter for 7 to 14 days in all fistula repairs. Elbakry (2) utilized suprapubic urinary diversion in cases involving large or multiple small fistulas. For a single small fistula, a urethral catheter was used for one day to prevent painful voiding. In our study, a urethral catheter was maintained for 10-12 days. We observed that the urethral catheter acted as a supporting structure, allowing for gentle compression by the external sterile dressing, stabilization of the repair, and optimization of

TVOG integration. Based on our findings, we recommend the use of a urethral catheter for 10-12 days in recurrent fistula cases treated with LPDF and TVOG.

Study Limitation

The limitations of the study include the small number of patients, the single-center and retrospective nature of the study, the need to compare more surgical techniques, and the short follow-up period. The limitations of our study are the lack of documentation of extremely important operation data such as the number of previous interventions, the time to revision from previous surgery, and the size of the fistula in patients undergoing surgery.

Conclusion

TVOG is a readily available, flexible, cost-effective material that is resistant to infection and traction, preserves erectile function, and has low morbidity. Based on our findings, the method has proven to be effective in the repair of persistent UCF. We emphasize the need for further prospective, randomized, and controlled studies to evaluate the effectiveness of this technique. Additionally, our study demonstrated that the LPDF method is not effective in the repair of persistent UCF. We further highlight the importance of conducting more prospective, randomized, and controlled studies to validate these findings.

Ethics

Ethics Committee Approval: The study was approved by the Non-Interventional Clinical Research Ethics Committee of Tokat Gaziosmanpaşa University Faculty of Medicine (approval no: 25-MOBAEK-052, date: 20.02.2025).

Informed Consent: Written consent was obtained from all participants.

Footnotes

Authorship Contributions

Surgical and Medical Practices: K.Y., E.K., F.F., Concept: K.Y., E.K., F.F., Design: K.Y., E.K., F.F., Data Collection or Processing: K.Y., E.K., F.F., Analysis or Interpretation: K.Y., E.K., F.F., Literature Search: K.Y., E.K., F.F., Writing: K.Y., E.K., F.F.

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References

1. Liao AY, Smith GH. Urethrocutaneous fistulae after hypospadias repair: when do they occur? J Paediatr Child Health. 2016;52:556-560. [Crossref]
2. Elbakry A. Management of urethrocutaneous fistula after hypospadias repair: 10 years' experience. BJU Int. 2001;88:590-595. [Crossref]
3. Hardwicke JT, Bechar JA, Hodson J, Osmani O, Park AJ. Fistula after single-stage primary hypospadias repair - a systematic review of the literature. J Plast Reconstr Aesthet Surg. 2015;68:1647-1655. [Crossref]
4. Pescheloche P, Parmentier B, Hor T, Chamond O, Chabaud M, Irtan S, Audry G. Tunica vaginalis flap for urethrocutaneous fistula repair after proximal and mid-shaft hypospadias surgery: a 12-year experience. J Pediatr Urol. 2018;14:421.e1-421.e6. [Crossref]
5. Richter F, Pinto PA, Stock JA, Hanna MK. Management of recurrent urethral fistulas after hypospadias repair. Urology. 2003;61:448-451. [Crossref]
6. Routh JC, Wolpert JJ, Reinberg Y. Tunneled tunica vaginalis flap for recurrent urethrocutaneous fistulae. Adv Urol. 2008;2008:615928. [Crossref]
7. Ahuja RB. A de-epithelialised 'turnover dartos flap' in the repair of urethral fistula. J Plast Reconstr Aesthet Surg. 2009;62:374-379. [Crossref]
8. Kadian YS, Singh M, Rattan KN. The role of tunica vaginalis flap in staged repair of hypospadias. Asian J Urol. 2017;4:107-110. [Crossref]
9. Smith D. A de-epithelialised overlap flap technique in the repair of hypospadias. Br J Plast Surg. 1973;26:106-114. [Crossref]
10. Belman AB. De-epithelialized skin flap coverage in hypospadias repair. J Urol. 1988;140:1273-1276. [Crossref]
11. Churchill BM, van Savage JG, Khoury AE, McLorie GA. The dartos flap as an adjunct in preventing urethrocutaneous fistulas in repeat hypospadias surgery. J Urol. 1996;156:2047-2049. [Crossref]
12. Yerkes EB, Adams MC, Miller DA, Pope JC 4th, Rink RC, Brock JW 3rd. Y-to-I wrap: use of the distal spongiosum for hypospadias repair. J Urol. 2000;163:1536-1538; discussion 1538-1539. [Crossref]
13. Snow BW. Use of tunica vaginalis to prevent fistulas in hypospadias surgery. J Urol. 1986;136:861-863. [Crossref]
14. Telfer JR, Quaba AA, Kwai Ben I, Peddi NC. An investigation into the role of waterproofing in a two-stage hypospadias repair. Br J Plast Surg. 1998;51:542-546. [Crossref]
15. Yassin T, Bahaaeldin KH, Husein A, Minawi HE. Assessment and management of urethrocutaneous fistula developing after hypospadias repair. Ann. Pediatr. Surg. 2011;7:88-93. [Crossref]
16. Barbagli G, Sansalone S, Djinovic R, Lazzeri M. Surgical repair of late complications in patients having undergone primary hypospadias repair during childhood: a new perspective. Adv Urol. 2012;2012:705212. [Crossref]
17. Hösli PO. Eine Technik zum verschluss von harnröhrenfisteln [method for the closure of urethral fistulas]. Urologe. 1970;9:129-130. [Crossref]
18. Snow BW, Cartwright PC, Unger K. Tunica vaginalis blanket wrap to prevent urethrocutaneous fistula: an 8-year experience. J Urol. 1995;153:472-473. [Crossref]
19. Landau EH, Gofrit ON, Meretyk S, Katz G, Golijanin D, Shenfeld OZ, Pode D. Outcome analysis of tunica vaginalis flap for the correction of recurrent urethrocutaneous fistula in children. J Urol. 2003;170:1596-1599; discussion 1599. [Crossref]
20. Routh JC, Wolpert JJ, Reinberg Y. Tunneled tunica vaginalis flap is an effective technique for recurrent urethrocutaneous fistulas following tubularized incised plate urethroplasty. J Urol. 2006;176:1578-1580; discussion 1581. [Crossref]
21. Pattaras JG, Rushton HG. Penile torque after the use of tunica vaginalis blanket wrap as an aid in hypospadias repair. J Urol. 1999;161:934-935. [Crossref]
22. Perlmutter AD, Montgomery BT, Steinhardt GF. Tunica vaginalis free graft for the correction of chordee. J Urol. 1985;134:311-313. [Crossref]
23. Kajbafzadeh AM, Arshadi H, Payabvash S, Salmasi AH, Najjaran-Tousi V, Sahebpor AR. Proximal hypospadias with severe chordee: single stage repair

using corporeal tunica vaginalis free graft. J Urol. 2007;178:1036-1042; discussion 1042. [Crossref]

24. Liu B, Li Q, Cheng G, Song N, Gu M, Wang Z. Surgical treatment of Peyronie's disease with autologous tunica vaginalis of testis. BMC Urol. 2016;16:1. [Crossref]
25. Yuanyuan M, Ning S, Yang W, Xiaoming Y, Lijie Z, Ninghan F. Testicular tunica vaginalis patch grafting for the treatment of Peyronie's disease. Cell Biochem Biophys. 2015;71:1117-1121. [Crossref]
26. Das S, Maggio AJ. Tunica vaginalis autografting for Peyronie's disease: an experimental study. Invest Urol. 1979;17:186-187. [Crossref]
27. Yalçın K, Kölükçü E, Fırat F, Erdemir F. Is testicular tunica vaginalis autologous graft successful in the surgical treatment of peyronie's disease? Androl Bul. 2024;26:270-276. [Crossref]
28. Kiss A, Pirót L, Karsza L, Merksz M. Use of buccal mucosa patch graft for recurrent large urethrocutaneous fistula after hypospadias repair. Urol Int. 2004;72:329-331; discussion 331. [Crossref]
29. Hosseini J, Kaviani A, Mohammadhosseini M, Rezaei A, Rezaei I, Javanmard B. Fistula repair after hypospadias surgery using buccal mucosal graft. Urol J. 2009;6:19-22. [Crossref]
30. Hafez AT, Smith CR, McLorie GA, El-Ghoneimi A, Herz DB, Bägli DJ, Khoury AE. Tunica vaginalis for correcting penile chordee in a rabbit model: is there a difference in flap versus graft? J Urol. 2001;166:1429-1432. [Crossref]
31. Voges GE, Riedmiller H, Hohenfellner R. Tunica vaginalis free grafts for closure of urethrocutaneous fistulas. Urol Int. 1990;45:88-91. [Crossref]
32. Aldaqadossi HA, Eladawy M, Shaker H, Kotb Y, Azazy S. Tunica vaginalis graft for recurrent urethrocutaneous fistula repair after hypospadias surgery. Int J Urol. 2020;27:726-730. [Crossref]
33. Waterman BJ, Renschler T, Cartwright PC, Snow BW, DeVries CR. Variables in successful repair of urethrocutaneous fistula after hypospadias surgery. J Urol. 2002;168:726-730; discussion 729-730.
34. Sharma N, Bajpai M, Panda SS, Singh A. Tunica vaginalis flap cover in repair of recurrent proximal urethrocutaneous fistula: a final solution. Afr J Paediatr Surg. 2013;10:311-314. [Crossref]
35. Chatterjee US, Mandal MK, Basu S, Das R, Majhi T. Comparative study of dartos fascia and tunica vaginalis pedicle wrap for the tubularized incised plate in primary hypospadias repair. BJU Int. 2004;94:1102-1104. [Crossref]
36. Sunay M, Dadali M, Karabulut A, Emir L, Erol D. Our 23-year experience in urethrocutaneous fistulas developing after hypospadias surgery. Urology. 2007;69:366-368. [Crossref]
37. Santangelo K, Rushton HG, Belman AB. Outcome analysis of simple and complex urethrocutaneous fistula closure using a de-epithelialized or full thickness skin advancement flap for coverage. J Urol. 2003;170:1589-1592; discussion 1592. [Crossref]
38. Redman JF. Results of undiverted simple closure of 51 urethrocutaneous fistulas in boys. Urology. 1993;41:369-371. [Crossref]
39. Eardley I, Whitaker RH. Surgery for hypospadias fistula. Br J Urol. 1992;69:306-310. [Crossref]

ORIGINAL RESEARCH
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Transition from Open Surgery to Robotic Assisted Partial Nephrectomy (RAPN): The Learning Curve for Experienced Open Surgeon

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

It is known that surgeons used to performing laparoscopic surgeries and naturally to migrate to robotic surgery. However, it is known that the learning curve for surgeons used to performing only open surgery present more difficult when they migrate to robotic surgery, and there are few publications about this and for this reason the study is significant.

Abstract

Objective: The robotic platform has become the most accessible minimally invasive surgery, even for surgeons with no previous training in laparoscopy. Partial nephrectomy is a well-established procedure that is highly complex and requires a long learning curve. To describe the learning curve of robotic assisted partial nephrectomy (RAPN) for a single surgeon with little previous experience in laparoscopy.

Materials and Methods: This was a retrospective study with a prospective collection of data from 58 patients undergoing RAPN by a single surgeon. Variables regarding the patient, tumor, RENAL score, and perioperative complications were analyzed in addition to factors connected with "Trifecta". Trifecta was defined as ischemia time 25 min, negative surgical margin, and absence of severe complications (Clavien >2). A proctor followed the surgery, making small interventions during the first 8 cases.

Results: The mean age of the patients was 54.5 years (18-84 years), the mean tumor size was 31 mm (8-115 mm), and the surgery was performed within a mean ischemia time of 22 min. All the anatomopathological tests showed negative surgical margins and no angiolymphatic invasion. Trifecta was achieved in 86.2% of the cases.

Conclusion: RAPN presents good functional and oncological outcomes; it is safe and effective, even for surgeons transitioning directly from the open technique to the robotic one.

Keywords: Kidney neoplasms, learning curve, nephrectomy, partial nephrectomy, robotic surgery, robotic surgical procedures, teaching, urooncology

Introduction

Surgical treatment is the gold standard in localized carcinoma cases. Nephron-sparing surgery is one of the procedures that should always be performed when possible, given its oncological and functional benefits (1,2). The most adequate access depends on the tumor characteristics and surgeon's experience (3,4).

Partial nephrectomy is a highly complex procedure that requires a highly trained team (3). The TRIFECTA concept (negative surgical margins, ischemia time (IHT) shorter than 25 minutes, and no severe complications) described by Gill et al. (5) is a way for the surgical success of partial nephrectomy to be assessed (6).

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Experience in renal cancer acquired over the years and evidenced through studies and publications shows that the indication for partial nephrectomy has grown exponentially in our country, particularly within the private network, as small renal masses have been accidentally more frequently found (7,8). The nephron-sparing technique, despite oncological outcomes similar to those of radical nephrectomy, provides better functional outcomes, with longer global survival and quality of life in the long term (9,10).

The robotic platform has been applied within the minimally invasive PN field, facilitating the realization of this challenging procedure, largely adopted worldwide (11). Nevertheless, the RAPN learning curve for a surgeon highly experienced in open surgery, however small experience in laparoscopy, has not been broadly assessed.

This study aims to show the learning curve for a single senior surgeon, largely experienced in open surgery, who transitioned directly to robotic surgery. It highlights the period in which a "proctor" was used and emphasizes the "Trifecta".

Materials and Methods

This retrospective study involved a prospective collection of data from 58 patients undergoing robotic assisted partial nephrectomy (RAPN) between January 2014 and November 21, at two private hospitals in São Paulo/SP (São Luiz and Sírio-Libanês), by a single surgeon with little previous training in video laparoscopy.

All procedures were performed by a single senior surgeon, highly experienced in open partial nephrectomy in private hospitals and teaching in urologic residency services at Universidade Federal de São Paulo (Unifesp), Universidade de São Paulo, and Casa de Saúde Santa Marcelina/SP.

The surgeon, at the beginning of this series, counted more than 50 robot-assisted radical prostatectomy and had a large experience in open PN; however, he had no experience in RAPN. RAPN was performed by transperitoneal approach in all cases.

Intraoperative ultrasonography (USG) was used in 13 patients with endophytic tumors to assess tumor depth and plan the excision margins. The renal nodules were classified according to RENAL score nephrometry and considered highly complex upon a >6 score. During the pre-operative period, the following information was obtained: age, gender, laterality, symptoms, and renal function (assessed according to serum creatinine). During surgery, the following data were collected: operative time, need for intraoperative USG, complications, and warm IHT. After surgery: hospital stay time, renal function, and complications (registered and classified according to the Clavien-Dindo system).

A successful surgery (TRIFECTA) was defined, according to Gill et al. (5), as follows: IHT 25 min, negative surgical margin, and no severe complications (Clavien ≤2) (6).

The entire analysis was descriptive. This is a retrospective study that analyses the records and lab tests of patients undergoing robotic partial nephrectomy and open surgery comparing both techniques to clarify whether they exist and what the differences might be, considering the oncological, functional and perioperative aspects. From January/2014 and November/2021, it was approved by the Institutional Review Board of Santa Marcelina Hospital under number 1,014,385 on February 25, 2015.

Statistical Analysis

The data analysis process began with a descriptive exploration of the data collected from electronic medical records, including the distribution of variables frequencies and calculation of parameters as mean, standard deviation, median and interquartile range.

For comparison of histological type, the chi-square test or Fisher's exact test were used for qualitative variables; and t-tests or Mann-Whitney test for quantitative variables. We used IBM SPSS 26 (IBM corp., 2019) and Microsoft Excel 365® Software. All tests carried out took into consideration a two-tailed 0.05 α significance and a 95% confidence interval (CI).

Results

The patients' mean age was 54.5 years (18-84 years); the mean tumor size was 31 mm (8-115 mm), and the surgery was performed within a mean IHT of 22 min (13-44 min). Regarding tumor complexity, 44.82% were classified as highly complex (RENAL score >6) (Tables 1,2).

As few as 2 patients (3.38%) had early symptoms (hematuria) and both had a histopathological diagnosis of clear cell renal cell carcinoma (RCC). The mean surgical time was 125 min (85-330 min), while 13 patients required intraoperative USG owing to the endophytic lesion characteristics.

Following histopathological analysis, 74.13% (43/58) of the cases were diagnosed with RCC, most of which were of the clear cell subtype. Oncocytomas, angiomyolipomas, and complex cysts (Bosnian III and IV) accounted for 25.86% (15/58) of the samples. Among the cancer lesions, 59.25% were Fuhrman 2 grade, and all cases had negative surgical margins and no angiolymphatic invasion (Table 3).

The mean hospital stay was 3 days, and none of the patients had any renal function alteration in the immediate postoperative. One patient alone had postoperative complications (respiratory failure), but required no invasive procedure.

Successful treatment (Trifecta) was achieved in 86.2% of the patients.

Discussion

This study shows the experience of a surgeon with little previous video laparoscopy training during the first 58 RAPN cases. From the beginning, the results were satisfactory, "Trifecta" being reached in 86.2% of the cases.

The robotic platform has made minimally invasive surgery more accessible, including for surgeons with no previous experience in video laparoscopy (12). The technology allows the learning curve to be shortened, thereby ensuring functional and oncological outcomes similar to those in conventional surgery (13).

At the private institutions where the surgeries for this study were performed, the robotic platform allowed for a broader access to the minimally invasive procedure, thus increasing the number of urologists applying the technique. Ghani et al. (14) reported a significant increase in the use of the robotic platform compared with laparoscopic surgery in partial nephrectomy in the USA. It was also suggested that it is possible to go from open surgery to robot-assisted surgery without learning video laparoscopy.

The rate of conversion to open surgery, complications, and positive margins are closely related to the surgeon's experience. Some series have reported greater conversion to open surgery during the first case, such as that of Haber et al. (13), where all conversions occurred in the first 20 patients. The satisfactory outcomes in this series, from the very first case, can be explained by the surgical standardization adopted, assisted by a PROCTOR to follow the first procedures, enabling a safe transition. The highest rate of complications in the literature ranges from 8% to 22% (15), whereas in our series it was 1.69 % (Clavien ≥3).

The warm IHT has already been largely studied and debated, particularly its relevance regarding renal function preservation (16). Originally, a 30-min time was considered the limit for preservation of the renal parenchyma (17); however, that value has been shortened over time. The concept used in our series was the one proposed by Gill et al. (5), who established a time goal of less than 25 min. The mean warm IHT in our series was 22 min. No significant changes in renal function were registered, which shows the safety of the nephron-sparing technique.

Regarding oncological outcomes, no positive margins were found in the patients in this study. It is always important to seek negative margins to ensure good oncologic surgery practice. However, it was not possible to demonstrate in the literature a greater risk for local recurrence or progression to metastatic disease in patients undergoing partial nephrectomy with positive margins (18). In our series, with a follow-up of approximately 5 years, no patient had local or systemic recurrence.

Table 1. Demographic data

Variables	Mean or number
Total of patients	58
Asymptomatic	56
Symptomatic	2
Age (years)	54.5
Gender	
Female	17 (29.3%)
Male	41 (70.7%)
Side of the tumor	
Left	27 (46.5%)
Right	31 (53.5%)
Tumor size	31 mm
Tumor location	
Upper	14 (24.1%)
Middle	22 (37.9%)
Lower	22 (37.9%)
RENAL score	
Low	32 (55.2%)
Intermediate	25 (43.1%)
High	1 (1.7%)
Preoperative Cr	0.9
Postoperative Cr	0.94
Hospital stay (days)	3

Table 2. Postoperative variables

Variables	Mean or number
Operative time	125 min
Vascular clamping	49 (84.5%)
Warm ischemia time	22 min
Patients with intraoperative USG	3 (22.4%)

USG: Ultrasonography

Table 3. Pathological data

Variables	Mean or number
Malignant histology	43 (74.1%)
Clear cells	27 (46.5%)
Papillary	14 (24.1%)
Chromophobe	2 (3.4%)
Fuhrman grade (clear cells)	
1	3 (11.1%)
2	16 (59.2%)
3	8 (29.6%)
Negative margins	100 %
No angiolymphatic invasion	100%
Benign tumors	15 (25.8%)
Oncocytoma	3
Angiomyolipoma	8
Complex cysts	4

In the study by Khalifeh et al. (19), a higher than 60% rate of trifecta was reached mainly after the first 50 patients, in line with other studies that reported a short and safe learning curve (20). We consider our outcomes favorable from the start of the learning curve, probably because of the standardization of the technique, in addition to a proctor's assistance in the first case (21).

Study Limitations

It is important to emphasize that this study has a few limitations. It is a small series with a short follow-up time compared with some other series already published in large centers in developed countries.

Conclusion

This study showed RAPN to present good functional and oncological outcomes, so that it is safe and effective, including for a surgeon transitioning directly from the open technique to the robotic one.

Ethics

Ethics Committee Approval: It was approved by the Institutional Review Board of Santa Marcelina Hospital under number 1,014,385 on February 25, 2015.

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: M.F.D., Concept: M.F.D., Design: M.F.D., Data Collection or Processing: M.M.P., F.K., J.O., Analysis or Interpretation: J.A.F.S.J., Literature Search: M.M.P., Writing: F.K., J.A.F.S.J.

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

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

References

1. Campbell SC, Novick AC, Belldegrun A, Blute ML, Chow GK, Derweesh IH, Faraday MM, Kaouk JH, Leveillee RJ, Matin SF, Russo P, Uzzo RG; Practice Guidelines Committee of the American Urological Association. Guideline for management of the clinical T1 renal mass. J Urol. 2009;182:1271-1279. [Crossref]
2. Van Poppel H, Becker F, Cadeddu JA, Gill IS, Janetschek G, Jewett MA, Laguna MP, Marberger M, Montorsi F, Polascik TJ, Ukimura O, Zhu G. Treatment of localised renal cell carcinoma. Eur Urol. 2011;60:662-672. [Crossref]
3. Lemos GC, Apezzato M, Borges LL, Colombo JR Jr. Robotic-assisted partial Nephrectomy: initial experience in South America. Int Braz J Urol. 2011;37:461-467. [Crossref]
4. Fergany AF, Hafez KS, Novick AC. Long-term results of nephron sparing surgery for localized renal cell carcinoma: 10-year followup. J Urol. 2000;163:442-445. [Crossref]
5. Gill IS, Kamoi K, Aron M, Desai MM. 800 Laparoscopic partial nephrectomies: a single surgeon series. J Urol. 2010;183:34-41. [Crossref]
6. Hung AJ, Cai J, Simmons MN, Gill IS. "Trifecta" in partial nephrectomy. J Urol. 2013;189:36-42. [Crossref]
7. Dall'Oglio MF, Coelho R, Lopes R, Antunes AA, Crippa A, Camara C, Leite KR, Srougi M. Significant heterogeneity in terms of diagnosis and treatment of renal cell carcinoma at a private and public hospital in Brazil. Int Braz J Urol. 2011;37:584-590. [Crossref]
8. Matos AC, Dall'Oglio MF, Colombo JR Jr, Crippa A, Juveniz JAQ, Argolo FC. Predicting outcomes in partial nephrectomy: is the renal score useful? Int Braz J Urol. 2017;43:422-431. [Crossref]
9. Riggs SB, Larochelle JC, Belldegrun AS. Partial nephrectomy: a contemporary review regarding outcomes and different techniques. Cancer J. 2008;14:302-307. [Crossref]
10. Zini L, Perrotte P, Capitanio U, Jeldres C, Shariat SF, Antebi E, Saad F, Patard JJ, Montorsi F, Karakiewicz PI. Radical versus partial nephrectomy: effect on overall and noncancer mortality. Cancer. 2009;115:1465-1471. [Crossref]
11. Xia L, Wang X, Xu T, Guzzo TJ. Systematic review and meta-analysis of comparative studies reporting perioperative outcomes of robot-assisted partial nephrectomy versus open partial nephrectomy. J Endourol. 2017;31:893-909. [Crossref]
12. Patel MN, Bhandari M, Menon M, Rogers CG. Robotic-assisted partial nephrectomy. BJU Int. 2009;103:1296-1311. [Crossref]
13. Haber GP, White WM, Crouzet S, White MA, Forest S, Autorino R, Kaouk JH. Robotic versus laparoscopic partial nephrectomy: single-surgeon matched cohort study of 150 patients. Urology. 2010;76:754-758. [Crossref]
14. Ghani KR, Sukumar S, Sammon JD, Rogers CG, Trinh QD, Menon M. Practice patterns and outcomes of open and minimally invasive partial nephrectomy since the introduction of robotic partial nephrectomy: results from the nationwide inpatient sample. J Urol. 2014;191:907-912. [Crossref]
15. Dulabon LM, Kaouk JH, Haber GP, Berkman DS, Rogers CG, Petros F, Bhayani SB, Stifelman MD. Multi-institutional analysis of robotic partial nephrectomy for hilar versus nonhilar lesions in 446 consecutive cases. Eur Urol. 2011;59:325-330. [Crossref]
16. Faria EF, Caputo PA, Wood CG, Karam JA, Nogueras-González GM, Matin SF. Robotic partial nephrectomy shortens warm ischemia time, reducing suturing time kinetics even for an experienced laparoscopic surgeon: a comparative analysis. World J Urol. 2014;32:265-271. [Crossref]
17. Gettman MT, Blute ML, Chow GK, Neururer R, Bartsch G, Peschel R. Robotic-assisted laparoscopic partial nephrectomy: technique and initial clinical experience with DaVinci robotic system. Urology. 2004;64:914-918. [Crossref]
18. Permpongkosol S, Colombo JR Jr, Gill IS, Kavoussi LR. Positive surgical parenchymal margin after laparoscopic partial nephrectomy for renal cell carcinoma: oncological outcomes. J Urol. 2006;176:2401-2404. [Crossref]
19. Khalifeh A, Autorino R, Hillyer SP, Laydner H, Eyraud R, Panumatrassamee K, Long JA, Kaouk JH. Comparative outcomes and assessment of trifecta in 500 robotic and laparoscopic partial nephrectomy cases: a single surgeon experience. J Urol. 2013;189:1236-1242. [Crossref]
20. Pierorazio PM, Patel HD, Feng T, Yohannan J, Hyams ES, Allaf ME. Robotic-assisted versus traditional laparoscopic partial nephrectomy: comparison of outcomes and evaluation of learning curve. Urology. 2011;78:813-819. [Crossref]
21. Passerotti CC, Pessoa R, da Cruz JA, Okano MT, Antunes AA, Nesrallah AJ, Dall'oglio MF, Andrade E, Srougi M. Robotic-assisted laparoscopic partial nephrectomy: initial experience in Brazil and a review of the literature. Int Braz J Urol. 2012;38:69-76. [Crossref]

ORIGINAL RESEARCH
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Comparison of the Effects of Multiple Retrograde Intrarenal Surgery and Single Access Conventional Percutaneous Nephrolithotomy Operation on Early Acute Kidney Injury

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

Conventional percutaneous nephrolithotomy (PCNL) may be risky in causing acute kidney injury (AKI), which is correlated with the number of accesses required. This study emphasized that similar to single-access PCNL, multiple sessions of retrograde intrarenal surgery (RIRS) can be recommended as an alternative method for AKI for kidney stones of similar size.

Abstract

Objective: This study compares the impact of multiple sessions of retrograde intrarenal surgery (RIRS) and a single access conventional percutaneous nephrolithotomy (PCNL) on acute kidney injury (AKI) in patients with nephrolithiasis.

Materials and Methods: Patients who underwent multiple RIRS within 3 months, in the same renal unit and single access PCNL operations between January 2018 and December 2023, were retrospectively included in the study. Patients were compared in terms of demographic (age, gender, body mass index, comorbidities) and clinical (stone volume, stone size, stone density, stone location, and operation time) characteristics. Serum creatinine levels were measured in the preoperative period and on the first postoperative day in all patients, and estimated glomerular filtration rates (eGFR) was calculated. The mean creatinine values were calculated and evaluated in patients who underwent multiple RIRS. The data were analyzed comparatively.

Results: Two hundred one patients underwent PCNL, and 163 patients underwent multiple RIRS. Of the patients who underwent RIRS, 148 underwent two surgeries, ten underwent three surgeries, four underwent four surgeries, and one underwent five surgeries. AKI developed in 6 (3.0%) PCNL patients and 3 (5.2%) RIRS patients within 48 hours of surgery. The demographic and operational results of the patients were statistically comparable ($p>0.05$). In PCNL cases, the rise in creatinine and the decrease in eGFR were greater than in RIRS cases; however, no statistically significant difference was seen ($p=0.054$ and $p=0.057$, respectively).

Conclusion: Multiple RIRS and single-access PCNL are comparable regarding AKI. Repeated RIRS is a feasible method for large kidney stones, that can be used safely, like PCNL, in suitable patients.

Keywords: Basic science, endourology, general urology, retrograde intrarenal surgery, percutaneous nephrolithotomy, acute kidney injury, kidney stone

Introduction

Nephrolithiasis is an integral aspect of everyday urologic practice, with a prevalence estimated between 1% and 13% in various global locations and 11.1% in Türkiye (1). Significant advancements have occurred in the treatment options for nephrolithiasis in recent years. Percutaneous nephrolithotomy (PCNL) is regarded as the gold standard therapy for upper urinary tract calculi over 2 cm (2). Although retrograde intrarenal surgery (RIRS) is routinely recommended for kidney stones smaller than

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2 cm, it has begun to be used with increasing frequency for larger stones with developing laser technology, and increased scope sophistication.

The minimally invasive characteristics of the PCNL treatment are coupled with greater effectiveness and a reduced complication rate. The influence of PCNL on renal function has been contentious. While stone removal often improves baseline renal function by alleviating blockage and addressing underlying infection (3), acute kidney injury (AKI) has been documented as a significant consequence of the PCNL operation. If this surgery is performed with multiple access points to the kidney, theoretically, AKI may deepen due to the parenchymal defect. However, there is a lack of literature regarding the effect of RIRS on kidney damage (4). RIRS-related complications vary from 9% to 25%, most of which are minor issues that do not need intervention, including fever, infection, hematuria, and postoperative pain (5). The rate of complications associated with PCNL, a more invasive technique, ranges from 3% to 34%. The incidence of RIRS-related problems may be linked to the progressive rise in its use (6).

The 2012 Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guideline categorizes AKI into three phases based on serum creatinine increase or reduction in urine output. AKI was defined as an increase in serum creatinine level of ≥0.3 mg/dL within 48 hours (7). This categorization approach has recently been evaluated in many published papers. This study aimed to compare the effects of repeated RIRS and single-access PCNL operations on early AKI.

Materials and Methods

With the approval of the Tekirdağ Namık Kemal University Non-Interventional Clinical Research Ethics Committee (number: 2024.265.09.15, date: 09.24.2024), patients who underwent multiple RIRS within the same renal unit within 3 months and single-access PNL operations, due to kidney stones in a single center between January 2018 and December 2023, were retrospectively included in the study. The only inclusion condition was RIRS for nephrolithiasis, while the exclusion criteria included individuals under 18 years of age, end-stage renal illness, solitary kidneys, and a single intervention. Similar exclusion criteria were applied for PCNL, but in addition, patients with multiple accesses to the same kidney were excluded.

All patients had a preoperative assessment following a standardized procedure, which included informed written consent, a full medical history, a physical examination, serum creatinine test, urinalysis, urine culture, and non-contrast computed tomography (NCCT). The volume and density of stones were assessed using NCCT images (8). All surgical interventions were performed under general anesthesia. Prophylactic injection of 2 grams intravenous third-generation cephalosporin (Ceftriaxone) antibiotics was usually administered around one hour prior to the surgical procedure.

Patient demographic and clinical data, including age, existence of concomitant systemic disorders, body mass index, stone location, stone size, Hounsfield units, preoperative and postoperative serum creatinine levels, and estimated glomerular filtration rates (eGFR) were compared. Serum creatinine levels were measured in all patients during the preoperative period and on the first postoperative day, followed by the calculation of eGFR. In patients who underwent multiple RIRS, mean creatinine values were evaluated. Data were analyzed comparatively.

Surgical Technique of Retrograde Intrarenal Surgery

All RIRS operations were conducted by an experienced surgeon (CMY). Patients were positioned in the lithotomy position and underwent active dilation via an 8-French semi-rigid ureteroscope (Karl Storz, Tuttlingen, Germany). Following the placement of the safety guidewire (0.035 inches), a standard 11-13 Fr Navigator HD (Boston Scientific, Marlborough, MA) ureteral access sheath (UAS) of either 36 or 46 cm was inserted over the guidewire, just below the ureteropelvic junction under fluoroscopy. In instances with ureteral diseases obstructing preventing the passage of a UAS, a JJ stent was inserted, and the procedure was delayed for two weeks. An 8.5 Fr reusable digital flexible ureteroscope (Flex-XC, Karl Storz, Tuttlingen, Germany) was placed into the UAS. The stones were fragmented using a 272 µm Holmium: YAG laser (Quanta System, Litho, Milan, Italy) until the pieces were small enough to pass out spontaneously. At the end of the procedure, a JJ stent was inserted, and it was removed postoperatively in the third week in the office.

Surgical Technique of Percutaneous Nephrolithotomy

PCNL operations were also performed by the same surgeon (CMY). Using cystourethroscopy performed in the lithotomy position, a standard 5 Fr ureteral catheter was placed into the ureter with a guidewire under fluoroscopy. Then, the patient was placed in the prone position. A retrograde contrast agent was introduced to the kidney with 18-gauge Chiba needles for access. Using the modified triangulation technique, a single sheath was used to access the stone from the most suitable location. Then, serial dilatation up to 30 Fr was performed with fascial dilators. A 30 Fr Amplatz sheath was placed, and access to the kidney was achieved with a 22 Fr nephroscope (Olympus, Hamburg, Germany). Stone fragmentation was performed with a pneumatic lithotripter (Vibrolith, Elmed Medical Systems). The stone fragments were removed using forceps if necessary. A postoperative 18/20 Fr re-entry malecot nephrostomy tube was placed and removed on the third postoperative day if there was no significant bleeding.

Statistical Analysis

Descriptive statistics, such as the mean, standard deviation, median, minimum, and maximum values, were used to describe the variables in the data analysis. Frequency and percentage values were used to characterize the categorical variables. The Student's t-test was used to compare the means of two independent groups. Paired t-tests were used to compare the means of two repeated measures (pre-post). Chi-square test statistics were used to assess the association between categorical variables. The level for statistical significance was established at $p<0.05$. Data analysis was performed using SPSS version 29 (IBM, Armonk, NY, USA) statistical software.

Results

The study included 201 PCNL and 163 recurrent RIRS cases. Of the recurrent RIRS cases, 148 (90.8%) underwent 2 operations, 10 (6.1%) underwent 3 operations, 4 (2.5%) underwent 4 operations, and 1 (0.6%) underwent 5 operations. The demographic and operative findings of the patients were statistically similar ($p>0.05$) (Table 1).

In a comparison of mean values of PCNL and multiple RIRS cases, postoperative creatinine increased compared to preoperative measurement, while eGFR decreased. It was observed that 6 (3.0%) of the patients who underwent PCNL and 3 (1.8%) of the patients who underwent RIRS developed stage 1 AKI within 48 hours postoperatively. In PCNL cases, the increase in creatinine and the drop in eGFR were higher than in RIRS cases, but no statistically significant differences were observed ($p=0.054$ and $p=0.057$, respectively) (Table 2).

Discussion

This research aimed to examine the effects of recurrent RIRS and single-session PCNL on AKI within 48 hours postoperatively. Our data demonstrate that although both treatments result in alterations in renal function, the difference in AKI incidence across the groups was not statistically significant. Nonetheless,

Table 1. Comparison of the demographic and operative data of the PCNL and RIRS cases

n	PCNL	Multiple RIRS	p
	201	163	
Age (mean ± SD)	53.2±12.3	51.2±12.6	0.251
Gender (n, %)			
Male	134 (66.7%)	39 (61.9%)	0.544
Female	67 (33.3%)	24 (38.1%)	
Surgical side (n, %)			
Right	88 (43.8%)	27 (42.9%)	0.992
Left	113 (56.2%)	36 (57.1%)	
Diabetes mellitus (n, %)	35 (17.4%)	15 (9.2%)	0.072
Hypertension (n, %)	44 (21.9%)	26 (15.9%)	0.372
Coronary artery disease (n, %)	21 (10.4%)	9 (5.5%)	0.215
Body mass index (kg/m²) (mean ± SD)	28.5±4.7	28.0±4.3	0.811
ESL history (n, %)	39 (19.4%)	47 (28.8%)	0.159
Number of stones			
Single	123 (61.2%)	96 (58.9%)	0.768
Multiple	78 (38.8%)	67 (41.1%)	
Stone volume (mm³) (mean ± SD)	4122.5±2345.3	3665.8±1467.3	0.456
Stone localization (n, %)			
Upper calyx	11 (5.5%)	3 (1.8%)	0.053
Middle calyx	41 (20.4%)	5 (3.1%)	
Lower calyx	38 (18.9%)	29 (17.8%)	
Renal pelvis	33 (16.4%)	44 (27.0%)	
Upper ureter	30 (14.9%)	29 (17.8%)	
Multiple location	48 (23.9%)	53 (32.5%)	
Stone density (HU) (mean ± SD)	1099.3±434.6	1089.1±220.0	0.848
Operation time (min.) (mean ± SD)	98.1±42.0	82.1±28.2	0.056

PCNL: Percutaneous nephrolithotomy, RIRS: Retrograde intrarenal surgery, HU: Hounsfield units, min.: Minute, SD: Standard deviation

Table 2. Comparison of the preoperative and postoperative AKI data of the PCNL and RIRS cases			
	PCNL	**Multiple RIRS**	**p**
Preoperative creatinine (mg/dL) (mean ± SD)	0.95±0.34	1.00±0.35	0.378
Postoperative creatinine (mg/dL) (mean ± SD)	0.96±0.33	1.06±0.32	0.054
Preoperative eGFR (mL/min) (mean ± SD)	86.1±31.6	84.2±20.5	0.551
Postoperative eGFR (mL/min) (mean ± SD)	83.3±36.5	82.3±20.5	0.179
Stage 1 AKI (n, %)	6 (3.0%)	3 (1.8%)	0.449
Increase in creatinine (mg/dL)	0.06	0.02	0.054
Drop in eGFR (mL/min)	2.83	1.71	0.057
PCNL: Percutaneous nephrolithotomy, RIRS: Retrograde intrarenal surgery, AKI: Acute kidney injury, eGFR: Estimated glomerular filtration rates, SD: Standard deviation			

there was a trend towards a greater rise in creatinine and a reduction in eGFR in the PCNL group relative to the multiple RIRS group, although the p-values were near they did not reach statistical significance. To our knowledge, this study is the first to compare this relationship in the literature.

Previous studies have shown that PCNL, owing to its invasive characteristics even with single access, may have a more significant effect on renal function than RIRS. Wollin and Preminger (6) highlighted that complications related to PCNL, particularly AKI, are often linked to variables such as hemorrhage and parenchymal damage. Research by Bayrak et al. (3) similarly revealed that PCNL may result in temporary reductions in renal function. Our investigation corroborates these findings since the PCNL group had a more pronounced deterioration in renal function relative to RIRS, although statistical significance was absent.

The incidence of AKI post-PCNL differs across recent studies, with reported rates between 4.4% and 25% (2,9-11). In our study, this rate was lower than the rate reported in the literature. This discrepancy may be ascribed to disparities in patient demographics, surgical methodologies, and the definitions of AKI used in the research. Advanced age, hypertension, diabetes mellitus, chronic renal disease, and chronic anemia increase the risk of AKI. Higher stone volume and density, staghorn calculi, multiple punctures, prolonged operational duration, and perioperative hypotension correlate with an elevated risk of AKI. Patients who have AKI after PCNL often endure extended hospitalizations and face an elevated risk of complications, including cardiovascular and neurological disorders, sepsis, and prolonged intensive care unit admissions. A portion of individuals may progress to chronic renal disease (12).

Conversely, new data indicate that repeated RIRS sessions may lead to renal damage, especially owing to extended operational durations and elevated intrarenal pressure. Göger et al. (4) posited that AKI after RIRS is affected by variables such as the use of ureteral access sheaths and irrigation pressures. Although our analysis did not reveal a significant difference in AKI rates between the two treatments, it underscores the need for more prospective studies to accurately delineate the long-term renal effects of recurrent RIRS.

The therapeutic significance of these results pertains to informing treatment decisions for nephrolithiasis, especially in individuals with an elevated risk of renal impairment. Considering that PCNL is conventionally used for bigger calculi and RIRS is progressively utilized for same indications, even for stones larger than 2 cm, understanding the impact of these treatments on renal function is essential. Our findings indicate that both treatments pose a risk of AKI; single-session PCNL may lead to more significant abnormalities in renal function compared to recurrent RIRS. However, the absence of substantial changes highlights the need for personalized surgical decision-making considering patient comorbidities, stone attributes, and surgeon experience.

Study Limitations

Several limitations must be recognized. The retrospective design of this research presents possible biases, such as selection bias and heterogeneity in surgical procedures. We only investigated AKI during the early postoperative phase, and long-term renal outcomes were not studied. Future multicenter studies with larger sample sizes and prolonged follow-up periods are necessary to better clarify the renal consequences of these treatments. Furthermore, including other indicators of renal damage (e.g. NGAL and KIM-1) or urine output assessments would provide a more thorough comprehension of alterations in postoperative renal function.

Conclusion

Our results demonstrate that recurrent RIRS and single-session, single-access PCNL are linked to temporary alterations in renal function postoperatively, with a non-significant risk of increased AKI in the PCNL cohort. The findings underscore the need for personalized treatment approaches and emphasize the significance of meticulous preoperative monitoring to reduce renal complications. Additional research with extended follow-up and larger patient populations is essential to corroborate these findings and enhance surgical decision-making in nephrolithiasis treatment.

Ethics

Ethics Committee Approval: Tekirdağ Namık Kemal University Non-Interventional Clinical Research Ethics Committee approval was obtained (number: 2024.265.09.15, date: 24.09.2024).

Informed Consent: A written informed consent was obtained from participants (for the ones under age 18, a written informed consent was obtained from their parent/legal guardian/next of kin) to participate in the study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: M.F.Ş., Ç.D., S.Ş., E.C.T., F.B.T., C.M.Y., Concept: M.F.Ş., Ç.D., S.Ş., E.C.T., F.B.T., C.M.Y., Design: M.F.Ş., Ç.D., S.Ş., E.C.T., F.B.T., C.M.Y., Data Collection or Processing: M.F.Ş., Ç.D., S.Ş., E.C.T., F.B.T., C.M.Y., Analysis or Interpretation: M.F.Ş., Ç.D., S.Ş., E.C.T., F.B.T., C.M.Y., Literature Search: M.F.Ş., Ç.D., S.Ş., E.C.T., F.B.T., C.M.Y., Writing: M.F.Ş., Ç.D., S.Ş., E.C.T., F.B.T., C.M.Y.

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References

1. Muslumanoglu AY, Binbay M, Yuruk E, Akman T, Tepeler A, Esen T, Tefekli AH. Updated epidemiologic study of urolithiasis in Turkey. I: changing characteristics of urolithiasis. Urol Res. 2011;39:309-314. [Crossref]
2. Paymannejad S, Dehghani M, Dehkordi RJ, Taheri S, Shamlou F, Salehi H, Kazemi R. Prevalence of acute kidney injury following percutaneous nephrolithotomy. J Res Med Sci. 2024;29:17. [Crossref]
3. Bayrak O, Seckiner I, Erturhan SM, Mizrak S, Erbagci A. Analysis of changes in the glomerular filtration rate as measured by the cockroft-gault formula in the early period after percutaneous nephrolithotomy. Korean J Urol. 2012;53:552-555. [Crossref]
4. Göger YE, Özkent MS, Kılınç MT, Erol E, Taşkapu HH. Influencing factors of acute kidney injury following retrograde intrarenal surgery. World J Urol. 2023;41:857-864. [Crossref]
5. Somani BK, Giusti G, Sun Y, Osther PJ, Frank M, De Sio M, Turna B, de la Rosette J. Complications associated with ureterorenoscopy (URS) related to treatment of urolithiasis: the Clinical Research Office of Endourological Society URS global study. World J Urol. 2017;35:675-681. [Crossref]
6. Wollin DA, Preminger GM. Percutaneous nephrolithotomy: complications and how to deal with them. Urolithiasis. 2018;46:87-97. [Crossref]
7. Sparrow HG, Swan JT, Moore LW, Gaber AO, Suki WN. Disparate outcomes observed within kidney disease: improving global outcomes (KDIGO) acute kidney injury stage 1. Kidney Int. 2019;95:905-913. [Crossref]
8. Sorokin I, Cardona-Grau DK, Rehfuss A, Birney A, Stavrakis C, Leinwand G, Herr A, Feustel PJ, White MD. Stone volume is best predictor of operative time required in retrograde intrarenal surgery for renal calculi: implications for surgical planning and quality improvement. Urolithiasis. 2016;44:545-550. [Crossref]
9. Reich DA, Adiyeke E, Ozrazgat-Baslanti T, Rabley AK, Bozorgmehri S, Bihorac A, Bird VG. Clinical considerations for patients experiencing acute kidney injury following percutaneous nephrolithotomy. Biomedicines. 2023;11:1712. [Crossref]
10. El-Nahas AR, Taha DE, Ali HM, Elshal AM, Zahran MH, El-Tabey NA, El-Assmy AM, Harraz AM, Moawad HE, Othman MM. Acute kidney injury after percutaneous nephrolithotomy for stones in solitary kidneys. Scand J Urol. 2017;51:165-169. [Crossref]
11. Fulla J, Prasanchaimontri P, Wright HC, Elia M, De S, Monga M, Calle J. Acute kidney injury and percutaneous nephrolithotomy: incidence and predictive factors. World J Urol. 2022;40:563-567. [Crossref]
12. Pillai S, Kriplani A, Chawla A, Somani B, Pandey A, Prabhu R, Choudhury A, Pandit S, Taori R, Hegde P. Acute kidney injury post-percutaneous nephrolithotomy (PNL): prospective outcomes from a university teaching hospital. J Clin Med. 2021;10:1373. [Crossref]

ORIGINAL RESEARCH
Andrology

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Penile Revascularization in Improving Erectile Function After Radical Prostatectomy: An Alternative Therapeutic Approach for Penile Rehabilitation

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

Erectile dysfunction is a common complication after radical prostatectomy due to neurovascular damage. When oral and intracavernosal treatments are insufficient for penile rehabilitation, penile prosthesis implantation is typically performed. This study demonstrates that penile revascularization surgery can be an effective treatment option for vascular-origin erectile dysfunction following radical prostatectomy, offering a more physiological and less invasive alternative to penile prosthesis implantation. It emphasizes the potential to improve erectile function before resorting to penile prosthesis implantation. Careful patient selection and long-term follow-up are crucial for treatment success.

Abstract

Objective: The aim of this study is to evaluate the therapeutic effects of penile revascularization, applied as a penile rehabilitation method, on erectile function in the treatment of vascular-origin erectile dysfunction that develops after radical prostatectomy.

Materials and Methods: A total of 21 cases who underwent radical prostatectomy due to localized prostate cancer between 2017 and 2024 and were diagnosed with postoperative erectile dysfunction were treated with penile revascularization surgery. All patients had undergone bilateral neurovascular bundle-sparing radical prostatectomy. All patients underwent penile color Doppler ultrasonography, corpus cavernosum electromyography, cavernosometry tests, the International Index of Erectile Function (IIEF) 5-15, and erectile hardness score questionnaires before penile revascularization and at the third, sixth, and twelfth postoperative months,

Results: The average age of the operated patients was found to be 59.05±3.05 years. The preoperative scores of the IIEF-5 and 15 were 8.57±1.16 and 21.33±1.60, respectively. In the postoperative final follow-up, these scores were 14.67±0.69 and 35.43±2.21. On penile color Doppler ultrasonography, the peak systolic velocity, end-diastolic velocity, and resistive index values were 16.68±1.85, 7.23±1.34, and 0.56±0.06, respectively, in the preoperative period. In the postoperative period, these values were 28.79±6.18, 3.76±1.02, and 0.87±0.06, respectively.

Conclusion: Penile revascularization surgery in cases of vascular-origin erectile dysfunction following radical prostatectomy can significantly contribute to the rehabilitation of erectile function by increasing penile blood flow. This procedure should be recommended to patients as an option prior to more invasive interventions, such as penile prosthesis implantation.

Keywords: Radical prostatectomy, erectile dysfunction, penile rehabilitation, penile revascularization

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Introduction

Prostate cancer is one of the most common malignancies in men, and its prevalence has been steadily increasing over time. Radical prostatectomy is a widely used surgical approach for the treatment of localized prostate cancer. Despite advances in the understanding of prostate anatomy and the use of minimally invasive techniques, postoperative erectile dysfunction (ED) remains a significant factor contributing to a decline in patients' quality of life (1). ED observed after radical prostatectomy may result from damage to the neurovascular bundle, mechanical manipulation, thermal injury, ischemic effects, local inflammation, or injury to the accessory pudendal artery (2). Even the use of neurovascular bundle-sparing techniques is insufficient to completely eliminate this complication (3). When the physiology of penile erection is disrupted, penile rehabilitation plays a key role in understanding the mechanisms leading to ED and in supporting the recovery of erectile function. In this context, treatment methods such as phosphodiesterase type 5 inhibitors, vacuum devices, intracavernosal injection therapy, and penile prosthesis implantation are commonly employed during the postoperative period (4). In this study, we evaluated the efficacy and safety of penile revascularization surgery in patients who developed vascular-origin ED after radical prostatectomy, and did not respond to oral or intracavernosal treatments during penile rehabilitation. The aim was to offer a more physiological treatment alternative prior to penile prosthesis implantation, which is considered an irreversible and final option.

Materials and Methods

This retrospectively designed study was conducted at a tertiary healthcare institution and received approval from the Ankara Bilkent City Hospital Ethics Committee (approval number: TABED 1-25-908, date: 12.03.2025). All procedures were carried out in accordance with the principles of the Declaration of Helsinki. The interventional and surgical procedures performed were part of the routine clinical evaluation and treatment processes of patients who had undergone radical prostatectomy and presented with complaints of ED. Although current clinical guidelines do not explicitly recommend penile revascularization for iatrogenic ED following radical prostatectomy, these procedures were performed based on our clinical experience and judgment, with the patients' best interests in mind. A total of 21 patients who underwent penile revascularization surgery for vascular-origin ED diagnosed after radical prostatectomy in our clinic between 2017 and 2023 were included in this study. At baseline, a detailed medical history was obtained for each patient, including age, duration of ED, comorbidities potentially contributing to ED, history of trauma, prior medical or surgical treatments, and lifestyle factors. After physical examination of all patients, the International Index of Erectile Function (IIEF) 5 and 15, and the erectile hardness score (EHS) questionnaires were completed. Penile color Doppler ultrasonography (PCDU), corpus cavernosum electromyography (CC-EMG), and cavernosometry tests were performed for all patients during the preoperative period. Total testosterone levels were measured in all patients. Phosphodiesterase type 5 inhibitors were routinely administered for 3 months before surgery, and intracavernosal alprostadil injections were recommended for patients who did not benefit from oral pharmacotherapy. Patients who did not benefit from these methods and had a regular sexual partner were included in the study. Additionally, patients were questioned about diabetes, hyperlipidemia, hypertension, and smoking, and their body mass indices were calculated. Patients were interviewed face-to-face at the 3rd, 6th, and 12th postoperative months. During these follow-ups, patients were re-evaluated using the IIEF-5 and IIEF-15, and EHS questionnaires; and PCDU was performed.

PCDU Technique

The PCDU was performed in a quiet and comfortable room to ensure the patients' comfort. To diagnose arterial insufficiency or veno-occlusive disease, PCDU (B-K Medical, Herlev, Denmark) was performed with the patient lying in the supine position. First, gray-scale imaging of the flaccid penile shaft in transverse and sagittal planes was performed to exclude intracavernosal fibrosis and calcifications. Subsequently, 60 mg of papaverine hydrochloride (Papaverine HCl®, Galen Medical Industry, Türkiye) was injected laterally into one of the corpora cavernosa using a 22-gauge needle. Twenty minutes after the papaverine hydrochloride injection, PCDU was performed using an 8 MHz linear probe at an angle of approximately 45 degrees. Peak systolic velocity (PSV) and end-diastolic velocity (EDV) values were measured and resistive index (RI) values of both cavernosal arteries were calculated using the measurements. In addition, the patency of the anastomosis was evaluated. Measurements were repeated at 5-minute intervals and continued for 30 minutes. Cases with PSV <25 cm/s were evaluated as having arterial insufficiency, whereas cases with PSV >25 cm/s, EDV >5 cm/s, and RI <0.80 were interpreted as having veno-occlusive disease. The RI was calculated using the formula: RI = (PSV-EDV)/PSV. Patients were informed about the risk of priapism following papaverine hydrochloride injection and were advised to consult the clinic immediately if an erection persisted for more than four hours.

CC-EMG Technique

Penile cavernous electrical activity (CEA) was recorded using a high-speed EMG module equipped with a computer (Medical Measurement Systems, Enschede, the Netherlands). The sampling frequency was 200 Hz, and a band-pass filter with a

cut-off frequency of 0.1-20 Hz was used. During the CC-EMG recordings, a monopolar needle electrode was used to measure CEA. A grounding electrode was placed on the patient's foot to avoid electrical activity originating simultaneously from non-penile areas, as such activity appears as a single line in the EMG recording. CC-EMG recordings were started after patients rested for 10 minutes in a quiet and dim room. CEA potentials were recorded for 10 minutes. Later, the CEA potentials of the penile cavernous nerves were assessed by detecting the peak-to-peak amplitudes. Ten minutes later, papaverine hydrochloride (60 mg) was injected into a single CC to avoid the pattern of discoordination, which is manifested by an increase or no change in the CEA recording and suggests neurogenic ED. A total of 29 cases showing a discoordination pattern on CC-EMG, indicating the vascular component of ED, were excluded from this study. The relaxation degree (RD) was calculated using the formula: RD = [(pre-injection CEA - post-injection CEA)/pre-injection CEA] × 100, as previously described (5).

Cavernosometry

The cavernosometry test was applied as an important part of our clinical evaluation protocol to objectively detect caverno-occlusive dysfunction and to perform a detailed hemodynamic analysis of vascular pathology. After the CC-EMG recordings were completed, cavernosometry was performed using the same device. A diagnosis of caverno-occlusive dysfunction was made based on the following criteria.

1. Requires a maintenance flow rate greater than 5 mL/min after revealed an intracavernous pressure of 150 mmHg with the artificial erection test.

2. The intracavernous pressure decreased by a minimum of 45 mmHg within 30 s following the termination of infusion.

Surgical Technique

The operations were conducted using the Furlow–Fisher procedure or the Virag-V technique (6). In contrast to the Furlow-Fisher procedure, the modified approach preserved the circumflex collaterals and did not disrupt the deep dorsal venous valves using a stripper. After the inferior epigastric artery was brought to the penile root through a subcutaneous tunnel, an end-to-side anastomosis was performed with the proximal part of the deep dorsal vein. A 7-0 polypropylene suture was used according to standard microsurgical technique. After the anastomosis, the deep dorsal vein was ligated proximal to the arteriovenous anastomosis (Figure 1). The procedure was performed under optical magnification (×2.5) to prevent damage to the neurovascular bundle. In the postoperative period, intravenous heparin (5000 IU/day) was administered for 3 days, and patients received 75 mg/day dipyridamole and 300 mg/day acetylsalicylic acid for three months. Patients were advised to abstain from sexual intercourse for 2 months following the surgery.

Statistical Analysis

All statistical analyses were performed using IBM SPSS Statistics for Windows, Version 21.0 (IBM Corp., Armonk, NY, USA). All patients completed the IIEF-5, IIEF-15, and EHS questionnaires during the preoperative period and throughout the postoperative follow-up. At the final postoperative evaluation, the outcomes were considered successful if there was an increase of at least five points in the IIEF-5 score compared to the preoperative period, a RI value above 0.80, an IIEF-15 score ≥26, and an EHS score ≥3. The normal distribution of continuous variables was assessed using the Shapiro-Wilk test. Descriptive statistics for normally distributed data were presented as mean ± standard deviation. The significance levels of normally distributed continuous variables were compared using the repeated measures ANOVA test. In cases where the ANOVA test revealed a significant difference, the Bonferroni post-hoc test was used to determine the specific time points between which the differences occurred. Statistically significant increases were observed in RI, IIEF-5, and IIEF-15 scores at all evaluation points over time ($p<0.05$). Post-hoc analyses showed that the improvements were particularly pronounced at the third and sixth months compared to the preoperative period. Moreover, a significant but more limited improvement was detected in IIEF-5 ($p=0.012$) and IIEF-15 ($p=0.004$) scores between the 6th and 12th months. For the comparison of categorical variables such as EHS, Fisher's exact test was applied. Categorical data were presented as numbers and percentages (%). Significant improvements were observed at the 3rd, 6th, and 12th postoperative months compared to the preoperative period ($p=0.015$, $p=0.0023$, and $p=0.0014$, respectively). However, no significant difference was found between the postoperative periods: 3rd vs. 6th month, 3rd vs. 12th month, and 6th vs. 12th month ($p>0.05$). A p-value of less than 0.05 was considered statistically significant.

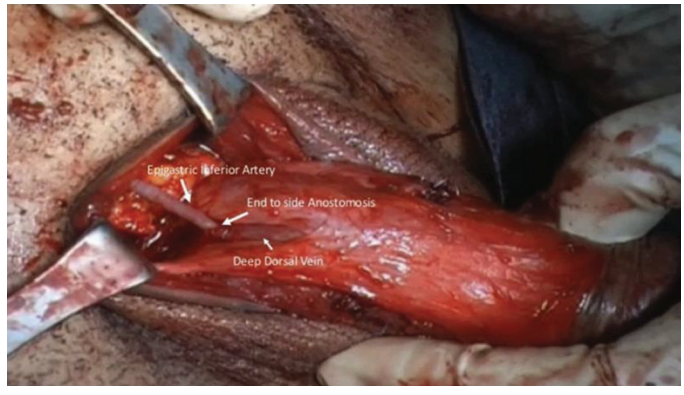

Figure 1. Epigastric artery and deep dorsal vein anastomosis

Results

At the time of surgery, the mean age of the patients was 59.05±3.05 (52-64) years. The demographic characteristics of the patients are shown in Table 1. According to preoperative PCDU, 11 patients had arterial insufficiency and 10 patients had both arterial and venous insufficiency. The mean IIEF-5 and 15 scores were found to be 8.57±1.16 and 21.33±1.60, respectively, before surgery. In the postoperative third, sixth and twelfth months, IIEF-5 scores were found to be 12.05±1.04, 13.71±0.86, 14.67±20.69, respectively. In the postoperative third, sixth, and twelfth months, IIEF-15 scores were found to be 30.43±3.17, 32.19±2.49, 35.43±2.21, respectively. The mean right and left cavernosal artery RI was 0.55±0.04, 0.57±0.03, respectively, before surgery. In the postoperative third, sixth, and twelfth months, right cavernozal artery RI was found to be 0.61±0.06, 0.72±0.04, 0.85±0.09, respectively. In the postoperative third, sixth, and twelfth months, left cavernozal artery RI was found to be 0.63±0.04, 0.73±0.02, 0.86±0.04 respectively. In the postoperative third, sixth, and twelfth months, anastomosis region RI was found to be 0.61±0.08, 0.78±0.09, 0.85±0.07, respectively. In 12 of the 21 operated cases, a significant increase of 5 points or more was observed in IIEF-5 scores; RI values were determined to be above 0.80. In the remaining 9 cases, no sufficient increase was detected in IIEF-5 and RI values, in the PCDU performed during postoperative controls, it was observed that the anastomosis in these cases was obliterated or thrombosed. According to the EHS questionnaire, no patients exhibited penile erection (EHS <3) in the preoperative period. However, at the 3rd postoperative month, 7 patients (33.3%) had; at the 6th month, 8 patients (38.1%) had; and at the 12th month, 10 patients (47.6%) had an EHS score of 3 or higher. Analysis showed that when comparing the preoperative period with any postoperative time point, statistically significant increases indicating surgical success were observed in all parameters (Tables 1 and 2).

Discussion

In parallel with advancements in diagnosis and treatment, the likelihood of detecting localized prostate cancer at younger ages has increased. Radical prostatectomy is the preferred method for treating localized prostate cancer. While this approach provides favorable outcomes in terms of cancer control, it can significantly impair patients' quality of life in the postoperative period, particularly regarding erectile function. Tal et al. (7), in

Table 1. Demographic characteristics, RI, IIEF-5, IIEF-15 and EHS results of the patients

Number of patients	21				
Age (year)	59.05±3.05 (52-64)				
Comorbidity					
Diabetes mellitus	4				
Smoking	3				
Obesity (body mass index >26)	4				
Hypertension or cardiovascular disease	4				
Hyperlipidemia	3				
Type of ED					
Aretial insufficiency (n)	11				
Both arterial and venous insufficiency (n)	10				
	Preoperative	**Postoperative 3rd month**	**Postoperative 6th month**	**Postoperative 12th month**	**p-value**
RI					<0.05
Right cavernosal artery	0.55±0.04	0.61±0.06	0.72±0.04	0.85±0.05	
Left cavernosal artery	0.57±0.03	0.63±0.04	0.73±0.02	0.86±0.04	
Anastomotic region	-	0.60±0.12	0.79±0.16	0.85±0.26	
IIEF-5	8.57±1.16	12.05±1.04	13.71±0.86	14.67±0.69	
IIEF-15	21.33±1.60	30.43±3.17	32.19±2.49	35.43±2.21	
EHS (n, %)					
<3	21 (100%)	14 (66.7%)	13 (61.9%)	11 (52.4%)	
≥3	- (0%)	7 (33.3%)	8 (38.1%)	10 (47.6%)	

Statistical analysis: The normality of continuous variables was assessed using the Shapiro-Wilk test. Descriptive statistics for normally distributed data were presented as mean ± standard deviation. The significance levels of normally distributed continuous variables were compared using the repeated measures ANOVA test. Fisher's exact test was applied for the comparison of categorical variables. Categorical data were expressed as numbers and percentages (%). A p-value of less than 0.05 was considered statistically significant. ED: Erectile dysfunction, RI: Resistive index, IIEF: International Index of Erectile Function, EHS: Erectile hardnes score

Table 2. The p-values of pairwise comparisons between parameters at different time points (pre-treatment and post-treatment at 3rd, 6th, and 12th months) are presented

	RCA-RI	LCA-RI	Anastomosis-RI	IIEF-5	IIEF-15	EHS
Preop vs. 3rd postop month	p<0.001	p<0.001	-	p<0.001	p<0.001	0.015
Preop vs. 6th postop month	p<0.001	p<0.001	-	p<0.001	p<0.001	0.002
Preop vs. 12th postop month	p<0.001	p<0.001	-	p<0.001	p<0.001	0.001
3rd month vs. 6th postop month	p<0.001	p<0.001	p<0.001	p<0.001	p<0.001	0.420
3rd month vs. 12th postop month	p<0.001	p<0.001	p<0.001	p<0.001	p<0.001	0.162
6th month vs. 12th postop month	p<0.001	p<0.001	p=0.036	p=0.012	p=0.004	0.798

Since the data showed a normal distribution, the repeated measures ANOVA test was used to analyze changes over time. Pairwise comparisons were performed with Bonferroni correction as a post-hoc analysis. A p-value of less than 0.05 was considered statistically significant. RCA-RI: Right cavernosal artery resistive index, LCA-RI: Left cavernosal artery resistive index, IIEF: International Index of Erectile Function, EHS: Erectile hardness score

their meta-analysis, reported that the incidence of postoperative ED following radical prostatectomy varies between 14% and 90%. Haglind et al. (8) prospectively followed 2,625 patients who underwent robotic and open radical prostatectomy for twelve months. They reported ED rates of 70.4% in the robotic group and 74.7% in the open surgery group. The cause of postoperative ED is multifactorial; however, the primary mechanism is damage to the neurovascular bundle during surgery. Neuropraxia, ischemic and hypoxic injuries, fibrosis, and remodeling all contribute to ED (9). The cavernous nerves travel very close to the prostate capsule alongside vascular structures, forming the neurovascular bundle, as described by Walsh (10). Parasympathetic innervation carried by the cavernous nerves relaxes arterial and cavernosal smooth muscles, increasing penile blood flow and resulting in an erection (11). In the postoperative period, neuropraxia of the neurovascular bundle, followed by Wallerian degeneration, disrupts penile erection. This reduces penile blood flow, leading to cavernosal hypoxia (12). While cavernous nerve damage is a significant factor in the development of postoperative ED, it is not the only mechanism. Additionally, injury to the accessory pudendal arteries during surgery, which occurs in up to 75% of patients, leads to penile hypoxia. These arteries play a key role in maintaining the integrity and function of erectile tissue by providing penile blood flow and cavernous oxygenation (13). Penile hypoxia has been shown to result in collagen accumulation, smooth muscle apoptosis, and cavernous fibrosis (14).

The penile arterial blood supply is primarily provided by the internal pudendal artery and, in some cases, the accessory pudendal artery. The significance of the accessory pudendal artery in supplying blood to the cavernous tissue has been demonstrated in cadaveric studies. The accessory pudendal artery most commonly originates from the obturator artery, the inferior vesical artery, or the external pudendal artery, and it courses parallel to the dorsal venous complex in the periprostatic region. After traversing the pelvic floor muscles, approximately 70% of the branches of the accessory pudendal artery enter the cavernous tissue. In a study by Gray et al. (15), the presence of accessory pudendal arteries was demonstrated in 14% of cases unilaterally and 7% bilaterally. In a study by Rosen et al. (16), the presence of accessory pudendal arteries was identified in 7% of cases. Additionally, these arteries were reported to be the primary structures responsible for supplying blood flow to the penile artery. Damage to the accessory pudendal artery has been shown to have a negative impact on postoperative erectile function (17). In a study comparing surgical techniques with and without preservation of the accessory pudendal artery, a statistically significant improvement in postoperative erectile function was observed in the group in which the artery was preserved (18). In contrast, Box et al. (19) reported no postoperative deterioration in erectile function in cases where the accessory pudendal artery was damaged.

Understanding the mechanisms that cause ED following radical prostatectomy, as well as the penile rehabilitation efforts aimed at improving these mechanisms, is of great importance. Penile rehabilitation is considered a standard component of postoperative care for patients undergoing radical prostatectomy. However, the evidence regarding the efficacy of phosphodiesterase inhibitors, which are commonly used as first-line therapy for this purpose, remains controversial. As second-line therapy, drugs administered via intracavernosal injection are somewhat more effective but still insufficient for achieving natural erections. Moreover, their injectable form requires a high level of patient compliance. Penile prostheses, on the other hand, are mechanical devices used as a last-resort treatment option. However, the need for patient compliance, potential complications, and the inability of these techniques to restore natural erections are considered negative factors (20). In addition, methods such as extracorporeal shock wave therapy, stem cell therapy, platelet-rich plasma, gene therapy, and nerve grafts have been explored in various studies. It has been reported that these methods may face issues related to surgical techniques, have limited data on efficacy and safety, and are based on studies with short follow-up periods -highlighting the need for long-term and larger-scale research (21).

Both arterial and venous insufficiency can occur following radical prostatectomy. Arterial insufficiency has been reported to be associated with injury to the accessory pudendal artery during the procedure. Early erectile loss due to neuroapraxia leads to impaired cavernosal oxygenation and smooth muscle apoptosis. The resulting damage to the cavernous tissue is suggested to be the cause of venous insufficiency (13). Penile revascularization increases blood flow to the cavernous tissues, thereby enhancing intracavernosal oxygenation. This approach aims to prevent cavernous smooth muscle damage and improve erectile function. Penile revascularization can contribute to the improvement of erections, particularly in cases with arterial insufficiency due to trauma. Goldstein reported an 80% success rate in young patients with ED due to internal pudendal or penile artery injuries resulting from pelvic trauma, following penile revascularization surgery (22). In another study, end-to-end anastomosis was performed between the inferior epigastric artery and the deep dorsal vein, with normal erections observed in 49% of patients and improvement in 20% of patients (23). Kayıgil et al. (24) reported an 81% success rate in the long-term follow-up of 110 patients who underwent penile revascularization.

In this study, penile revascularization surgery was performed for the treatment of vascular-origin ED that developed after radical prostatectomy. In 1989, Hauri et al. (25) performed penile revascularization surgery on two cases for penile rehabilitation after radical prostatectomy, reporting unsuccessful outcomes in both cases. However, the reporting of only two cases in that study indicates an insufficient sample size to evaluate the effectiveness of the method. In our study, a larger sample size was used, microsurgical techniques were applied, and a multidisciplinary approach was adopted. In our study, successful outcomes were achieved in 12 out of 21 patients who underwent penile revascularization, while failure was observed in the other 9. The literature generally recommends penile prosthesis implantation for patients in whom oral and intracavernous treatments are unsuccessful. However, contrary to classical treatment approaches, we recommend performing penile revascularization surgery before resorting to highly invasive and irreversible procedures, such as penile prosthesis implantation. Our study demonstrates that successful outcomes can be achieved in cases of vascular-origin ED detected after radical prostatectomy. In conclusion, we believe that this study highlights the effectiveness of penile revascularization in selected cases and makes a significant contribution to the literature in this field. Patient selection based on specific criteria, the use of objective and comprehensive methods for diagnosis and treatment, and long-term follow-ups enhance the reliability of our results.

Study Limitations

However, its limitations include a single-center study, a retrospective design, and a limited number of patients.

Conclusion

Penile revascularization is considered an effective treatment option for penile rehabilitation following radical prostatectomy. The results indicate that penile revascularization shows promise in improving erectile function, especially in cases of vascular-origin ED. These findings support considering penile revascularization as an option before resorting to more invasive procedures, such as penile prosthesis implantation.

Ethics

Ethics Committee Approval: This retrospectively designed study was conducted at a tertiary healthcare institution and received approval from the Ankara Bilkent City Hospital Ethics Committee (approval number: TABED 1-25-908, date: 12.03.2025).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: F.A., Ö.K., Concept: F.A., Ö.K., Design: F.A., Ö.K., Data Collection or Processing: F.A., Ö.K., Analysis or Interpretation: F.A., Ö.K., Literature Search: F.A., Ö.K., Writing: F.A., Ö.K.

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References

1. Liu C, Lopez DS, Chen M, Wang R. Penile rehabilitation therapy following radical prostatectomy: a meta-analysis. J Sex Med. 2017;14:1496-1503. [Crossref]
2. Fode M, Borre M, Ohl DA, Lichtbach J, Sønksen J. Penile vibratory stimulation in the recovery of urinary continence and erectile function after nerve-sparing radical prostatectomy: a randomized, controlled trial. BJU Int. 2014;114:111-117. [Crossref]
3. Mulhall J. Neuroimmunophilin ligands protect cavernous nerves after crush injury in the rat: new experimental paradigms. European Urology. 2007;51:1488-1489. [Crossref]
4. Emanu JC, Avildsen IK, Nelson CJ. Erectile dysfunction after radical prostatectomy: prevalence, medical treatments, and psychosocial interventions. Curr Opin Support Palliat Care. 2016;10:102-107. [Crossref]
5. Kayigil O, Metin A. Relaxation degree: a new concept in erectile dysfunction. Int Urol Nephrol. 2001;33:391-394. [Crossref]
6. Furlow WL, Fisher J, Knoll LD: Current status of penile revascularization with deep dorsal vein arterialization: experience with 95 patients. International Journal Of Impotance Researche 1990;2:348. [Crossref]

7. Tal R, Alphs HH, Krebs P, Nelson CJ, Mulhall JP. Erectile function recovery rate after radical prostatectomy: a meta-analysis. J Sex Med. 2009;6:2538-2546. [Crossref]
8. Haglind E, Carlsson S, Stranne J, Wallerstedt A, Wilderäng U, Thorsteinsdottir T, Lagerkvist M, Damber JE, Bjartell A, Hugosson J, Wiklund P, Steineck G; LAPPRO steering committee. Urinary incontinence and erectile dysfunction after robotic versus open radical prostatectomy: a prospective, controlled, nonrandomised trial. Eur Urol. 2015;68:216-225. [Crossref]
9. Clavell-Hernández J, Wang R. The controversy surrounding penile rehabilitation after radical prostatectomy. Transl Androl Urol. 2017;6:2-11. [Crossref]
10. Walsh PC. The discovery of the cavernous nerves and development of nerve sparing radical retropubic prostatectomy. J Urol. 2007;177:1632-1635. [Crossref]
11. Gratzke C, Angulo J, Chitaley K, Dai YT, Kim NN, Paick JS, Simonsen U, Uckert S, Wespes E, Andersson KE, Lue TF, Stief CG. Anatomy, physiology, and pathophysiology of erectile dysfunction. J Sex Med. 2010;7:445-475. Erratum in: J Sex Med. 2010;7:1316. [Crossref]
12. Castiglione F, Ralph DJ, Muneer A. Surgical techniques for managing post-prostatectomy erectile dysfunction. Curr Urol Rep. 2017;18:90. [Crossref]
13. Mulhall JP, Secin FP, Guillonneau B. Artery sparing radical prostatectomy--myth or reality? J Urol. 2008;179:827-831. [Crossref]
14. Sopko NA, Burnett AL. Erection rehabilitation following prostatectomy--current strategies and future directions. Nat Rev Urol. 2016;13:216-225. [Crossref]
15. Gray RR, Keresteci AG, St Louis EL, Grosman H, Jewett MA, Rankin JT, Provan JL. Investigation of impotence by internal pudendal angiography: experience with 73 cases. Radiology. 1982;144:773-780. [Crossref]
16. Rosen MP, Greenfield AJ, Walker TG, Grant P, Guben JK, Dubrow J, Bettmann MA, Goldstein I. Arteriogenic impotence: findings in 195 impotent men examined with selective internal pudendal angiography. Young investigator's award. Radiology. 1990;174:1043-1048. [Crossref]
17. Wang R. Penile rehabilitation after radical prostatectomy: where do we stand and where are we going? J Sex Med. 2007;4:1085-1097. [Crossref]
18. Rogers CG, Trock BP, Walsh PC. Preservation of accessory pudendal arteries during radical retropubic prostatectomy: surgical technique and results. Urology. 2004;64:148-151. [Crossref]
19. Box GN, Kaplan AG, Rodriguez E Jr, Skarecky DW, Osann KE, Finley DS, Ahlering TE. Sacrifice of accessory pudendal arteries in normally potent men during robot-assisted radical prostatectomy does not impact potency. J Sex Med. 2010;7:298-303. [Crossref]
20. Chung E, Gillman M. Prostate cancer survivorship: a review of erectile dysfunction and penile rehabilitation after prostate cancer therapy. Med J Aust. 2014;200:582-585. [Crossref]
21. Chung E. Regenerative technology to restore and preserve erectile function in men following prostate cancer treatment: evidence for penile rehabilitation in the context of prostate cancer survivorship. Ther Adv Urol. 2021;13:17562872211026421. [Crossref]
22. Goldstein I. Overview of types and results of vascular surgical procedures for impotence. Cardiovasc Intervent Radiol. 1988;11:240-244. [Crossref]
23. Virag R, Spencer PP, Frydman D. Artificial erection in diagnosis and treatment of impotence. Urology. 1984;24:157-161. [Crossref]
24. Kayıgil O, Okulu E, Aldemir M, Onen E. Penile revascularization in vasculogenic erectile dysfunction (ED): long-term follow-up. BJU Int. 2012;109:109-115. [Crossref]
25. Hauri D, Knönagel H, Konstantinidis K. Radical prostatectomy in cases of prostatic carcinoma: the problem concerning erectile impotence. Urol Int. 1989;44:272-278. [Crossref]

ORIGINAL RESEARCH
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Preoperative Systemic Inflammatory Indices as Predictors of Malignant Pathology in Repeat Transurethral Resection for High-risk Non-muscle Invasive Bladder Cancer: Insights from a Cross-Sectional Study

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

The clinical importance of repeat transuretral resection of bladder tumour (Re-TUR-BT) is to prevent understaging of non-muscle invasive bladder cancer (NMIBC), to remove any residual cancer that may have been overlooked during the first procedure, and to provide additional prognostic data. The pathological results from Re-TUR-BT operations are fundamental to the management of high-risk NMIBC patients. These results guide crucial decisions regarding bladder-sparing approaches versus radical cystectomy. The necessity for Re-TUR-BT procedures is well-documented in both the European Urological Association and American Urological Association guidelines. While the correlation between high-risk NMIBC and systemic inflammation indices has been extensively explored in the literature, our current study specifically investigates the impact of systemic inflammation indices derived from blood measurements taken immediately prior to Re-TUR-BT in predicting bladder cancer pathology. Our findings suggest that elevated levels of inflammation indices in patients with high-risk bladder cancer may significantly support the performance of Re-TUR-BT. This insight could enhance clinical decision-making and improve management strategies for patients facing high-risk NMIBC.

Abstract

Objective: This study investigates the predictive value of systemic inflammatory indices for repeat transuretral resection of bladder tumour (Re-TUR-BT) pathology in patients with high-risk non-muscle invasive bladder cancer (NMIBC).

Materials and Methods: We conducted a retrospective analysis of 83 patients diagnosed with primary bladder tumors who underwent Re-TUR-BT based on initial pathology results from January 2014 to December 2023. Patients were categorized into two groups based on Re-TUR-BT pathology: Group 1 (non-malignant at Re-TUR-BT) and group 2 (malignant at Re-TUR-BT). We compared systemic inflammatory markers between these groups.

Results: Of the 83 patients, 55 (82.5%) were in group 1 and 28 (17.5%) in group 2. Demographic characteristics showed no significant differences between the groups. However, upon comparison of operative and histopathological features, the incidence of T1 classification in first TUR-BT pathology, was significantly higher in group 2. Additionally, group 1 had a higher proportion of single tumors, whereas group 2 exhibited a greater incidence of two or more tumors, a difference that was statistically significant. Analysis of systemic inflammatory indices revealed no significant differences in the complete blood count results before the initial TUR-BT. However, both the systemic immune-inflammation index (SII) and neutrophil-to-lymphocyte ratio (NLR) showed significant differences before Re-TUR-BT.

Conclusion: Our study indicates that SII and NLR calculated prior to Re-TUR-BT can predict malignant pathology persistence in high-risk NMIBC patients. These findings underscore the potential of systemic inflammatory indices as valuable biomarkers in clinical practice.

Keywords: Bladder cancer, SII, NLR, TUR-BT

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Introduction

Bladder cancer (BC) is categorized into two main subtypes: Non-muscle-invasive BC (NMIBC) and muscle-invasive BC (MIBC), based on their clinical progression and prognosis. The standard treatment approach for NMIBC primarily consists of transurethral resection of the bladder tumour (TUR-BT), followed by intravesical instillation of either chemotherapy or immunotherapy, tailored to the patient's risk of disease recurrence and progression. To mitigate the risk of understaging that can occur during the initial TUR-BT, clinical guidelines recommend performing a second resection (Re-TUR-BT) within 4 to 6 weeks following the initial procedure (1). The rationale behind Re-TUR-BT is to prevent understaging of NMIBC, to remove any residual cancer that may have been overlooked during the first procedure, and to provide additional prognostic data. The incidence of understaging in NMIBC cases ranges from approximately 7% to 30%, and this figure can rise to as high as 45% when the initial TUR-BT specimen lacks detrusor muscle (2). The incidence of understaging in NMIBC cases is reported to range from approximately 7% to 30%. This percentage can increase to as much as 45% when the initial TUR-BT specimen does not contain detrusor muscle (2). Additionally, a recent study found that among 31 patients with T1 high-grade tumors, there was a high rate of Re-TUR-BT positivity, recorded at 58.5 % (3).

Despite patients achieving complete resection of NMIBC and undergoing adjuvant intravesical instillation therapy, it is noted that approximately 70% of them will experience disease recurrence. Furthermore, around 30% of these individuals may ultimately face disease progression (4). Recent studies have explored various prognostic models and biomarkers as potential predictors of BC recurrence to enhance clinical decision-making and patient counseling (5). Indeed, while the identification of biomarkers for BC has the potential to enhance prognostic accuracy and treatment personalization, several challenges have impeded their integration into routine clinical practice. High costs associated with these biomarkers, along with a lack of standardization across different laboratories and methods, have limited their widespread adoption.

The relationship between the body's inflammatory response and the development of cancer, including BC, has garnered significant attention in recent years. The connection between inflammation and tumors was first observed by Virchow in 1863 (6). Inflammation not only contributes to malignant transformation and metastasis but also forms an integral part of the tumor's local environment (7).

Emerging evidence indicates that inflammatory responses within the tumor microenvironment (TME) are crucial in BC tumorigenesis, proliferation, progression, and metastasis. The immune system, together with the inflammatory response and the TME, significantly influences the clinical and biological behavior and outcomes of BC (7).

Researchers have extensively investigated the prognostic value of inflammatory response markers in cancer through ratios such as the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), monocyte-to-lymphocyte ratio, and systemic immune-inflammation index (SII). These markers have been studied for their potential to predict cancer prognosis, offering insights into the complex interactions between inflammation and cancer dynamics (8).

To the best of our knowledge, no studies have specifically evaluated inflammatory indices for predicting Re-TUR-BT outcomes, despite their prognostic value in other BC contexts. In our study, we explored the relationship between inflammation indices and the likelihood of malignant pathology results in patients undergoing Re-TUR-BT for high-risk BC. Inflammatory indices may be important predictors of malignant pathology outcomes in patients undergoing Re-TUR-BT for high-risk BC, and their assessment may improve preoperative evaluation and treatment decision-making.

Materials and Methods

Ethics Statement

This research was carried out in accordance with the ethical guidelines established in the Declaration of Helsinki. All participants received comprehensive information regarding the study's objectives and provided their written informed consent. The Local Ethics Committee of Health Science University İstanbul Training and Research Hospital granted ethical approval for this study (approval number: 2024-97, date: 18.10.2024).

Study Design

In this study, we conducted a retrospective analysis of patients diagnosed with primary bladder tumors who underwent Re-TUR-BT operation based on their initial pathology results. The objective of the study was to investigate the predictive role of inflammatory indexes in assessing the likelihood of malignant pathology results within this high-risk patient cohort.

Selection of Participants

The study participants were high grade NMIBC patients who underwent Re-TUR-BT operation between January and December 2023. Patients with concomitant malignancies, a history of upper urinary tract transitional cell carcinoma, rheumatic diseases, prior cardiac surgery, and chronic renal failure were excluded from the analysis. A total of 83 patients who met the inclusion criteria were retrospectively analyzed (Figure 1).

Study Variables

Routine complete blood count measurements were obtained from all patients scheduled to undergo initial TUR-BT, diagnosed with primary bladder tumors, and from patients requiring Re-TUR-BT based on the findings of the initial pathology. These measurements were analyzed for the purpose of calculating systemic inflammatory indices. The time interval from the first operation to the second was recorded in days. The NLR, lymphocyte-to-monocyte ratio (LMR), PLR, monocyte-to-white blood cell ratio (MWR), SII, and systemic inflammatory response index (SIRI) were calculated using the following formulas: NLR = neutrophil/lymphocyte ratio; LMR = lymphocyte/monocyte ratio; PLR = platelet/lymphocyte ratio; MWR = monocyte/white blood cell ratio; SII = (neutrophil × platelet)/lymphocyte ratio; SIRI = (neutrophil × monocyte)/lymphocyte ratio.

At the commencement of the first operation, data regarding tumor size, number, and appearance type (papillary or solid) were retrospectively reviewed and utilized for analysis. Pathology specimens obtained from both the initial and Re-TUR-BT procedures were evaluated by the same pathologist at a single pathology clinic. Patients were categorized into two groups based on the pathology results of the Re-TUR-BT operation. The absence of any tumour detected on re-TURB was considered non-malignant, while the detection of Ta/T1 high-grade or carcinoma *in situ* (CIS) was considered malignant (group 1: Non-malignant at Re-TUR-BT, group 2: Malignant at Re-TUR-BT). Values were compared for both groups (Figure 1).

Statistical Analysis

Descriptive statistics were calculated for demographic and clinical characteristics. Continuous variables were expressed as median and interquartile range while categorical variables were expressed as frequencies and percentages. Mann-Whitney U test was used to compare non-normally distributed continuous variables, and chi-square tests were employed for categorical variables. The chi-square test was employed to analyze categorical data. A significance level of $p<0.05$ was established for all analyses.All statistical analyses were performed using SPSS version 28.0. Furthermore, a separate receiver operating characteristic (ROC) analysis was conducted to calculate the area under the curve (AUC) for distinguishing malignant pathology within each group.

Results

After applying the exclusion criteria, the study population was stratified into two groups based on the pathology results from the Re-TUR-BT operation. Group 1 consisted of 55 patients with non-malignant pathology findings, while group 2 included 28 patients with malignant pathology results.

The comparison of the demographic characteristics of the two groups is summarized in Table 1. There were no statistically significant differences in terms of age, gender, body mass index, smoking status, or comorbid conditions between the groups ($p>0.05$, for each).

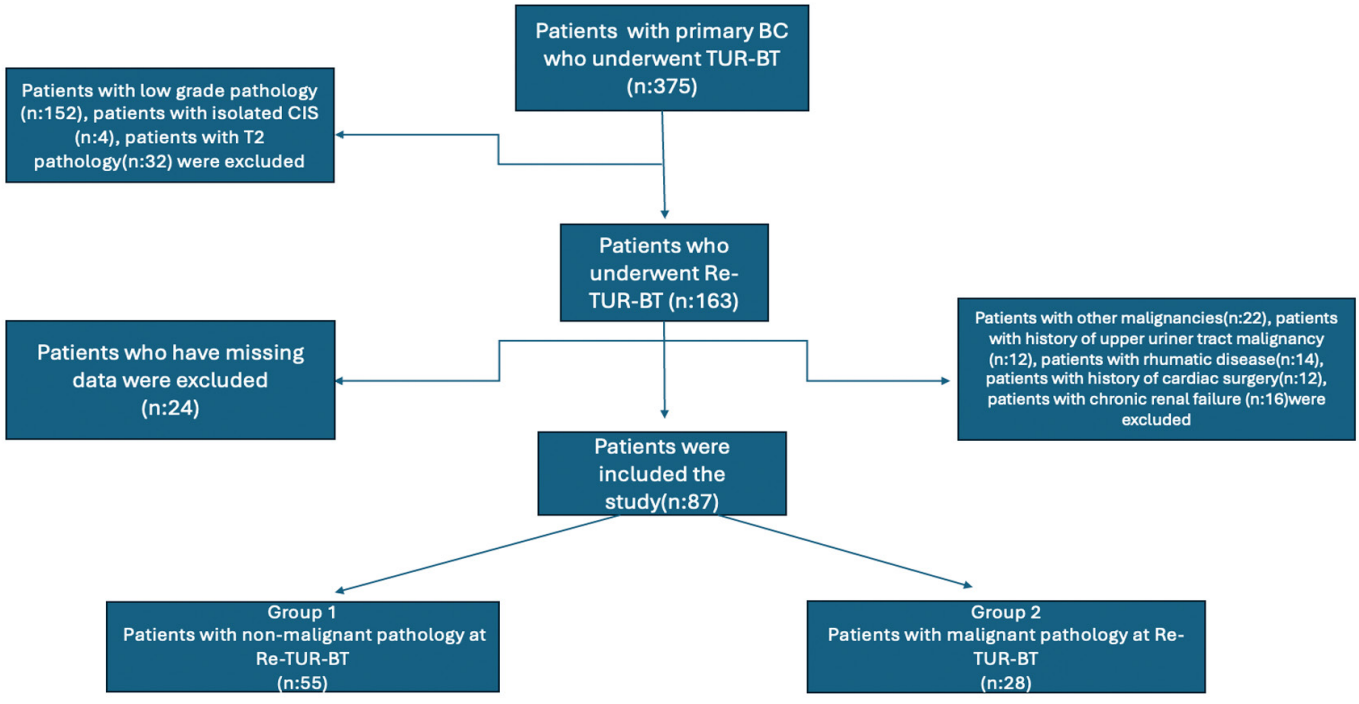

Figure 1. Flow chart of the patient's selection

CIS: Carcinoma in situ, TUR-BT: Transurethral resection of bladder tumor, BC: Bladder cancer

According to the results of initial TUR-BT pathology, forty (48.2%) of the patients had pTa high-grade pathology and 43 (51.8%) had pT1 high-grade pathology. In addition, 24 (28.9%) had concomitant CIS.

The comparison of the groups in terms of operative and histopathological features is summarised in Table 2. There were no statistically significant differences between the two groups regarding the presence of concomitant carcinoma in situ, tumor size, tumor characteristics (papillary or solid), and time to the second TUR-BT. However, the number of patients with initial TUR-BT pathology classified as T1 was significantly higher in group 2 ($p<0.05$). Additionally, group 1 exhibited a higher proportion of single tumors, whereas group 2 showed a greater proportion of two or more tumors ($p<0.05$).

The results of the comparison of the systemic inflammatory indices between the two groups are summarized in Table 3. There was no significant difference between the groups regarding the SII calculated from complete blood count results before the initial TURB. However, both the SII and the NLR showed statistically significant differences in the systemic inflammatory indices before Re-TUR-BT in group 2 ($p=0.017$ and $p=0.029$, respectively).

The SII values measured before the Re-TUR-BT operation demonstrated significant efficacy in differentiating between non-malignant and malignant pathology, with an AUC of 0.660 [95% confidence interval (CI): 0.538-0.783; $p=0.010$] as illustrated in Figure 1. Additionally, the NLR values obtained prior to the Re-TUR-BT were also significant, demonstrating

Table 1. Comparison of demographic characteristics of groups

	Group 1 (non-malignant at Re-TUR-BT) (n=55)	Grup 2 (malignant at Re-TUR-BT) (n=28)	p
Age [year, median (IQR), (min-max)]	63.05 (18) (41-86)	63.8 (15) (36-86)	0.962[m]
Sex (M/F) [n (%)]	49 (89.1)/6 (10.9)	27 (96.4)/1 (3.6)	0.255[k]
BMI [median (IQR), (min-max)]	26.12 (5.2) (17-39)	25.86 (6.6) (20-33)	0.847[m]
Smoking [n (%)]	46 (83.6)	24 (85.7)	0.805[k]
Diabetes mellitus [n (%)]	10 (18.2)	2 (7.1)	0.176[k]
Hypertension [n (%)]	20 (36.4)	9 (32.1)	0.703[k]
COPD [n (%)]	9 (16.4)	4 (14.3)	0.805[k]

[m]: Mann-Whitney U test, [k]: Chi-square test, BMI: Body mass index, COPD: Chronic obstructive pulmonary disease, Re-TUR-BT: Repeat transuretral resection of bladder tumour, M/F: Male/female, min-max: Minimum-maximum, IQR: Interquartile range

Table 2. Comparison of operative and histopathological features between groups

	Group 1 (non-malignant at Re-TUR-BT) (n=55)	Grup 2 (malignant at Re-TUR-BT) (n=28)	p
Tumour T stage (pT) [n (%)]			
pTa	31 (56.4)	9 (32.1)	**0.037[k]**
pT1	24 (43.6)	19 (67.9)	
CIS [n (%)]	14 (25.5)	10 (35.7)	0.330[k]
Tumour size [n (%)]			
<3 cm	20 (36.4)	9 (32.1)	0.703[k]
≥3 cm	35 (63.6)	19 (67.9)	
Tumour number [n (%)]			
1	30 (54.5)	7 (25)	**0.037[k]**
2-7	21 (38.2)	18 (64.3)	
>7	4 (7.3)	3 (10.7)	
Tumour characteristics [n (%)]			
Papillary	42 (76.4)	22 (78.6)	0.821[k]
Solid	13 (23.6)	5 (21.4)	
Time to re-TUR-BT [day, median (IQR), (min-max)]	36 (20) (20-114)	38 (17) (19-99)	0.167[m]

CIS: Carcinoma *in situ*, [k]: Chi-square test, [m]: Mann-Whitney U test, Re-TUR-BT: Repeat transuretral resection of bladder tumour, IQR: Interquartile range, min-max: Minimum-maximum

diagnostic value in predicting malignant pathology. This was confirmed through ROC analysis, yielding an AUC of 0.647 (95% CI: 0.524-0.770; p=0.020), as shown in Figure 2.

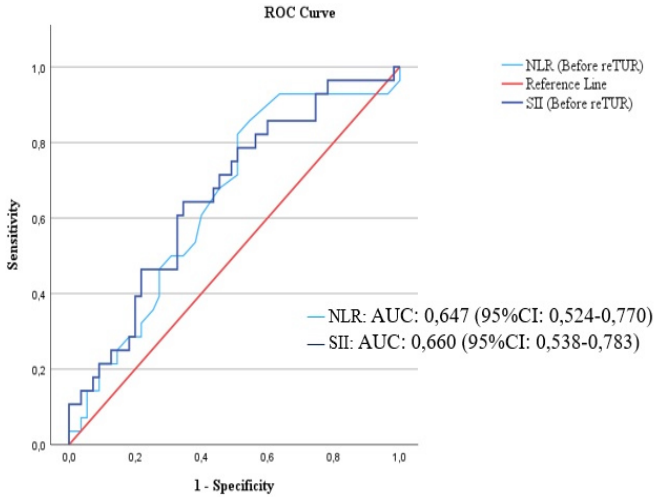

Figure 2. The effectiveness of the before Re-TUR-BT SII and NLR values in predicting malignant pathology

Re-TUR-BT: Repeat transurethral resection of bladder tumor, SII: Systemic immune-inflammation index, NLR: Neutrophil-to-lymphocyte ratio, AUC: Area under the curve

Discussion

The SII, a composite marker derived from peripheral blood counts, has garnered increasing attention in recent years due to its prognostic utility across various medical fields. Studies have demonstrated its relevance not only in oncology but also in cardiovascular diseases, autoimmune disorders, and infectious diseases, where systemic inflammation plays a critical role in disease pathophysiology and progression (3,9). The ability of SII to reflect the dynamic balance between immune activation and suppression positions it as a potentially valuable tool in clinical decision-making, especially in oncology. Its accessibility, cost-effectiveness, and reproducibility make it an attractive option for risk stratification and patient management across diverse clinical contexts (10,11). While the role of SII in oncology (particularly in predicting outcomes in malignancies such as bladder cancer) has been well documented, emerging evidence suggests that SII may also serve as a valuable biomarker in the diagnosis, monitoring, and prognostication of various cancers. This underscores its potential to enhance clinical practice by improving patient outcomes through more tailored management strategies.

Table 3. Comparison of systemic inflammatory indices between groups

	Group 1 (non-malignant at Re-TUR-BT) (n=55)	Grup 2 (malignant at Re-TUR-BT) (n=28)	p
SII before initial TUR-BT [median (IQR), (min-max)]	475.4 (332.9) (175.4-1621.2)	525.1 (562.5) (219.4-2642.2)	0.272[m]
SIRI before initial TUR-BT [median (IQR), (min-max)]	1.17 (1.1) (0.4-4.2)	1.08 (1.3) (0.4-8.7)	0.441[m]
NLR before initial TUR-BT [median (IQR), (min-max)]	2.17 (1.3) (0.7-7)	2.15 (2) (0.9-13.8)	0.303[m]
LMR before initial TUR-BT [median (IQR), (min-max)]	4 (1.9) (1.4-9.2)	3.55 (3) (0.9-6.9)	0.765[m]
PLR before initial TUR-BT [median (IQR), (min-max)]	104.9 (42.7) (48.1-278.3)	120.7 (76.7) (64.2-379.3)	0.141[m]
MWR before initial TUR-BT [median(IQR), (min-max)]	0.07 (0) (0-0.1)	0.07 (0) (0-0.1)	0.729[m]
SII before Re-TUR-BT [median (IQR), (min-max)]	443.4 (355.6) (179.8-1809.9)	576.4 (532) (219.4-2857.6)	**0.017[m]**
SIRI before Re-TUR-BT [median (IQR), (min-max)]	1 (0.9) (0.4-5)	1.3 (1.3) (0.4-4.7)	0.088[m]
NLR before Re-TUR-BT [median (IQR), (min-max)]	1.9 (1.7) (1-8.2)	2.35 (2) (0.9-8.3)	**0.029[m]**
LMR before Re-TUR-BT [median (IQR), (min-max)]	4,3 (1.7) (1.4-9.2)	3.7 (2.4) (1.4-7.3)	0.285[m]
PLR before Re-TUR-BT [median (IQR), (min-max)]	110.3 (31.5) (60.9-258.4)	119.1 (96.6) (73.1-416.6)	0.134[m]
MWR before Re-TUR-BT [median (IQR), (min-max)]	0.07 (0) (0-0.1)	0.07 (0) (0.1-0.1)	0.531[m]

SII: Systemic inflammatory index, SIRI: Systemic inflammatory response index, NLR: Neutrophil/lymphocyte ratio, LMR: Lymphocyte/monocyte ratio, PLR: Platelet/lymphocyte ratio, MWR: Monocyte/white blood cell ratio, [m]: Mann-Whitney U test, IQR: Interquartile, Re-TUR-BT: Repeat transuretral resection of bladder tumour, min-max: Minimum-maximum

In this single-center retrospective study, we examined the clinical significance of preoperative blood-based systemic inflammatory indices in patients with high-risk NMIBC who required Re-TUR-BT. Our findings demonstrated that elevated levels of the SII and NLR were independent predictive factors for malignant pathology in Re-TUR-BT specimens. This suggests that these inflammatory markers may serve as valuable tools in the preoperative assessment and risk stratification of patients undergoing Re-TUR-BT for high-risk NMIBC.

Numerous recent studies have highlighted the benefits of Re-TUR-BT in patients with high-risk NMIBC (3,12). This procedure improves diagnostic precision and aids in the removal of any remaining cancerous tissue. A recent meta-analysis that included 29 studies found a combined prevalence of 56% for residual tumors and 10% for upstaging to T2 among 3,566 and 2,556 patients, respectively (13). The pathology results from Re-TUR-BT hold significant prognostic value and are deemed the most important predictor of early recurrence and progression. Herr and Donat (14) reported that the presence of T1 tumors at second-look TUR-BT is associated with a progression rate of 76% within five years. Palou and colleagues conducted an analysis involving a cohort of 2,451 patients to investigate the prognostic significance of pathology findings from second-look TUR-BT. Their study established that T1 tumors identified during the second-look TUR-BT were associated with a higher likelihood of recurrence, progression, and mortality due to the disease. In a multivariate model that included factors such as tumor multiplicity, concomitant CIS, and BCG maintenance, second-look TUR-BT pathology emerged as the most critical prognostic factor for these outcomes (15).

Additionally, the therapeutic benefits of Re-TUR-BT have been noted. Comparisons between second-look TUR-BT and observation have shown significantly lower recurrence rates at 3 to 6 months post-cystoscopy for both T1 and high-grade Ta tumors (16). A recent study indicated that patients who underwent second-look TUR-BT had statistically significant improvements in cancer-specific survival (CSS) ($p=0.009$) and overall survival ($p<0.001$) compared to those who did not (17).

In this study, we aimed to identify the factors that may serve as predictors of tumor persistence following the initial TUR-BT. Specifically, we focused on patients' cohort whose tumors were found to be persistent based on the pathological findings from the subsequent Re-TUR-BT procedure. Our investigation involved a comprehensive analysis of various biochemical, pathological, and demographic variables that could potentially influence the likelihood of tumor persistence.

Tumor-related factors, including pathological tissue type, grade, and stage, are critical for predicting the progression and prognosis of cancer patients. These factors provide essential insights into the biological behavior of tumors, enabling clinicians to stratify patients according to their risk of recurrence and progression. In our study, we observed that the number of patients whose initial TUR-BT pathology was classified as T1 was significantly higher in group 2. These findings align with those of Divrik et al. (2), who conducted a prospective randomized trial involving T1 patients undergoing either a single TUR-BT or a second TUR-BT. They reported 5-year recurrence-free survival rates of 32% and 59%, respectively, and noted that 33% of patients had residual tumor at the time of the second TUR-BT. Additionally, our study revealed a higher incidence of single tumors in group 1, while group 2 exhibited a greater prevalence of multifocal tumors. Previous research has supported these results, for example, Ferro et al. (18) identified a statistically significant association between the presence of T1 high-grade BC at Re-TUR-BT and factors such as multifocality, tumor size greater than 3 cm, and the presence of CIS at the first TURB. Furthermore, Kamiya et al. (19) demonstrated that multifocality at the first TUR-BT is an independent predictor of high-grade T1, at Re-TUR-BT. In our study, although we noted a higher rate of tumor diameter exceeding 3 cm and the presence of concomitant CIS in group 2, these differences did not reach statistical significance. According to a recent study, the primary distinctions between patients with and without T1 high grade tumors at Re-TUR-BT were related to the size of the main lesion and multifocality. Notably, 13.9% of patients lacked a muscle layer, and 15.1% presented with CIS; however, the differences between those with and without T1 high grade at Re-TUR-BT were not significant (20).

In addition to these tumor-related factors, patient-related elements also play a crucial role in predicting cancer outcomes. One such area of interest is the assessment of systemic inflammatory indices (21). Inflammatory mechanisms, initiated by substances such as chemokines and cytokines, are essential for supporting the proliferation and persistence of cancer cells through several pathways, including the stimulation of blood vessel formation and the enhancement of metastatic spread. At the same time, the activation of oncogenes initiates inflammatory pathways from within the cancer cells themselves. This relationship underscores the significant connection between inflammation and cancer, as inflammatory responses can foster an environment that supports the development and advancement of tumors (22).

Our results identified the SII and NLR as two significant systemic inflammatory indices that can predict malignant pathology following Re-TUR-BT operations. The SII has been established as an independent prognostic indicator for patients with BC undergoing radical cystectomy (RC) or TUR-BT. A comprehensive meta-analysis conducted by Li et al. (23), which included ten studies, found that elevated SII levels are associated with markedly decreased overall survival rates, CSS rates, and

recurrence-free survival rates in BC patients. These findings also highlighted a considerable degree of heterogeneity across the studies. Furthermore, prior studies have demonstrated a correlation between adverse prognosis in BC and the NLR. The report by Mari et al. (24) highlighted that elevated preoperative NLR levels were independently linked to increased overall mortality in BC patients following RC. Additionally, a previous study has also found that high NLR is associated with high grade disease (25). An increased NLR indicates a relative increase in neutrophils, which release inflammatory factors and specific proteases that induce extracellular matrix remodeling. This creates a favorable microenvironment for tumor cell migration and progression (26). The results imply that SII and NLR appear to be valuable biomarkers in assessing the prognosis and potential outcomes of patients with BC, especially in relation to surgical interventions.

We further analyzed the diagnostic value of inflammatory indices in Re-TUR-BT pathology and calculated the AUC from ROC curves. Our findings indicate that SII and NLR possess diagnostic utility for predicting malignant pathology. According to established literature, an AUC value between 0.7 and 0.8 is considered acceptable, while values between 0.6 and 0.7 are regarded as poor, and values below 0.6 indicate no diagnostic ability (27). Although both SII and NLR, assessed prior to re-TURBT, demonstrate some diagnostic value for identifying malignant pathology, their AUC values fall within the range of 0.6 to 0.7. This suggests that while these indices can provide insights, their diagnostic capability for predicting malignant pathology is limited.

Study Limitations

To highlight some important strengths of our study, to our knowledge, this is the first investigation in the literature exploring the value of systemic inflammatory indices for predicting pathology outcomes following Re-TUR-BT. Furthermore, all surgical procedures were conducted at a single center by a uro-oncological surgeon who specializes in bladder cancer, and the pathology results were interpreted by a single pathologist with expertise in urooncology. This consistency in both surgical technique and pathological evaluation enhances the quality and reliability of our findings, suggesting that single-center research can provide valuable insights. Despite the strengths of the study, several limitations warrant acknowledgment. First, the small sample size associated with a single-institute study may restrict the generalizability of the findings. Secondly, the retrospective cohort design could introduce selection bias, and the reliance on existing medical records for data collection may result in underreporting of comorbidities. This underreporting could significantly impact the validity of the results, as unrecognized comorbid conditions may confound the relationship between the variable of interest and the observed outcomes. The other potential limitation of this study is the lack of multivariate analysis, which may have overlooked the influence of confounding variables on the observed outcomes. Additionally, the modest AUC values observed in our analysis suggest that the diagnostic power of the tested model is limited. This indicates that while the model may have some utility in distinguishing between conditions, its overall accuracy and reliability in a clinical setting may not be sufficient to warrant widespread application. Finally, the study did not assess several important inflammation-and nutrition-based indicators, such as the Glasgow prognostic score, the albumin/globulin ratio, and the C-reactive protein/albumin ratio. Including these metrics could have provided deeper insights into the relationship between systemic inflammation and patient outcomes. Given these limitations, we recommend larger, multicenter prospective cohort studies to confirm the preliminary results of this investigation and further evaluate the prognostic value of systemic inflammatory indices in high-risk NMIBC patients.

Conclusion

Our study shows that SII and NLR calculated before Re-TUR-BT have potential predictive values in detecting the persistence of malignant pathology in Re-TUR-BT among high-risk NMIBC patients. These findings highlight the potential utility of these systemic inflammatory indices as biomarkers in clinical practice. Given the significance of our results, we advocate for larger, multicenter studies to further validate these findings. Such research would enhance our understanding of the role of SII and NLR, helping to establish their potential as reliable tools for clinical decision-making in the management of high-risk NMIBC patients.

Ethics

Ethics Committee Approval: The Local Ethics Committee of Health Science University İstanbul Training and Research Hospital granted ethical approval for this study (approval number: 2024-97, date: 18.10.2024).

Informed Consent: All participants received comprehensive information regarding the study's objectives and provided their written informed consent.

Footnotes

Authorship Contributions

Surgical and Medical Practices: U.Y., T.M., M.H.E.A., Concept: H.A.A., E.O., Y.Ş., E.S., E.E., Design: H.A.A., M.Ç., E.E., Data Collection or Processing: T.M., M.Ç., M.H.E.A., Analysis or Interpretation: U.Y., E.S., Literature Search: H.A.A., E.O., Writing: H.A.A., Y.Ş., E.E.

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

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References

1. Babjuk M, Burger M, Capoun O, Cohen D, Compérat EM, Dominguez Escrig JL, Gontero P, Liedberg F, Masson-Lecomte A, Mostafid AH, Palou J, van Rhijn BWG, Rouprêt M, Shariat SF, Seisen T, Soukup V, Sylvester RJ. European Association of Urology Guidelines on non-muscle-invasive bladder cancer (Ta, T1, and carcinoma in situ). Eur Urol. 2022;81:75-94. [Crossref]
2. Divrik RT, Sahin AF, Yildirim U, Altok M, Zorlu F. Impact of routine second transurethral resection on the long-term outcome of patients with newly diagnosed pT1 urothelial carcinoma with respect to recurrence, progression rate, and disease-specific survival: a prospective randomised clinical trial. Eur Urol. 2010;58:185-190. [Crossref]
3. Murat Akgül, Çağrı Doğan, Cenk Murat Yazıcı, Mehmet Fatih Şahin, Ayşegül İsal Arslan, Meltem Öznur. Which non-muscle invasive bladder cancer is more valuable for re-transurethral resection? Ann Clin Anal Med 2021;12:1258-1262. [Crossref]
4. Sylvester RJ, van der Meijden AP, Oosterlinck W, Witjes JA, Bouffioux C, Denis L, Newling DW, Kurth K. Predicting recurrence and progression in individual patients with stage Ta T1 bladder cancer using EORTC risk tables: a combined analysis of 2596 patients from seven EORTC trials. Eur Urol. 2006;49:466-465; discussion 475-477. [Crossref]
5. Sahin Y, Yucetas U, Ates HA, Erkan E, Yucetas E, Temiz MZ, Toktas MG, Kadihasanoglu M, Topkaya BC. Improving the diagnosis of high grade and stage bladder cancer by detecting increased urinary calprotectin expression in tumor tissue and tumor-associated inflammatory response. Investig Clin Urol. 2019;60:343-350. [Crossref]
6. Balkwill F, Mantovani A. Inflammation and cancer: back to Virchow? Lancet. 2001;357:539-545. [Crossref]
7. Thompson DB, Siref LE, Feloney MP, Hauke RJ, Agrawal DK. Immunological basis in the pathogenesis and treatment of bladder cancer. Expert Rev Clin Immunol. 2015;11:265-279. [Crossref]
8. Cantiello F, Russo GI, Vartolomei MD, Farhan ARA, Terracciano D, Musi G, Lucarelli G, Di Stasi SM, Hurle R, Serretta V, Busetto GM, Scafuro C, Perdonà S, Borghesi M, Schiavina R, Cioffi A, De Berardinis E, Almeida GL, Bove P, Lima E, Ucciero G, Matei DV, Crisan N, Verze P, Battaglia M, Guazzoni G, Autorino R, Morgia G, Damiano R, de Cobelli O, Mirone V, Shariat SF, Ferro M. Systemic inflammatory markers and oncologic outcomes in patients with high-risk non-muscle-invasive urothelial bladder cancer. Eur Urol Oncol. 2018;1:403-410. [Crossref]
9. Yang YL, Wu CH, Hsu PF, Chen SC, Huang SS, Chan WL, Lin SJ, Chou CY, Chen JW, Pan JP, Charng MJ, Chen YH, Wu TC, Lu TM, Huang PH, Cheng HM, Huang CC, Sung SH, Lin YJ, Leu HB. Systemic immune-inflammation index (SII) predicted clinical outcome in patients with coronary artery disease. Eur J Clin Invest. 2020;50:e13230. [Crossref]
10. Yang R, Chang Q, Meng X, Gao N, Wang W. Prognostic value of Systemic immune-inflammation index in cancer: A meta-analysis. J Cancer. 2018;9:3295-3302. [Crossref]
11. Arikan MG, Akgul M, Akdeniz E, Iskan G, Arda E. The value of hematological inflammatory parameters in the differential diagnosis of testicular torsion and epididymorchitis. Am J Clin Exp Urol. 2021;9:96-100. [Crossref]
12. Dobruch J, Borówka A, Herr HW. Clinical value of transurethral second resection of bladder tumor: systematic review. Urology. 2014;84:881-885. [Crossref]
13. Naselli A, Hurle R, Paparella S, Buffi NM, Lughezzani G, Lista G, Casale P, Saita A, Lazzeri M, Guazzoni G. Role of restaging transurethral resection for T1 non-muscle invasive bladder cancer: a systematic review and meta-analysis. Eur Urol Focus. 2018;4:558-567. [Crossref]
14. Herr HW, Donat SM. A re-staging transurethral resection predicts early progression of superficial bladder cancer. BJU Int. 2006;97:1194-1198. [Crossref]
15. Palou J, Pisano F, Sylvester R, Joniau S, Serretta V, Larré S, Di Stasi S, van Rhijn B, Witjes AJ, Grotenhuis A, Colombo R, Briganti A, Babjuk M, Soukup V, Malmstrom PU, Irani J, Malats N, Baniel J, Mano R, Cai T, Cha EK, Ardelt P, Varkarakis J, Bartoletti R, Dalbagni G, Shariat SF, Xylinas E, Karnes RJ, Gontero P. Recurrence, progression and cancer-specific mortality according to stage at re-TUR in T1G3 bladder cancer patients treated with BCG: not as bad as previously thought. World J Urol. 2018;36:1621-1627. [Crossref]
16. Gendy R, Delprado W, Brenner P, Brooks A, Coombes G, Cozzi P, Nash P, Patel MI. Repeat transurethral resection for non-muscle-invasive bladder cancer: a contemporary series. BJU Int. 2016;117(Suppl 4):54-59. [Crossref]
17. Gordon PC, Thomas F, Noon AP, Rosario DJ, Catto JWF. Long-term outcomes from re-resection for high-risk non-muscle-invasive bladder cancer: a potential to rationalize use. Eur Urol Focus. 2019;5:650-657. [Crossref]
18. Ferro M, Vartolomei MD, Cantiello F, Lucarelli G, Di Stasi SM, Hurle R, Guazzoni G, Busetto GM, De Berardinis E, Damiano R, Perdonà S, Borghesi M, Schiavina R, Almeida GL, Bove P, Lima E, Grimaldi G, Autorino R, Crisan N, Abu Farhan AR, Verze P, Battaglia M, Serretta V, Russo GI, Morgia G, Musi G, de Cobelli O, Mirone V, Shariat SF. High-grade T1 on re-transurethral resection after initial high-grade T1 confers worse oncological outcomes: results of a multi-institutional study. Urol Int. 2018;101:7-15. [Crossref]
19. Kamiya N, Suzuki H, Suyama T, Kobayashi M, Fukasawa S, Sekita N, Mikami K, Nihei N, Naya Y, Ichikawa T. Clinical outcomes of second transurethral resection in non-muscle invasive high-grade bladder cancer: a retrospective, multi-institutional, collaborative study. Int J Clin Oncol. 2017;22:353-358. [Crossref]
20. Gobbo A, Fasulo V, Contieri R, Uleri A, Avolio PP, Frego N, Lughezzani G, Saitta C, Taverna G, Zanoni M, Mancon S, Colombo P, Valeri M, Saita A, Lazzeri M, Buffi NM, Hurle R, Casale P. Clinical and pathological predictors of persistent T1 HG at second resection. Urologia. 2023;90:482-490. [Crossref]
21. Diakos CI, Charles KA, McMillan DC, Clarke SJ. Cancer-related inflammation and treatment effectiveness. Lancet Oncol. 2014;15:e493-e503. [Crossref]
22. Candido J, Hagemann T. Cancer-related inflammation. J Clin Immunol. 2013;33(Suppl 1):S79-S84. [Crossref]
23. Li J, Cao D, Huang Y, Xiong Q, Tan D, Liu L, Lin T, Wei Q. The prognostic and clinicopathological significance of systemic immune-inflammation index in bladder cancer. Front Immunol. 2022;13:865643. [Crossref]
24. Mari A, Muto G, Di Maida F, Tellini R, Bossa R, Bisegna C, Campi R, Cocci A, Viola L, Grosso A, Scelzi S, Lapini A, Carini M, Minervini A. Oncological impact of inflammatory biomarkers in elderly patients treated with radical cystectomy for urothelial bladder cancer. Arab J Urol. 2020;19:2-8. [Crossref]
25. Tang X, Wang S, An C, Du P, Yang Y. Preoperative high neutrophil-to-lymphocyte ratio is associated with high-grade bladder cancer. Anticancer Res. 2017;37:4659-4663. [Crossref]
26. De Larco JE, Wuertz BR, Furcht LT. The potential role of neutrophils in promoting the metastatic phenotype of tumors releasing interleukin-8. Clin Cancer Res. 2004;10:4895-4900. [Crossref]
27. Mandrekar JN. Receiver operating characteristic curve in diagnostic test assessment. J Thorac Oncol. 2010;5:1315-1316. [Crossref]

CASE REPORT
Urooncology

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Renal Paraganglioma: A Rare Case of Secondary Hypertension in a Young Patient

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Abstract

Paragangliomas are catecholamine-secreting neuroendocrine tumors that form outside of the adrenal gland. A 19-year-old woman with a history of hypertension was found to have an incidental mass on the inferior right kidney on imaging after presenting to the emergency department with acute abdominal pain. The mass was removed via right robotic-assisted laparoscopic partial nephrectomy; histopathological findings supported the diagnosis of paraganglioma. The hypertension resolved following removal and genetic syndrome tests were negative. This case emphasizes the importance of a broad differential diagnosis in young patients presenting with hypertension, reviews genetic and histological associations with paragangliomas, and discusses treatment of these catecholamine-secreting tumors.

Keywords: Hypertension, paraganglioma, pathology, urooncology

Introduction

Sympathetic paraganglioma are extra-adrenal neuroendocrine tumors that produce catecholamines and can lead to a myriad of symptoms including hypertension, tachycardia, and sweating (1). Paragangliomas and their intra-adrenal counterpart, pheochromocytomas, are exceptionally rare and have a reported incidence of approximately 2-8 cases per million, with roughly 20% of these cases occurring among the pediatric cohort (2). Paragangliomas/pheochromocytomas can be a sign of genetic syndromes, as up to 40% of individuals presenting with these tumors have germline mutations that leave them susceptible to syndromes such as Von-Hippel Lindau syndrome (*VHL* gene), multiple endocrine neoplasia type 2 (MEN2) (*RET* gene), and succinate dehydrogenase subunits (SDHX)-associated Hereditary Paraganglioma-Pheochromocytoma Syndrome (*SDHB* gene) (3,4). We present a rare case of a 19-year-old female with hypertension and renal paraganglioma.

Case Presentation

A 19-year-old woman with a medical history of hypertension, hypomagnesemia, hypokalemia, and lower extremity edema presented with chronic abdominal pain and an incidental right renal mass. An informed consent patient consent was obtained. Following a cholecystectomy in May 2023, an abdominal ultrasound ordered for acute abdominal pain revealed a faint oval isoechoic right lower pole renal mass measuring 2.8x2.7 - 3 cm with minimal internal color flow. The patient was admitted to the emergency department in July 2023 after developing abdominal pain and vomiting. The patient was found to have elevated troponin I levels and non-specific ST and T wave abnormalities on electrocardiography; the patient was discharged the following day after acute myocardial infarction was ruled out. The patient was subsequently referred to the cardiology department and was found to have mild concentric left ventricular hypertrophy and mild mitral valve regurgitation on echocardiogram. Due to concerns of her hypertension, the patient was to continue following up with cardiology in the outpatient setting.

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The patient was ultimately referred to urology for management of her right renal mass, and a computed tomography (CT) scan performed at that time demonstrated an oval-shaped, ill-defined, hypodense mass measuring 3x2.7 cm in the lower pole of the right kidney (Figures 1a,1b). The patient underwent an uncomplicated right robotic-assisted laparoscopic partial nephrectomy, which revealed a pT1NxMx renal paraganglioma. Immunohistochemical stains of the specimen included tumor cells positive for GATA3, synaptophysin, and CD56 and negative for AE1/3, PAX8, chromogranin, and isthmin-1 (ISM-1) (Figures 2c, 2d and 2e). S100 staining indicated sustentacular cells and a Ki-67 index of 10% in hotspot areas, findings consistent with paraganglioma (Figure 2f). Her severe hypertension normalized postoperatively.

Given the concern for hereditary paraganglioma-pheochromocytoma syndrome, the patient was referred for genetic counseling and testing. The patient tested negative for disease-causing mutations in genes associated with paraganglioma development, including *EGLN1*, *FH*, KIF1B, *MAX*, MEN1, *NF1*, *RET*, *SDHA*, *SDHAF2*, *SDHB*, *SDHC*, *SDHD*, *TMEM127*, and *VHL*.

Discussion

Sympathetic paraganglioma are norepinephrine-secreting neuroendocrine tumors that can be found along the sympathetic chain from the skull base to the pelvic region (5). The incidence of paraganglioma is exceedingly rare, occurring in approximately 2-8 per million individuals; genitourinary paraganglioma are reported to make up roughly 7% of these cases in the United States (2,6). A previous systematic literature review revealed only 13 reported cases of intrarenal paraganglioma, with a mean patient age at presentation of 42.6 years (7). The mean age for diagnosis of paraganglioma and pheochromocytoma is approximately 40 years, which can often make this diagnosis difficult in younger adults, as seen in our case (8). The initial disease presentation of sympathetic paraganglioma often includes hypertension with associated symptoms such as palpitations, sweating, and headache (9). The hypertension is often refractory to medical management and may require multidrug regimens to obtain adequate blood pressure control. Misattribution of classic pheochromocytoma symptoms to anxiety can further exacerbate diagnostic delays (10). This emphasizes the importance of documenting an extensive patient history and maintaining a broad differential diagnosis for causes of both primary and secondary hypertension. Secondary hypertension comprises approximately 5-10% of hypertension cases in adults, with renal parenchymal disease being the most common cause (11,12). In addition to paraganglioma, the differential diagnosis of secondary hypertension in a young adult should include renal artery stenosis caused by fibromuscular dysplasia, primary hyperaldosteronism, and oral contraceptive use (11,13).

Following an extensive review of patient history, the diagnosis of paraganglioma includes biochemical testing, imaging, and genetic testing. Initial biochemical testing of suspected paraganglioma often involves the measurement of urinary and plasma catecholamines, urinary fractionated metanephrines, plasma free metanephrines, and urinary vanillylmandelic acid (14). CT imaging of a paraganglioma typically reveals a mass with an unenhanced density greater than 10 Hounsfield units with a dense capillary network, delayed washout, and possible

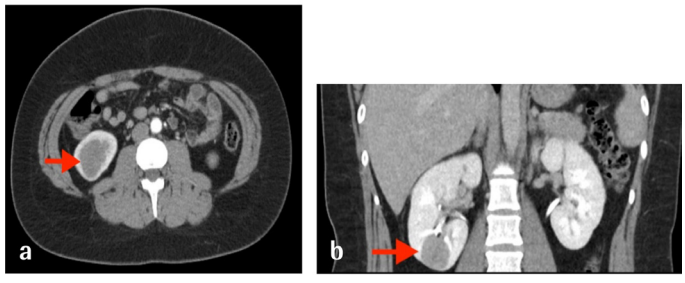

Figure 1. Computed tomography visualization of paraganglioma. Coronal view measuring 2.7 cm (a). Axial view measuring 3.0 cm (b)

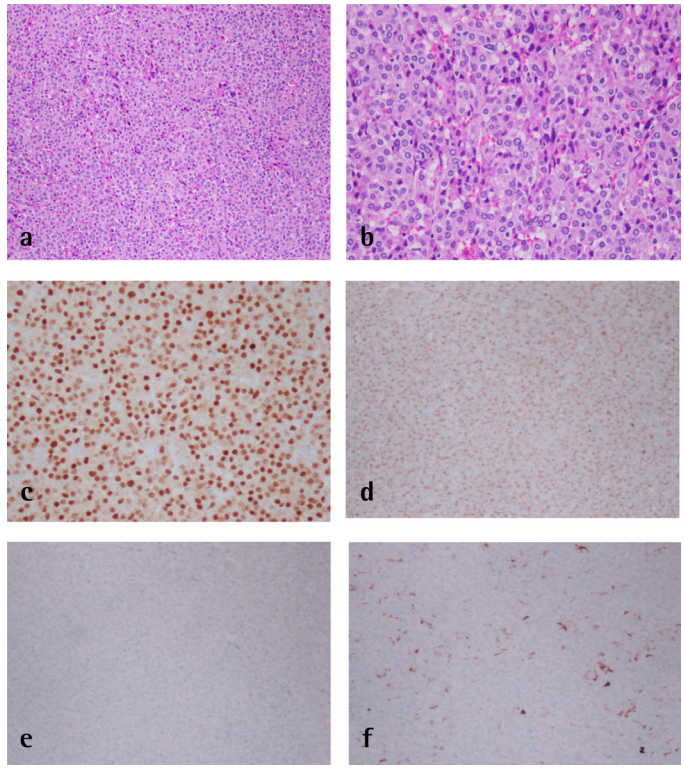

Figure 2. H&E and immunohistological staining of paraganglioma. H&E 100x (a) and H&E 200x (b) illuminate sheets of tumor cells arranged in vague nests or zellballen pattern with fibrovascular stroma. The cells have abundant finely granular cytoplasm and salt and pepper chromatin. IHC stain shop tumor cells positive for GATA3 (c) and a neuroendocrine marker, synaptophysin (d), while negative for pancytokeratin AE1/3 (e). Sustentacular cells are highlighted by S100 (f)

IHC: Immunohistochemistry, H&E: Hematoxylin and eosin

cystic changes; however, there is no method to differentiate between paraganglioma and renal cell carcinoma on imaging (15,16). 40% of paragangliomas and pheochromocytomas are associated with genetic syndromes, including von Hippel Lindau disease, MEN2, and neurofibromatosis type 1, which should prompt screening for germline mutations in *VHL*, *RET*, and *NF1* genes, respectively. Germline mutations in SDHx, Myc-associated *MAX*, hypoxia-inducible factor 2 alpha, and malate dehydrogenase 2 have also been associated with tumor development (17).

Primary management of non-metastatic paraganglioma involves surgical removal of the tumor, with radiotherapy/radiosurgery reserved for patients with surgical contraindications (18). Preoperative alpha-blockade is necessary to prevent perioperative hypertensive episodes caused by systemic tumor catecholamine release. However, as seen in our case, successful paraganglioma resection can be achieved without pre-operative alpha-blockade when the presence of paraganglioma is not suspected or diagnosed pre-operatively (19). Regardless of tumor location and preoperative alpha-blockade, careful intraoperative blood pressure monitoring and management are imperative to reduce the morbidity of surgical resection. This includes administration of an alpha blocker preoperatively and a reduction or cessation of other antihypertensive therapies (20). Medications such as dopamine D2 receptor antagonists, B-adrenergic receptor blockers, and tricyclic antidepressants are contraindicated prior to the administration of alpha blockade in order to prevent hypertensive crises due to unopposed a-adrenoreceptor stimulation during surgery (21).

The "gold standard" of paraganglioma diagnosis is lesional biopsy (5). These tumors can be diagnosed histologically by the presence of cells in well-circumscribed nests, known as the Zelballen pattern, surrounded by a stromal component along with cells in the periphery of the Zellballen, known as "sustentacular" cells (Figures 2a,2b) (22,23). Considering the neuroendocrine origin of these tumors, paragangliomas often stain positively for markers such as neuron specific enolase, S-100 protein, synaptophysin, and CD56 (22). As seen in our case, paragangliomas can also stain positively for GATA3, an essential zinc-finger transcription factor in neuronal embryogenesis (24).

In conclusion, we present a rare case of a 19-year-old female with hypertension and renal paraganglioma. The general rarity and abnormal location of this neuroendocrine tumor emphasizes the importance of creating a broad differential diagnosis for secondary causes of hypertension in young adults. A heightened index of suspicion for paraganglioma should be maintained in young patients presenting with renal mass and moderate to severe or uncontrolled hypertension.

Ethics

Informed Consent: Written consent has been given for patient data.

Footnotes

Authorship Contributions

Surgical and Medical Practices: A.S., N.M., M.Z., A.G.A., J.T., Concept: M.J.F., A.S., N.M., M.Z., J.T., Design: M.J.F., A.S., N.M., M.Z., J.T., Data Collection or Processing: M.J.F., A.G.A., J.T., Analysis or Interpretation: M.J.F., A.G.A., J.T., Literature Search: M.J.F., Writing: M.J.F., A.S., M.Z., A.G.A., J.T.

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References

1. Joynt KE, Moslehi JJ, Baughman KL. Paragangliomas: etiology, presentation, and management. Cardiol Rev. 2009;17:159-164. [Crossref]
2. Aygun N, Uludag M. Pheochromocytoma and paraganglioma: from epidemiology to clinical findings. Sisli Etfal Hastan Tip Bul. 2020;54:159-168. [Crossref]
3. Jochmanova I, Wolf KI, King KS, Nambuba J, Wesley R, Martucci V, Raygada M, Adams KT, Prodanov T, Fojo AT, Lazurova I, Pacak K. SDHB-related pheochromocytoma and paraganglioma penetrance and genotype-phenotype correlations. J Cancer Res Clin Oncol. 2017;143:1421-1435. [Crossref]
4. Turin CG, Crenshaw MM, Fishbein L. Pheochromocytoma and paraganglioma: germline genetics and hereditary syndromes. Endocr Oncol. 2022;2:R65-R77. [Crossref]
5. Ikram A, Rehman A. Paraganglioma. [Updated 2024 Feb 29]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan-. [Crossref]
6. Purnell S, Sidana A, Maruf M, Grant C, Agarwal PK. Genitourinary paraganglioma: demographic, pathologic, and clinical characteristics in the surveillance, epidemiology, and end results database (2000-2012). Urol Oncol. 2017;35:457.e9-457.e14. [Crossref]
7. Bahar B, Pambuccian SE, Gupta GN, Barkan GA. Renal paraganglioma: report of a case managed by robotic assisted laparoscopic partial nephrectomy and review of the literature. Case Rep Urol. 2014;2014:527592. [Crossref]
8. Eisenhofer G, Timmers HJ, Lenders JW, Bornstein SR, Tiebel O, Mannelli M, King KS, Vocke CD, Linehan WM, Bratslavsky G, Pacak K. Age at diagnosis of pheochromocytoma differs according to catecholamine phenotype and tumor location. J Clin Endocrinol Metab. 2011;96:375-384. [Crossref]
9. Mulenga K, Kazuma SME, Nonde J, Mbewe C, Volodymyr P, Musowoya J. Retroperitoneal paraganglioma in a young patient presenting with hypertensive crisis and transient loss of sight; a rare case report and literature review. Int J Surg Case Rep. 2022;101:107781. [Crossref]
10. Neumann HPH, Young WF Jr, Eng C. Pheochromocytoma and paraganglioma. N Engl J Med. 2019;381:552-565. [Crossref]
11. Viera AJ, Neutze DM. Diagnosis of secondary hypertension: an age-based approach. Am Fam Physician. 2010;82:1471-1478. [Crossref]
12. Hegde S, Ahmed I, Aeddula NR. Secondary Hypertension. [Updated 2023 Jul 30]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan-. [Crossref]

13. Noilhan C, Barigou M, Bieler L, Amar J, Chamontin B, Bouhanick B. Causes of secondary hypertension in the young population: a monocentric study. Ann Cardiol Angeiol (Paris). 2016;65:159-164. [Crossref]

14. Shen Y, Cheng L. Biochemical diagnosis of pheochromocytoma and paraganglioma. In: Mariani-Costantini R, editor. Paraganglioma: A Multidisciplinary Approach [Internet]. Brisbane (AU): Codon Publications; 2019 Jul 2. Chapter 2. [Crossref]

15. Baez JC, Jagannathan JP, Krajewski K, O'Regan K, Zukotynski K, Kulke M, Ramaiya NH. Pheochromocytoma and paraganglioma: imaging characteristics. Cancer Imaging. 2012;12:153-162. [Crossref]

16. Manekar AA, Sahoo SK, Tripathy BB, Nayak P, Sable MN, Mohanty MK. A rare case of intra-renal paraganglioma in a child masquerading as renal cell carcinoma. Indian Pediatrics Case Reports. 2023;3:31-34. [Crossref]

17. Pereira BD, Luiz HV, Ferreira AG, Portugal J. Genetics of pheochromocytoma and paraganglioma. In: Mariani-Costantini R, editor. Paraganglioma: A Multidisciplinary Approach [Internet]. Brisbane (AU): Codon Publications; 2019 Jul 2. Chapter 1. [Crossref]

18. Nölting S, Ullrich M, Pietzsch J, Ziegler CG, Eisenhofer G, Grossman A, Pacak K. Current management of pheochromocytoma/paraganglioma: a guide for the practicing clinician in the era of precision medicine. Cancers (Basel). 2019;11:1505. [Crossref]

19. Isaacs M, Lee P. Preoperative alpha-blockade in phaeochromocytoma and paraganglioma: is it always necessary? Clin Endocrinol (Oxf). 2017;86:309-314. [Crossref]

20. Li N, Kong H, Li SL, Zhu SN, Zhang Z, Wang DX. Intraoperative hypotension is associated with increased postoperative complications in patients undergoing surgery for pheochromocytoma-paraganglioma: a retrospective cohort study. BMC Anesthesiol. 2020;20:147. [Crossref]

21. Karel P. Preoperative management of the pheochromocytoma patient. J Clin Endocrinol Metab. 2007;92:4069-4079. [Crossref]

22. Feng N, Zhang WY, Wu XT. Clinicopathological analysis of paraganglioma with literature review. World J Gastroenterol. 2009;15:3003-3008. [Crossref]

23. Wieneke JA, Smith A. Paraganglioma: carotid body tumor. Head Neck Pathol. 2009;3:303-306. [Crossref]

24. Mamilla D, Manukyan I, Fetsch PA, Pacak K, Miettinen M. Immunohistochemical distinction of paragangliomas from epithelial neuroendocrine tumors-gangliocytic duodenal and cauda equina paragangliomas align with epithelial neuroendocrine tumors. Hum Pathol. 2020;103:72-82. [Crossref]

CASE REPORT
Urooncology

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Primary Bladder Amyloidosis Mimicking Bladder Cancer: A Rare Case Report

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Abstract

Bladder amyloidosis is a rare condition that can mimic malignancy clinically and radiologically. A 44-year-old female patient was admitted to our clinic with macroscopic hematuria and dysuria. A 2-cm nodular lesion was detected next to the left ureteral orifice in the bladder on abdominal ultrasound. The lesions were excised via transurethral resection. Pathological examination revealed amyloidosis. After internal medicine evaluation, the patient was diagnosed with primary bladder amyloidosis, and it was decided to follow-up the patient with cystoscopy.

Keywords: Amyloidosis, bladder amyloidosis, bladder cancer, endoscopy, pathology

Introduction

Amyloidosis is a disease caused by the accumulation of amorphous proteins in many organs and tissues in the extracellular space. It is divided into two groups; primary and secondary amyloidosis. Primary amyloidosis is a systemic disease that can affect multiple organs and is caused by plasma cell dyscrasia (1). Although bladder amyloidosis is very rare, it can mimic bladder malignancy clinically and radiologically (2). Clinically, it can present with symptoms such as gross painless hematuria, microscopic hematuria, dysuria, and irritative voiding symptoms. A definitive diagnosis is made by histopathological examination of tissues that show Congo red staining and apple green fluorescence. We present a case of bladder amyloidosis, which is rarely reported in the literature.

Case Presentation

A 44-year-old female patient was admitted to our clinic with macroscopic hematuria and dysuria. The urine culture was sterile, and red blood cell 17/(HPF), leukocyte esterase (-), and protein (-) in urine test. The hemogram, kidney, and liver function tests were all within normal limits. A 2-cm nodular lesion was detected next to the left ureteral orifice in the bladder on abdominal ultrasound. Computed tomography (CT) urography revealed two nodular lesions measuring 9 and 4 mm next to the left ureteral orifice (Figure 1). A diagnostic cystoscopy was performed; two nodular bullous lesions measuring 15 mm and 5 mm next to the left ureteral orifice were removed via transurethral resection (TUR). Pathological examination revealed amyloidosis (Figure 2). The patient was consulted by the internal medicine and nephrology departments, and systemic amyloidosis was not considered. The patient was diagnosed with primary bladder amyloidosis, and it was decided to follow-up the patient with cystoscopy. Recurrence was detected during the first year of cystoscopy, and the pathological result revealed the presence of amyloidosis. The patient is currently followed up with annual cystoscopy. An informed consent patient consent was obtained.

Discussion

Amyloidosis is a rare disease caused by the accumulation of amorphous proteins in the extracellular space. It is classified as localized amyloidosis when it occurs in a single organ and as systemic amyloidosis when it occurs in multiple organs. Primary amyloidosis is caused by immune cell disorders, such as multiple myeloma and other immune cell anomalies (1). Secondary amyloidosis is a reactive condition caused by diseases leading to chronic inflammation and tissue destruction (3). While amyloidosis can accumulate anywhere in the urinary system, the bladder and kidney are the most commonly affected organs (4).

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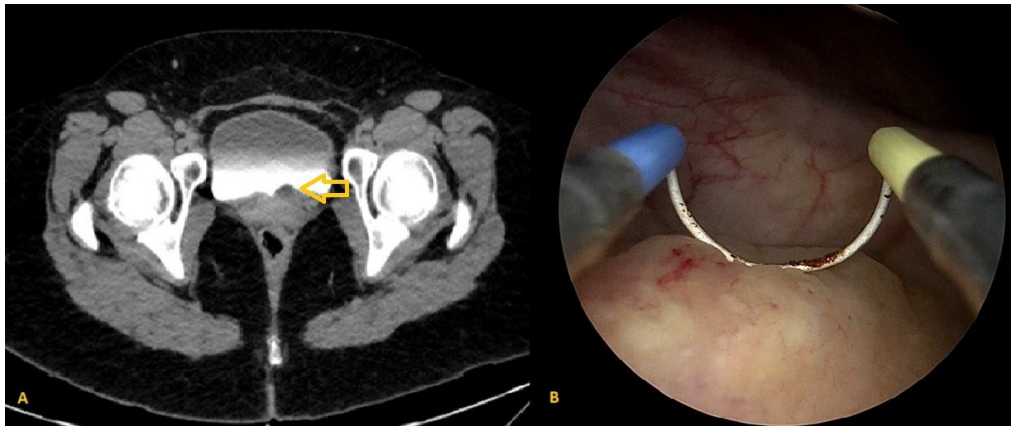

Figure 1. A nodular lesion in the lateral side of the left ureter orifice of the bladder (A. CT transverse section, B. Endoscopic images of nodular lesions in the bladder)

CT: Computed tomography

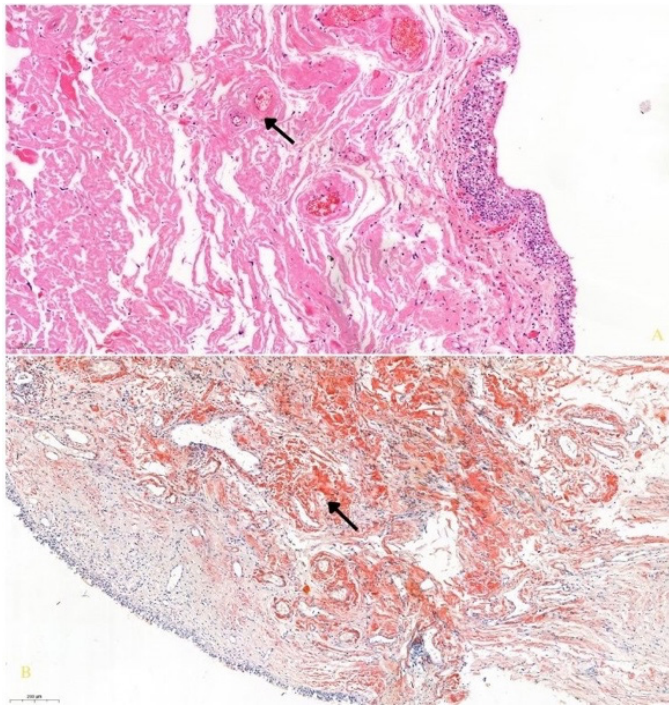

Figure 2. The histopathological staining of patient. A. Extracellular eosinophilic, amorphous, and homogeneous amyloid deposits with hematoxylin-eosin, B. Amyloid in Congo red appears orange-red when viewed under a transmitted-light microscope

Patients with bladder amyloidosis often present with common complaints, such as macroscopic painless hematuria (>80% of the patients), irritative urinary symptoms, and symptoms similar to cystitis (5). Ultrasonography and CT urography may detect mass lesions, filling defects, and wall thickening, which may mimic bladder malignancy (2,6). The lesion may appear polypoid or nodular during cystoscopy. Due to the similarity of symptoms and imaging findings to bladder malignancy, cystoscopy should be performed, and histopathological differential diagnosis should be made using TUR or biopsy (2). The diagnosis of amyloidosis is made by Congo red immunostaining, which gives an apple green reflection under polarized light (3). AL amyloidosis is the most common type encountered in bladder amyloidosis, but AA, ATTR and other types of amyloidosis can also be observed. Patients should also be evaluated for systemic amyloidosis. TUR is the first diagnostic and treatment method for primary bladder amyloidosis (7). In untreated cases, lesion's dimensional progression and obstructive uropathy can be detected during follow-up. Postoperative adjuvant treatment with colchicine and intravesical dimethylsulfoxide (DMSO) has been tried in many cases to prevent recurrence. Patients with diffuse multifocal bladder amyloidosis who could not be completely resected through TUR. The addition of colchicine may improve outcomes by mitigating local inflammation and leading to regression of the lesions. Moreover, intravesical treatment with DMSO every week or every 2 weeks for 3-6 months may dissolve insoluble amyloid fibrils and lead to symptom remission (8).

Patients with diffuse multifocal bladder amyloidosis who experience clinically insignificant improvement in symptoms may benefit from these treatments. Partial or total cystectomy may be required in some cases of bladder amyloidosis (9). For patients who are refractory to all treatments, cystectomy may be an option. Due to the high recurrence rate and diffuse involvement, periodic cystoscopy follow-up is required. Cystoscopy is recommended at 3 months after the first TUR and annually thereafter for the first and second years. In addition, cystoscopic evaluation should be performed if there is hematuria, irritative lower urinary symptoms, or symptoms similar to cystitis, which may indicate recurrence. There are cases of *de novo* urothelial carcinoma with localized amyloidosis (8). However, the optimal treatment and follow-up strategies for primary bladder amyloidosis are not clear in the literature (8). Progression of systemic amyloidosis in patients diagnosed with localized amyloidosis was 1% in all cases. Although rare, this condition must also be followed up from this perspective (8).

Conclusion

Primary bladder amyloidosis is a rare disease that clinically and radiologically mimics bladder malignancy. A definitive diagnosis should be made through histopathological examination. Patients should be referred for further evaluation of the possibility of systemic amyloidosis. Although it is a benign lesion, there is a risk of obstruction, recurrence, and *de novo* urothelial carcinoma. Therefore, follow-up should include interval cystoscopy and, if necessary, TUR.

Ethics

Informed Consent: Patient consent was obtained.

Footnotes

Authorship Contributions

Surgical and Medical Practices: C.S., V.Ş., E.B.T., O.B., Concept: C.S., V.Ş., E.B.T., O.B., Design: C.S., V.Ş., E.B.T., O.B., Data Collection or Processing: C.S., V.Ş., E.B.T., O.B., Analysis or Interpretation: C.S., V.Ş., E.B.T., O.B., Literature Search C.S., V.Ş., E.B.T., O.B., Writing: C.S., V.Ş., E.B.T., O.B.

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References

1. Gertz MA, Dispenzieri A. Systemic amyloidosis recognition, prognosis, and therapy: a systematic review. JAMA. 2020;324:79-89. [Crossref]
2. Patel P, Pourmandi M, Lombard JS. Primary amyloidosis of the bladder mimicking probable malignancy: a case report. Urol Case Rep. 2019;26:100944. [Crossref]
3. Mayor N, Coppola ASJ, Knights H, Nazar T, Hunter H, Mostafid H. Localised amyloidosis of the bladder: a rare mimic of urinary tract malignancy (case report and literature review). Int J Surg Case Rep. 2020;77:708-710. [Crossref]
4. Al-Obaidy KI, Grignon DJ. Primary amyloidosis of the genitourinary tract. Arch Pathol Lab Med. 2021;145:699-703. [Crossref]
5. Yu ZY, Yan L, Wang HK, Hang G, Wang YY, Wen Q, Chen B. Bladder triangle amyloidosis: a case report and literature review. Medicine (Baltimore). 2022;101:e32179. [Crossref]
6. Chuang E, Hori AM, Hesketh CD, Shorter J. Amyloid assembly and disassembly. J Cell Sci. 2018;131:jcs189928. [Crossref]
7. Monge M, Chauveau D, Cordonnier C, Noël LH, Presne C, Makdassi R, Jauréguy M, Lecaque C, Renou M, Grünfeld JP, Choukroun G. Localized amyloidosis of the genitourinary tract: report of 5 new cases and review of the literature. Medicine (Baltimore). 2011;90:212-222. [Crossref]
8. Pyrgidis N, Mykoniatis I, Pegios VF, Sokolakis I, Hatzichristodoulou G, Bourdoumis A, Vakalopoulos I, Sountoulides P. Amyloidosis of the urinary bladder: a systematic review and a proposed management algorithm. Urology. 2021;156:e12-e19. [Crossref]
9. Chan ES, Ng CF, Chui KL, Hou SM, Yip SK. Primary bladder amyloidosis--case report of a patient with delayed upper urinary tract obstruction 3 years after the diagnosis. Amyloid. 2010;17:36-38. [Crossref]

VIDEO ARTICLE
General Urology

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J Urol Surg 2025;12(3):196-199

The T-incision: A Practical Approach to Initiating Apical Dissection in Prostate Enucleation

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Abstract

Holmium:YAG laser enucleation of prostate (HoLEP) and thulium fiber laser enucleation of prostate (ThuFLEP) are advanced surgical techniques for treating benign prostatic obstruction, both being forms of Anatomical Endoscopic Enucleation of Prostate. These procedures have evolved to provide enhanced efficacy, reduced operation times, and improved continence outcomes. One key factor for preserving continence is early apical release (EAR), a delicate technique that involves releasing the apical mucosa to prevent damage to the external urethral sphincter. This video-article explores a practical and safe technique involving a T-incision-combining anterior commissurotomy and anterior plane dissection-performed at the beginning of the enucleation process. Two cases, one using ThuFLEP and the other HoLEP, were edited to emphasize the T-incision's role in facilitating EAR. Results demonstrated that both techniques utilized the T-incision to ease the dissection of the external sphincter complex, improving enucleation and connecting the lateral to anterior planes. The study found differences between the two lasers, with ThuFLEP offering better coagulation and precision, and HoLEP excelling in dissection and tissue preservation. Both patients had short hospital stays, rapid catheter removal, and full continence by postoperative day 10. The T-incision, especially during the learning phase of the procedure, aids in smoother dissection, facilitates easier alignment of enucleation planes, and may accelerate a surgeon's learning curve. This video-article highlights the replicability and benefits of the T-incision in both HoLEP and ThuFLEP surgeries.

Keywords: HoLEP, ThuFLEP, early apical release, T-incision, enucleation, benign prostatic obstruction, external urethral sphincter, learning curve

Introduction

Holmium:YAG (Ho:YAG) laser enucleation of prostate (HoLEP) and thulium fiber laser enucleation of prostate (ThuFLEP), which are subtypes of anatomical endoscopic enucleation of prostate (AEEP), are the most versatile and efficient surgical techniques for the treatment of benign prostatic obstruction (BPO) due to the latest developments in surgical and laser technologies. The surgical technique has evolved throughout the years to provide the best outcomes possible in terms of efficacy, operation duration, and continence. There are different approaches to enucleation of the adenomas, such as en-bloc, two-lobe, or three-lobe techniques. Although the choice mainly depends on the surgeon's preference, there are studies showing advantages of the en-bloc technique over the others (1,2).

The most important step for the preservation and early recovery of continence is the apical dissection during AEEP. Early apical release (EAR) at the beginning of the enucleation process has been shown to reduce incontinence rates to a great extent (3). Regardless of the enucleation technique, EAR should be carried out to preserve the external urethral sphincter.

EAR is a technique that is delicate and hard to master. With this video-article, we aim to describe a technique that is both practical and safe which combines anterior commissurotomy and anterior plane dissection using a T-incision.

Materials and Methods

For this video article, two prostate enucleation videos are edited and combined. In both surgeries, EAR is performed to preserve

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the external sphincteric complex and thus maintain continence. In the first video, a ThuFLEP surgery is depicted where the T-incision is performed before marking and detachment of the apical mucosa. In the second video, the T-incision is performed after marking of the apical border of the enucleation and detachment of the apical mucosa (Figure 1). The videos are edited for content and speed to better emphasize the T-incision effect on the EAR process.

Although the videos are anonymously edited and prepared, informed consent is taken from the patients for the use of video recordings for scientific purposes and for publishing in scientific journals.

Results

Both patients underwent en-bloc enucleation of prostatic adenomas. In both patients, the EAR technique was used, with a T-incision performed at the beginning. The effect of different lasers on dissection, cutting, and coagulation of the tissues showed marked differences, which is an expected outcome due to the different wavelengths of the lasers used. The Thulium fiber laser showed better coagulation and more precise cutting, while Ho:YAG showed better dissecting properties of the enucleation plane and lower charring of the prostatic tissues. In both patients, the T-incision was useful to lower the apical part of the prostate, and to make it easier to connect the lateral planes to the anterior plane.

The prostate volume was 60 g for ThuFLEP and 90 g for the HoLEP surgery. The overall time spent on the total dissection of the external sphincteric complex was comparable between the two different surgeries, being 12 min for ThuFLEP and 10 min for HoLEP, with the total enucleation duration being 40 min for ThuFLEP and 45 min for HoLEP. In both patients, the catheter was removed on postoperative day 2, and the patients were discharged without any complications. Both patients were continent on postoperative day 10.

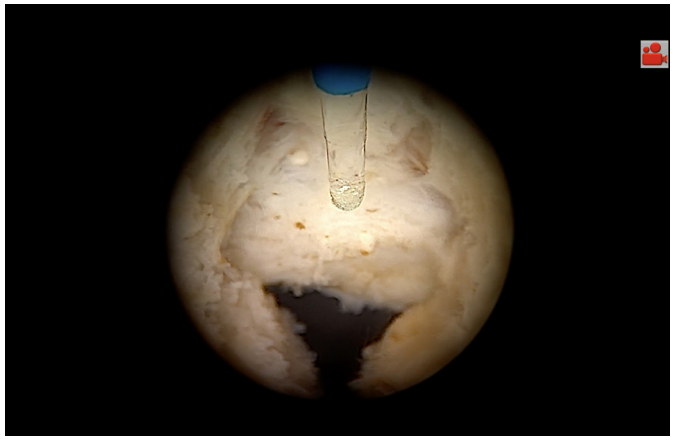

Figure 1. The T-incision

In these videos, the HoLEP procedures begin with apical mucosal incisions, which circumferentially separate the apical prostatic mucosa from the sphincteric mucosa. Subsequently, a T-incision is performed by making a full-thickness incision at the 12 o'clock position, starting from the bladder neck and extending to the apex. The anterior plane is then expanded horizontally with lateral incisions from the midline toward the lateral walls. This maneuver creates an empty space shaped like a "T," where the horizontal space is formed by the lateral incisions and the vertical space is defined by the urethra. After completing the T-incision, the dissection of the posterior and lateral planes is undertaken. The posterior plane is accessed through laser incisions made on both sides of the verumontanum. The verumontanum is carefully dissected away from the adenoma with a proximal incision. The posterior plane is then developed, and the incision is extended laterally toward the 1 o'clock and 11 o'clock positions. Since the anterior plane has already been created with the T-incision, the apical part of the prostate drops downward, facilitating the connection between the anterior plane and the lateral incisions. The apical release is finalized by incising the remaining connections using an approach from the anterior plane toward the lateral wall. The residual connections between the prostate and the capsule are gradually incised until the bladder neck fibers are encountered. The final attachments are severed, and the prostate is removed and extracted from the body. Following thorough coagulation to ensure a clean field for morcellation, it is performed until all tissues are removed. A final inspection is conducted to confirm effective hemostasis, intact ureteral orifices, an undamaged sphincteric complex, and the integrity of the capsule (Video 1).

Discussion

Among the surgical approaches for BPO, AEEP is becoming the new gold standard surgical approach because the removal of the entire benign prostatic hyperplasia component of the prostate is performed. For men with either lower urinary tract symptoms or urinary retention, regardless of prostate volume, detrusor contractility, and age, AEEP can provide safe and effective treatment for a wider range of patients than any other BPO procedure (4). Tan et al. (5) published in 2003 that HoLEP is superior to transurethral prostate resection (TURP) in terms of removed prostate tissue, and provides faster catheter removal times and shorter hospital stays. With all the new advances in the field, technology, and techniques, the enucleation techniques have consolidated their position. In recent publications, AEEP was demonstrated to provide more tissue retrieval, showed stronger symptom improvement, compared to TURP with similar and low complication rates for both techniques (6,7).

There are different surgical techniques for performing AEEP: en-bloc, two-lobe, and three-lobe techniques. The enucleation techniques, especially HoLEP, were initially developed as a three-lobe technique. Over time, advancements and modifications led to the introduction of two-lobe and en-bloc techniques. The comparison of these 3 techniques was published by Rücker et al. (1) in their prospective study comprising 600 patients; and the data revealed that all three enucleation techniques showed similar postoperative outcomes; however, en-bloc and two-lobe techniques provided significantly shorter operative times and higher efficiency compared to the three-lobe technique. Enikeev et al. (8) also compared the en-bloc and two-lobe techniques during both HoLEP and ThuFLEP. The authors reported that the techniques with both lasers provided comparable outcomes and complication rates. Practically, the choice of enucleation technique depends on the surgeon's preference and experience.

Surgical experience is one of the keys to a successful enucleation. For this reason, the surgeons should go through a steep learning curve to reach proficiency. The learning curve for HoLEP is notably steep, requiring substantial training and experience. During the initial phase, surgeons may encounter challenges such as prolonged operative times, increased rates of intraoperative complications, and difficulties with tissue morcellation and enucleation techniques. However, as experience grows, surgeons become more familiar with navigating anatomical planes and performing the procedure, eventually resulting in better outcomes, reduced operative times and fewer complications (9,10). Studies indicate that approximately 50 cases are needed to overcome the learning curve, though this can vary depending on prior endourological experience and access to mentorship or proctorship (9,11).

During the learning phase, one of the most important steps to achieve proficiency is the EAR. This step is crucial, especially in the beginning of the surgery, as it spares the continence mechanism and prevents any mechanical, thermal or incisional damage to the external urethral sphincteric complex. EAR facilitates better identification of the surgical plane while preserving the external sphincter's mucosa, resulting in low rates of post-operative stress incontinence . In a recent study by Ericson et al. (12) in 2023, results about EAR and the en-bloc no-touch technique reported that EAR, especially in the learning curve, resulted in longer operation durations. Heidenberg et al. (13) published a comparison of the EAR and non-EAR HoLEP results on postoperative incontinence and quality of life in 2024. In this retrospective analysis of a total of 114 patients, the authors commented that the EAR technique provided an earlier return of continence and improved quality of life.

Although it is crucial, the EAR is important and hard to master. A T-incision made at the start of the EAR in HoLEP or ThuFLEP helps facilitate the lowering of prostatic adenomas and may aid in connecting the lateral and anterior planes, ensuring smoother alignment of these enucleation planes. This maneuver can also help surgeons better understand and identify the trajectory and the concept of the enucleation process, especially when they are enucleation process, especially when they are at their learning curve. With this video-article, we provide a depiction of the T-incision during AEEP and the replicability of this maneuver with both Ho:YAG laser and thulium fiber laser.

Conclusion

The T-incision, which consists of combining the anterior commissurotomy and anterior plane dissection, helps lower the anterior aspect of the external sphincter towards the verumontanum and facilitates the connection of posterior and lateral planes to the anterior plane, thereby providing a fast and safe dissection of the sphincteric complex. T-incision during HoLEP makes it easier to perform the EAR and may also have positive effects on the learning curve.

The T-incision helps lower the apical part of the prostate, facilitating the connection of the lateral planes to the anterior plane. This ensures easier alignment and integration of the separately created enucleation planes. So, as the anatomical planes align correctly, the process of enucleation proceeds effectively.

Video 1.

Ethics

Informed Consent: Although the videos are anonymously edited and prepared, informed consent is taken from the patients for the use of video recordings for scientific purposes and for publishing in scientific journals.

Footnotes

Authorship Contributions

Surgical and Medical Practices: T.E.Ş., L.D., Concept: T.E.Ş., L.D., Design: T.E.Ş., L.D., Data Collection or Processing: T.E.Ş., L.D., Analysis or Interpretation: T.E.Ş., L.D., Literature Search: T.E.Ş., L.D., Writing: T.E.Ş., L.D.

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References

1. Rücker F, Lehrich K, Böhme A, Zacharias M, Ahyai SA, Hansen J. A call for HoLEP: en-bloc vs. two-lobe vs. three-lobe. World J Urol. 2021;39:2337-2345. [Crossref]
2. Tamalunas A, Schott M, Keller P, Atzler M, Ebner B, Hennenberg M, Stief CG, Magistro G. Efficacy, efficiency, and safety of en-bloc vs three-lobe enucleation of the prostate: a propensity score-matched analysis. Urology. 2023;175:48-55. [Crossref]
3. Saitta G, Becerra JEA, Del Álamo JF, González LL, Elbers JR, Suardi N, Gómez-Sancha F. 'En bloc' HoLEP with early apical release in men with benign prostatic hyperplasia. World J Urol. 2019;37:2451-2458. [Crossref]
4. Aho T, Armitage J, Kastner C. Anatomical endoscopic enucleation of the prostate: the next gold standard? Yes! Andrologia. 2020;52:e13643. [Crossref]
5. Tan AH, Gilling PJ, Kennett KM, Frampton C, Westenberg AM, Fraundorfer MR. A randomized trial comparing holmium laser enucleation of the prostate with transurethral resection of the prostate for the treatment of bladder outlet obstruction secondary to benign prostatic hyperplasia in large glands (40 to 200 grams). J Urol. 2003;170:1270-1274. [Crossref]
6. Westhofen T, Schott M, Keller P, Tamalunas A, Stief CG, Magistro G. Superiority of holmium laser enucleation of the prostate over transurethral resection of the prostate in a matched-pair analysis of bleeding complications under various antithrombotic regimens. J Endourol. 2021;35:328-334. [Crossref]
7. Magistro G, Schott M, Keller P, Tamalunas A, Atzler M, Stief CG, Westhofen T. Enucleation vs. resection: a matched-pair analysis of TURP, HoLEP and bipolar TUEP in medium-sized prostates. Urology. 2021;154:221-226. [Crossref]
8. Enikeev D, Taratkin M, Laukhtina E, Alekseeva T, Snurnitsyna O, Potoldykova N, Gerasimov A, Glybochko P. En bloc and two-lobe techniques for laser endoscopic enucleation of the prostate: retrospective comparative analysis of peri- and postoperative outcomes. Int Urol Nephrol. 2019;51:1969-1974. [Crossref]
9. Ditonno F, Bianchi A, Fumanelli F, Brancelli C, Malandra S, Rizzetto R, Balzarro M, Rubilotta E, Autorino R, Bertolo R, Veccia A, Antonelli A. The learning curve for holmium laser enucleation of the prostate: a single-center analysis of surgical and functional outcomes. J Endourol. 2024;38:1226-1233. [Crossref]
10. Martinez-Salas AJ, Garcia-Rivera OU, Reyna-Blanco I, Jimenez-Garcia AD, Rosas-Hernandez H. Adequate mentorship program for holmium laser enucleation of the prostate (HoLEP) leads to satisfactory short-term outcomes in the early learning curve of young urologists: first-year outcomes of a newly established mentorship training in Mexico. Cureus. 2023;15:e41756. [Crossref]
11. Chavali JSS, Rivera ME, Lingeman JE. HoLEP learning curve-resident perspective: survey of senior residents from high-volume tertiary center. J Endourol. 2024;38:977-981. [Crossref]
12. Ericson CA, Baird BA, Mauler DJ, Lyon TD, Ball CT, Dora CD. Early apical release versus en-bloc no touch technique for holmium laser enucleation of the prostate: a high-volume single-surgeon cohort study. World J Urol. 2023;41:167-172. [Crossref]
13. Heidenberg DJ, Choudry MM, Wymer K, Stagg J, Parker N, Campagna J, Narang G, Humphreys MR, Cheney SM. The impact of standard vs early apical release holmium laser enucleation of the prostate technique on postoperative incontinence and quality of life. Urology. 2024;189:101-107. [Crossref]

VIDEO ARTICLE
Functional Urology

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Staged Urethroplasty in a Patient with Urethral Stricture Following Female to Male Transgender Surgery

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Abstract

Complications of urethral reconstruction are common in patients who have undergone female to male transgender surgery. Patients may develop urethral strictures and fistulas, which lead to repeated surgery. Our aim was to present a case of staged buccal mucosal graft urethroplasty in a patient who developed urethral stricture after gender-affirming surgery from female to male.

Keywords: Functional urology, general urology, reconstructive urology

Introduction

Urethral reconstruction complications are common in female to male transgender surgery. In the long term, patients may develop urethral strictures and fistulas, which may lead to repeated surgeries (1). Endoscopic techniques can be used in patients with short segment stenosis. Skin flaps, free mucosal grafts, and skin autografts are used to treat complications in urethral defects and long urethral strictures (2). We aimed to present staged buccal mucosal graft (BMG) urethroplasty in a patient who developed urethral stricture after female-to-male transgender surgery.

Case Presentation

A 26-year-old patient with no known comorbidities underwent female-to-male transgender surgery (mastectomy + urethra prefabrication), by the plastic surgery and reconstruction team. Radial forearm free flap was used for phalloplasty and neourethral reconstruction. After the 12th postoperative month, the patient had a history of multiple surgeries due to separation between the neourethra and the native urethra, and development of a fistula from the neourethra to the skin. The patient underwent percutaneous suprapubic cystostomy catheter placement for preoperative urethral preparation. After that, staged urethroplasty was planned. During the 1st stage of urethroplasty and perioperative examination of the patient in high lithotomy position it was observed that the external meatus was 1 cm ventral to the tip of the penis and stenotic in the constructed penile tissue. The urethra was completely contracted up to the level of the anastomosis site with the native urethra. The native urethra was exposed and patency was confirmed with a Foley catheter. Scar tissue on the urethral bed in the neophallus was cleaned and prepared for placement of the BMG. The length of the prepared urethral bed was measured to be 12 cm, and grafts were taken from bilateral buccal mucosa, each measuring 12 cm in length and 2 cm in width. The buccal mucosa grafts were sutured continuously to the healthy ventral bed with 4/0 monofilament absorbable suture after defatting and fenestration. The procedure was completed after the application of a sterile pressure dressing. The patient was discharged on postoperative day 4 without any complications. The patient's catheter was removed on postoperative week 4, and a second stage was scheduled for 6 months later.

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During the second stage of urethroplasty, in the high lithotomy position, an incision was made with a lateral margin of approximately 1 cm for tubularization of the urethral bed created with the BMG in the neophallus. A 12-Fr Foley catheter was passed through the proximal native urethra into the bladder. The neourethra was tubularized over the catheter with 4/0 monofilament absorbable suture. After tubularization of the urethra, reconstruction of the vaginal cuff was performed. Subcutaneous and skin tissues were sutured in line with anatomical layers, and the procedure was completed after sterile pressure dressing. The patient was discharged on postoperative day 4 without any complications. The patient's catheter was removed in the 4th postoperative week, and no complications occurred in the follow-up. The uroflowmetry performed at the 6th post-operative month, showed a maximum flow rate of 16 mL/sec (Video 1).

Discussion

Urethral fistula and urethral stricture are still the most common complications of phalloplasty and often require revision surgery. Urethral strictures may present either as short strictures at the anastomosis between the native and neourethra or as long urethral defects along the entire urethra. Fistula and stricture rates in the postoperative period vary by technique, from 5 to 60.3% and 2 to 56%, respectively (1). Short segment strictures can be treated with endoscopic methods or single-stage urethroplasty, while two-stage urethroplasty is preferred, especially for long segment complicated strictures (2,3). With the use of oral mucosal grafts, success rates have reached 80% (4). Current series report excellent efficacy of multi-stage repair of complex anterior urethral strictures with acceptable long-term recurrence rates in the range of 0-18% (5).

Conclusion

In conclusion, staged BMG urethroplasty is a successful treatment option for the management of complex urethral strictures. We believe that performing the procedure in a multidisciplinary team in experienced centers will increase success rates and decrease complication rates.

Video 1.

Ethics

Informed Consent: Written informed consent was obtained from the patient.

Footnotes

Authorship Contributions

Surgical and Medical Practices: O.B., C.S., K.D., A.E.S., S.E.A., C.D., V.Ş., A.A.E., Concept: O.B., C.S., Design: O.B., C.S., Data Collection or Processing: C.S., Analysis or Interpretation: O.B., C.S., Literature Search: C.S., M.S.Ö., A.G., V.Ş., Writing: O.B., C.S., A.E.S.

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References

1. Nassiri N, Maas M, Basin M, Cacciamani GE, Doumanian LR. Urethral complications after gender reassignment surgery: a systematic review. Int J Impot Res. 2020;33:793-800. [Crossref]
2. Waterschoot M, Claeys W, Hoebeke P, Verla W, Waterloos M, Wirtz M, Buncamper M, Lumen N. Treatment of urethral strictures in transmasculine patients. J Clin Med. 2021;10:3912. [Crossref]
3. Abdel-Rassoul M, El Shorbagy G, Kotb S, Alagha A, Zamel S, Rammah AM. Management of urethral complications after total phallic reconstruction: a single center experience. Cent European J Urol. 2024;77:310-319. [Crossref]
4. Barbagli G, De Angelis M, Palminteri E, Lazzeri M. Failed hypospadias repair presenting in adults. Eur Urol. 2006;49:887-894. [Crossref]
5. Mori RL, Angermeier KW. Staged urethroplasty in the management of complex anterior urethral stricture disease. Transl Androl Urol. 2015;4:29-34. [Crossref]