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REVIEW

Management of penile urethral strictures: Challenges and future directions

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Abstract

The anatomy of the penile urethra presents additional challenges when compared to other urethral segments during open stricture surgery particularly because of its unsuitability for excision and primary anastomosis and its relatively deficient corpus spongiosum. Stricture aetiology, location, length and previous surgical intervention remain the primary factors influencing the choice of penile urethroplasty technique. We have identified what we feel are the most important challenges and controversies in penile urethral stricture reconstruction, namely the use of flaps *vs* grafts, use of skin or oral mucosal tissue for augmentation/substitution and when a single or a staged approach is indicated to give the best possible outcome. The management of more complex cases such as pan-urethral lichen-sclerosus strictures and hypospadias "cripples" is outlined and potential developments for the future are presented.

Key words: Reconstructive surgical procedures; Anterior urethral stricture; Oral mucosa; Tissue transplants; Skin grafting; Hypospadias; Lichen sclerosus

Core tip: The anatomy of the penile urethra presents additional challenges when compared to other urethral segments. Stricture aetiology, location, length and previous surgical intervention remain the primary factors influencing the choice of penile urethroplasty technique. We described the most important challenges and controversies in penile urethral stricture reconstruction: Use of flaps *vs* grafts, use of skin or oral mucosal tissue for augmentation/substitution and when a single or a staged approach is indicated to give the best possible outcome. The management of more complex cases (pan-urethral lichen-sclerosus strictures and hypospadias "cripples") is outlined and potential developments for the

future are presented.

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INTRODUCTION

The treatment of penile urethral strictures is generally more complex when compared with other segments of the urethra by virtue of various anatomical considerations. This is evidenced by the variety of techniques with have been described for reconstruction in this area[1]. Achieving a satisfactory and durable functional outcome (*i.e.,* unobstructed voiding) is the main goal but the cosmetic appearance of the male genitalia also deserves due consideration[2]. Penile shape and length should be preserved and ultimately restored if damaged by injury or scarring from previous surgery[3].

A further concern with penile urethroplasty is erectile function, and in particular, penile shortening and curvature. The risk of transient erectile dysfunction after urethroplasty is clearly described[4]. Loss of penile length and penile curvature are more common after penile urethral surgery[5], particularly when local flaps are used[6].

Mucosal and skin grafts, or local skin flaps, may be considered for penile urethral reconstruction. Consequently the reconstructive surgeon should be skilled at a broad range of techniques and be able to carefully evaluate the benefits and adverse effects of each in individual circumstances[1].

There is a paucity of sound scientific evidence in this field of urology, most of the available literature being based on descriptive case series (not always with homogeneous cohorts of patients) and expert opinions[1,7]. In this paper, we address current practice and the challenges and controversies faced by the reconstructive surgeon in the management of penile urethral strictures. Future developments in this field are also explored.

ANATOMICAL CONSIDERATIONS

The penile (or pendulous) urethra is the distal part of the male anterior urethra. It is about 15 cm in length and extends from the external meatus, the narrowest part of the urethra (21-27 F), to the penoscrotal junction where the bulbar segment starts. The penile urethra presents important anatomical differences compared with the bulbar segment[8]. It is surrounded by the thinnest part of the corpus spongiosum in the penile shaft, meaning that it does not provide the best vascular support for a graft. The glans penis, which is the expanded distal end of the corpus spongiosum, surrounds the navicular fossa and external meatus[9]. On the contrary, this rich glanular blood supply provides an ideal vascular bed for successful graft take.

The urethra and the spongiosum are covered by the anterior extension of Bucki's fascia, and a layer of dartos areolar tissue (continuation of Colles fascia) that provides blood supply to the penile shaft skin[10]. This dartos tissue is also very well vascularised, making it an ideal graft bed or a pedicle for skin grafts.

Unlike the bulbar urethra, which can be mobilised proximally and distally to allow excision of a stricture and a tension-free primary anastomosis, this is not possible in the penile urethra due to the risk of loss of length and curvature during erection. This means that reconstructive techniques in the penile urethra are limited to augmentation or substitution using free grafts or flaps which in themselves may also result in chordee if used incorrectly. Moreover, pendulous strictures usually tend to be longer[11] (in some series nearly twice as long) than in the bulbar urethra.

IMPORTANCE OF STRICTURE AETIOLOGY

The commonest identifiable cause of penile strictures in young and middle-aged adults is lichen sclerosus (LS) or balanitis xerotica obliterans[12] (Figure 1). This was recently evidenced in a large European cohort of patients[13]. The proposed pathophysiology of penile strictures secondary to LS is that the initial changes occur at the urethral meatus when it becomes involved by the scarring affecting the rest of the glans and prepuce[14]. This atrophic fibrosis can extend proximally, affecting the fossa navicularis and penile urethra, which may be associated with palpable thickening at the level of the strictures. The progression of a distal stricture proximally is related to metaplastic changes due to chronic distension and extravasation of urine with subsequent inflammation of the peri-urethral glands as a result of pressure during voiding. This may be reversible if the obstruction is relieved early[12].

The penile urethra is also susceptible to strictures resulting from infection and traumatic instrumentation during catheterisation or transurethral procedures[15]. These are most commonly located in the navicular fossa and at the peno-scrotal junction[2].

The incidence of each causative factor remains unclear, however in some series it is suggested that fossa navicularis strictures are equally of iatrogenic, idiopathic, and inflammatory origin (including LS) but not the result of external trauma[11]. LS is the most common cause of strictures affecting the entire penile and bulbar urethral segments[16].

Another common occurrence is a recurrent penile urethral stricture following previous failed urethroplasty, particularly in hypospadias-related strictures (Figure 2). Recurrence after hypospadias surgery is the most frequent cause of complex anterior urethral strictures[17]

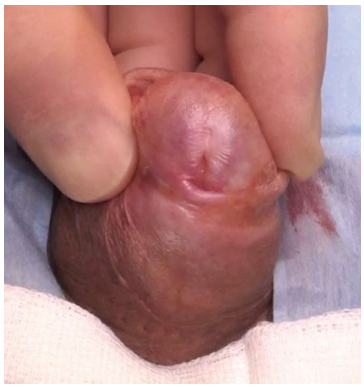

Figure 1 Typical appearance of lichen sclerosus with scarring on the glans, loss of the normal contour of the glans and coronal sulcus, meatal regression and stenosis.

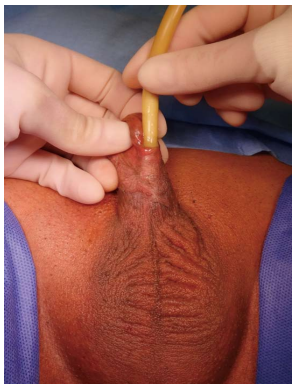

Figure 2 Urethral stricture after failed mid-penile hypospadias reconstruction.

and in some series from tertiary referral centers is the most common indication for staged penile reconstruction[18]. Strictures following failed hypospadias surgery usually occur as a result of early postoperative complications such as infection and consequently become apparent shortly after the surgery. They may however also manifest themselves many years later due to failure of the graft or flap[19].

Stricture aetiology is one of the most important factors determining the choice of management strategy of penile urethral strictures (and indeed all urethral strictures) and particularly the choice of surgical reconstructive procedure[1]. In LS-related strictures the use of mucosal grafts (usually oral but bladder or rectal also possible) is recommended since LS is a skin condition and any skin used for reconstruction is either already, or has the potential to become involved by the disease process[20]. On the other hand, genital skin is suitable for use as a flap or graft for reconstructing the urethra in selected patients with previous hypospadias surgery or instrumentation-related strictures[21].

DISCUSSION

Controversies

Flaps or grafts for penile urethroplasty: In 1968, Orandi[22] first reported on reconstruction of the anterior urethra using a pedicled skin flap. The Orandi longitudinal flap provides a long strip of penile skin with a consistent blood supply, adequate to augment the urethral lumen. This urethroplasty technique has proved to be useful for non-obliterative strictures within the penile shaft that are not secondary to LS[1]. Other skin flaps have been described using preputial, penile and scrotal skin[23-25] to treat strictures in any part of the penile urethra. These flaps achieved satisfactory outcomes in selected cases, mainly as an augmentation patch[26] after having excluded LS as a causative factor[27]. It has been shown that such skin flaps, when tubularised, are associated with a higher failure rate; up to 58% in the intermediate-term[26]. In addition, pedicled flaps are associated with other problems. When penile shaft skin is used, patients tend to report unacceptable scars at the donor site incisions, as well as irregularity of the skin caused by raising and rotating the dartos fascia as a pedicle. Furthermore, a degree of penile torsion can occur as a consequence of the pedicle[21]. In cases reconstructed using a circumferential skin tube, "bow-stringing" of the neo-urethra away from the corpora cavernosa can occur, giving the appearance of ventral webbing of the penis[21]. Scrotal skin is associated with the added complication of hair growth resulting in recurrent urethral obstruction by hairballs and stones.

Traditionally penile flaps were preferred to free grafts for penile urethral reconstruction. This was related to the perception of an initial high failure rate of grafts reported in the penile urethra[8]. A graft is only as good as its bed, and unfortunately, the anatomy of the penile spongiosum means that this is not always guaranteed. The rich glanular tissue on the other hand provides a healthy scaffold for grafting, but adequate penile spongiosal tissue and dartos fascia are not always available and thus do not ensure sufficient support for a graft in all patients.

The use of skin grafts for hypospadias surgery has long been described, as a single procedure[28], or as a staged approach[29], when still present, the foreskin has been the preferred graft source[30]. Since the popularisation of oral tissue as a substitution graft for urethroplasty in 1993[31], it has become the material of choice due to certain characteristic properties[32]. Oral mucosa is typically harvested from the cheek but can also be taken from the tongue and inner lip, resulting in a relatively concealed donor site scar and also providing sufficient graft material for almost every length of stricture[33]. A lack of oral tissue for grafting is usually associated with previous failed procedures.

Early reports suggested that outcomes with oral mucosal grafts were better when used as a patch because the failure rates when used as a tubed substitution were high, similar to the previous experience with tubularised flaps. The management of penile urethral strictures changed dramatically with the description of the dorsal free oral mucosal graft technique[34]. Those patients previously treated using a circumferential substitution in one stage with a tubularised local flap began to be managed in a staged fashion using buccal grafts

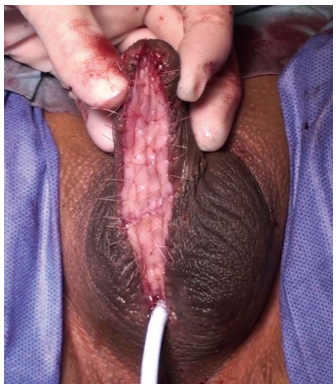

Figure 3 Operative image showing a complete first stage full-length penile urethroplasty using bilateral buccal mucosal grafts quilted dorsally to create a neo-urethral plate of adequate calibre to be retubularised in the second stage.

instead[21] (Figure 3).

In summary, the answer to the question "graft *vs* flap?" needs to be answered on the operating table, each case taken on its own merit, after a careful intraoperative evaluation based on the above-mentioned factors. However as a general rule, one would use a local pedicled flap with its own blood supply preferentially to a free graft in situations where the graft bed is poor, as with severe scarring or following radiotherapy[1].

Skin or oral mucosal grafts for augmentation or substitution: Oral mucosa has become the most widely utilised free graft for urethral reconstruction[35]. The advantages of a concealed donor site and availability have already been alluded to. Harvesting the graft is relatively easy and associated with low morbidity[32,36] (Figure 4). Biological and clinical characteristics explain the consistently good results associated with its use since it was first described[37-39]. Oral mucosa is resistant to infection. It usually hosts a variety of microorganisms hence its minimal inflammatory response to organisms[38]. LS does not tend to recur in oral mucosa as it does in skin[20]. Further anatomical advantages are related to a thick elastin-rich epithelium and a highly resilient lamina propria-oral epithelium interface, making it easy to manipulate. A thin and highly vascular lamina propria facilitates inosculation and imbibition, hence improving graft take. These structural features are retained once transplanted to the genital area with histological studies demonstrating that once in the urethra, buccal graft is often indistinguishable from host tissues[40].

The commonest site for free skin grafts is the prepuce[28] (Figure 5), due to its relative ease of harvesting, it being hairless as well as the satisfactory cosmetic appearance of the circumcising incision. Other non-hairy skin donor sites have been suggested such as the medial aspect of the upper arm and the posterior auricular area[28]. Postauricular skin, when used as a full-thickness free graft (Wolfe graft), is associated with a very satisfactory outcome which may be comparable to that obtained using oral mucosa[21]. Facial skin has a particularly dense subdermal plexus, which allows for better graft take and prevents contraction when used as a full-thickness graft. Full thickness skin grafts generally do not take as well as split-skin grafts, but when they do they tend to contract far less (around 20%)[41].

Some authors suggest that the choice of substitution material (oral mucosa *vs* preputial skin) should be based primarily on surgeon preference and experience[42]. However, several factors need to be taken into consideration including aetiology (skin contraindicated in LS), availability of oral mucosa (such as in revision procedures) and the consequence of any degree of contraction of the grafts particularly chordee, which suggests that split-skin grafts are not suitable for use in the penile urethra.

Single stage or multi-staged penile urethroplasty: When the residual urethral plate is of adequate calibre and the corpus spongiosum, dartos fascia and penile skin are preserved, single stage reconstruction is possible and preferable[18]. Besides avoiding a proximal urethrostomy and its negative impact on quality of life[3,43] for 3-6 mo, the main advantage of a single stage approach is the fewer number of procedures. The staged approach for penile urethral reconstruction is associated with a reported first stage revision rate for graft contracture of between 20% and 31%[18,21,44] ultimately resulting in a three- or more staged procedure.

Several techniques are available for single stage penile urethroplasty. Local skin flaps such as the McAninch preputial flap[24] have been described if the urethral plate can be preserved and no features of LS are evident. The Orandi procedure[22] is recommended by some authors as the best choice for penile urethral augmentation in selected mid-penile short strictures which are not related to LS[1]. Barbagli *et al*[34] described the dorsal free graft oral mucosal graft technique to augment strictures in the penile urethra in a single stage in addition to the well-known dorsal approach to bulbar urethroplasty.

Another technique for the treatment of distal penile strictures using grafts has been suggested as an evolution of the Snodgrass longitudinal incision of the urethral plate in which an oral mucosal graft is placed as an inlay into the incised urethral plate[45]. Based on the same principle of preserving the native urethral plate when available, Asopa *et al*[46] described the technique of dorsal augmentation with skin or oral mucosa as a dorsal inlay *via* a ventral urethrotomy. This procedure is not recommended in cases when the urethral plate is severely scarred, fibrotic or narrowed, but is suitable for less complicated strictures, with the advantage of a less invasive approach through a circumcision incision. Placement of the oral mucosal graft ventrally has also been described in the penile urethra, however due to the lack of adequate spongiosal support, a pseudospongioplasty with dartos tissues is necessary and is not recommended as standard treatment[47].

A significant development in the single stage reconstruction of long penile urethral strictures with a

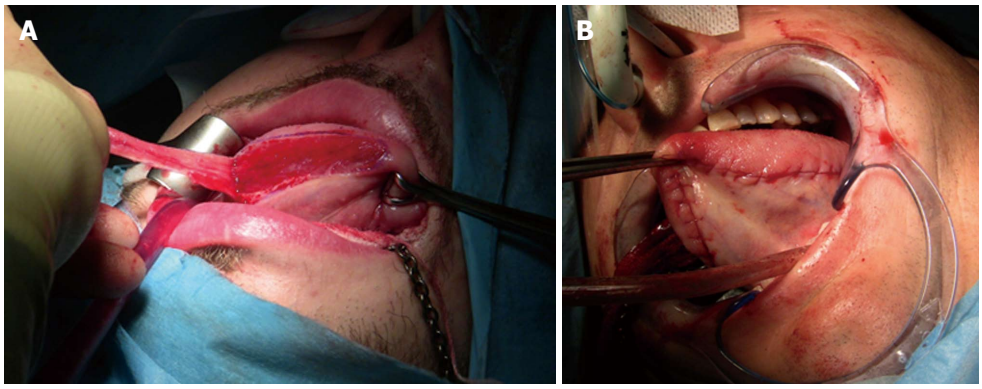

Figure 4 Operative image showing (A) harvesting of a sublingual graft and (B) bilateral sublingual graft donor sites closed primarily.

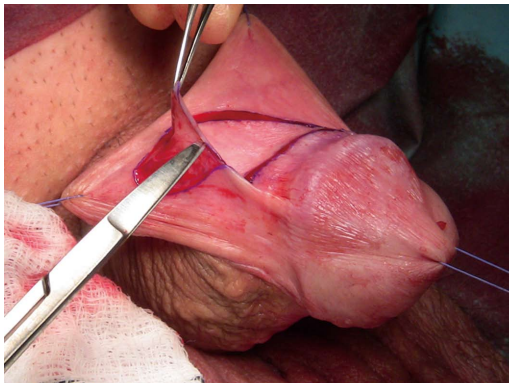

Figure 5 Operative image showing a preputial skin free graft being harvested.

salvageable urethral plate is dorso-lateral augmentation using oral mucosal graft *via* a transperineal approach with invagination of the penis as described by Kulkarni *et al*[48] (Figure 6). This technique is associated with excellent success rates of up to 92% in the short term (12 mo)[48] and 83.7% in the intermediate term (5 years)[49].

Circumferential reconstruction in a single stage using a tubularised local skin flap is associated with an unacceptably high failure rate[24]. A tubularised repair using oral mucosal grafts in one stage has also been described in the penile urethra but the reported outcomes were similar to previous reports using tubularised skin flaps and are therefore not usually recommended[39]. Consequently those patients in whom complete urethral substitution is necessary due to an unsalvageable urethral plate are preferentially managed *via* a staged approach using oral mucosal grafts[21]. A stricturotomy is performed and the diseased segment excised. A roof strip is reconstructed using graft during the first stage to produce a neo-urethral plate of adequate width which is then rolled back into a tube in the second stage 3-6 mo later. The success rate of this staged approach is up to 96% in tertiary referral centers[18]. However, complication rates of up to 35% are reported in some series[50].

We have recently shown that in selected cases it is possible to excise the spongiofibrosis, create a neo-urethral plate using oral mucosa and tubularise it, all in a single stage (Figure 7). We refer to this as a "two-in-one" stage urethroplasty and is dependent on glans size, spongiosal thickness and adequate dartos to provide support for the graft and allow enough tissue mobility for tension-free retubularisation. Previously unoperated, LS-related navicular fossa and distal penile urethral strictures are most suitable for this technique which is associated with a success rate of 90% at a mean follow-up of 16.2 mo[51].

In some cases, such as following failed hypospadias surgery, absence of an adequate spongiosum or lack of dartos and/or penile skin, a staged approach is recommended[52] for the reasons described above. However, as with all urethroplasties, but particularly in the penile urethra, it is not always possible to predict the quality of the local tissues or the residual urethral plate available for reconstruction prior to the surgery. Consequently, in our practice, patients undergoing penile urethroplasty are consented for either approach. The decision as to whether or not a single staged approach should be avoided in favour of a staged procedure is always based on a thorough intraoperative evaluation by an experienced reconstructive surgeon who is able to predict the likelihood of success and complications of either approach[21].

Management of complex cases: Penile urethral strictures range from short strictures (Figure 8) in which the urethral plate is preserved and which are relatively easily treated by augmentation techniques, to complete obliteration of the entire length of the penile urethra due to severe LS or failed hypospadias surgery (Figure 9). Management of the latter, especially those after previous failed attempts at reconstruction, presents additional challenges. The literature relating to these complex cases is sparse and does not provide reliable guidelines[42], particularly because of the heterogeneity of this group of patients. Treatment of such complex strictures commonly involves excision of the original obliterated skin tube and substitution of the entire diseased segment. These cases are often complicated further by urethrocutaneous

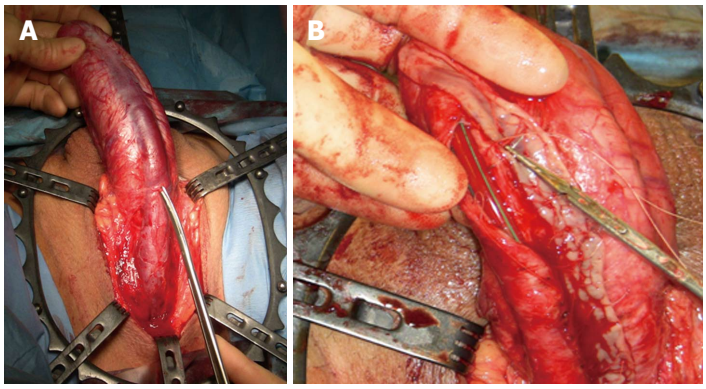

Figure 6 Kulkarni technique for long penile strictures *via* a transperineal approach with (A) invagination of the penis and (B) dorsolateral placement of the sublingual graft.

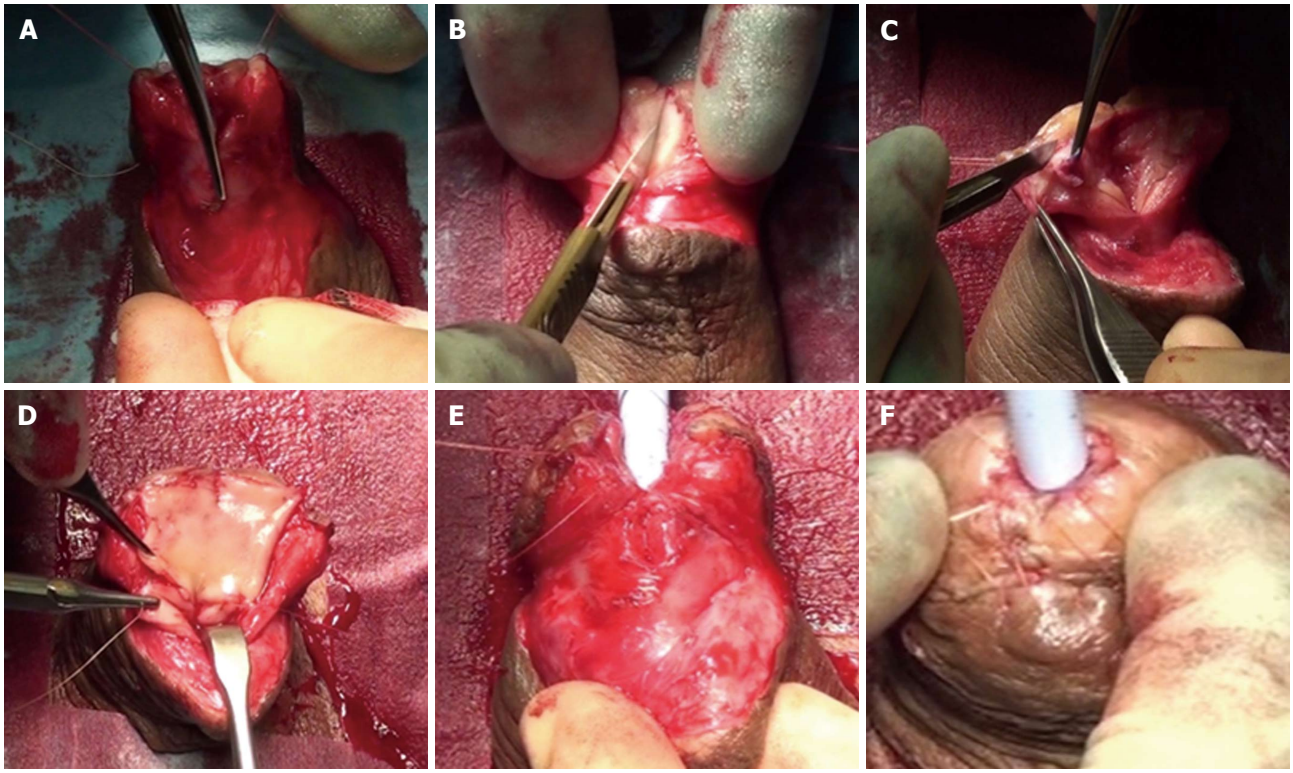

Figure 7 "Two-in-one" stage approach for a distal penile urethral stricture using oral mucosal graft. A: Ventral stricturotomy; B: Glans cleft deepened; C: Spongiofibrosis excised; D: Neo-urethral plate created using oral mucosa; E and F: Retubularised in layers in one stage.

fistulae (Figure 10), penile curvature and loss of penile length. In fact, in some series of penile urethroplasty[17], the reconstruction was restricted solely to the urethra in only 25.5% of the cases, with the rest requiring additional procedures such as correction of chordee or penile lengthening. A staged approach is preferable in these cases[29].

Such surgery, involving reconstruction of the urethra and the corpora cavernosa, should be performed by experienced surgeons in high volume, tertiary referral centres to ensure the best cosmetic and functional outcome for these patients[53]. The best outcome in these patients is achievable during the first reconstructive procedure, with salvage surgery becoming increasingly complex and associated with an increased failure rate.

Not all complex penile urethral strictures are amenable to reconstruction[54] and indeed some patients may not be keen on having further surgical intervention or may not be medically fit for major surgery. In these patients a regime of interval urethral dilatation may be feasible to preserve urethral voiding and adjunctive self-dilatation may prolong the interval between recurrence[55]. Many find this unsustainable due to pain, bleeding and recurrent infections and is generally associated with a poor quality of life[56]. Perineal urethrostomy, though not immediately acceptable to many, does present a feasible salvage treatment option in these patients with a reasonably good functional outcome and minimal

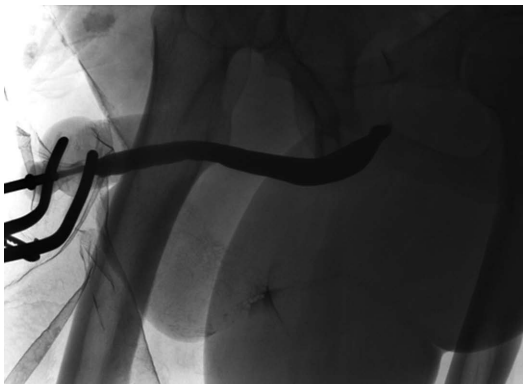

Figure 8 Ascending urethrogram showing a short penile urethral stricture limited to the fossa navicularis.

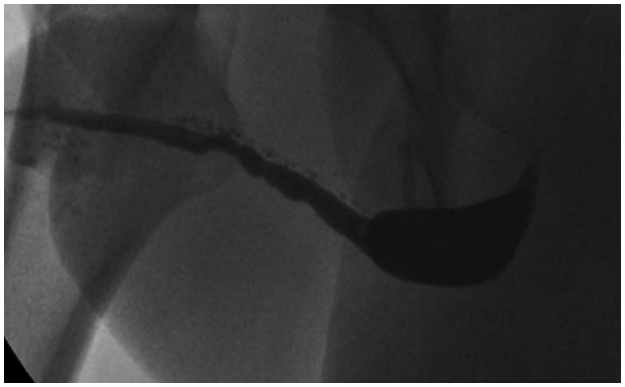

Figure 9 Entire penile and distal bulbar urethra affected by a Lichen Sclerosus-related stricture.

complications[57].

Future directions: Penile urethroplasty has evolved since first attempts at reconstruction using foreskin tubes[28] or a staged approach using penile skin[58]. An increased understanding of the pathophysiology of LS together with the high recurrence rate if skin was used for reconstruction led to the recommended use of oral mucosal grafts in LS strictures[20]. However, to date, very little benefit has been achieved with non-surgical treatment options[59]. Further research in this field may lead to the development of ways and means of stabilising or even inducing remission in this recalcitrant skin pathology.

The main limitations of current penile urethroplasty techniques are the frequent requirement of a staged procedure with its associated patient inconvenience and 20%-31% incidence of graft failure following the first stage requiring further revision surgery prior to retubularisation. Lack of available oral mucosa in full-length penile strictures, particularly in revision cases, presents additional problems. The inability to simply excise obliterative strictures and perform an end-to-end anastomosis means that substitution techniques become necessary however tubularised substitution is inherently associated with a high failure rate.

Extensive research has been carried out in the fields of biomaterials, regenerative medicine and tissue engineering in order to try and overcome some of the limitations related to current penile urethral stricture management outlined above. The primary aim has been to generate a graft with properties similar to oral mucosa but which is readily available "off the shelf", in unlimited quantities and with no morbidity associated with graft harvesting. Despite significant advances, the ideal biomaterial or composite graft has not yet been identified for use in routine clinical practice[60].

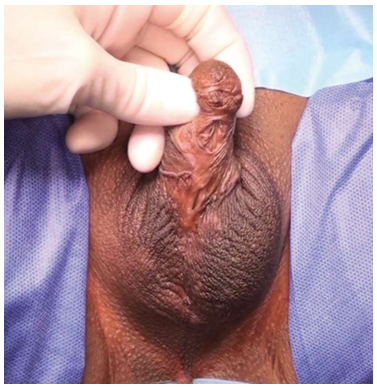

Figure 10 Multiple urethrocutaneous fistulae after failed hypospadias repair.

Numerous animal models and clinical studies have tested a variety of engineered urethral substitutes over the past 30 years. Both natural and synthetic matrices, biodegradeable and non-absorbable, seeded and unseeded, have been studied. Unseeded, "off the shelf" tubularised grafts have only been successful in replacing urethral defects less than 0.5 cm in length due to failure of epithelialisation of longer grafts from healthy surrounding tissues[61]. Unseeded grafts used as a patch in an onlay or inlay fashion have shown better results in clinical trials[62,63]. Unfortunately this has not been replicated in longer strictures. One hundred percent failure rates were reported in strictures longer than 4 cm[64]. Suboptimal results were demonstrated in patients who have had previous failed urethroplasties or those with an unhealthy vascular bed[65], two patient populations in whom alternatives to conventional substitution materials are generally sought.

In order to treat longer strictures cellularised scaffolds seem to be necessary since graft survival would be independent of epithelial cell ingrowth. Tubularised seeded grafts have shown positive results in a canine model[66] and in the only clinical trial to date[67] albeit both in the bulbar or posterior urethra. A recent review on tissue engineered oral mucosa[68] has shown this to be a "promising alternative" but requires long-term large cohort clinical trials before being advocated for widespread use. Moreover, cellularised grafts require a source of cells for seeding, are laborious, time-consuming and expensive to manufacture[69] which defeat the purpose of having a readily available off the shelf tissue substitute.

Even though the ideal tissue engineered urethral sub-

stitute may be several years away, what can and should certainly be addressed right away is the awareness amongst urological surgeons that urethral reconstruction is a highly specialised discipline and should only be undertaken by experienced surgeons in high volume tertiary units in order to ensure the best possible outcome for patients[70] particularly given the fact that the first procedure is usually the one with the best results.

CONCLUSION

Penile urethral strictures present a therapeutic challenge to the reconstructive urologist and are also associated with a significant negative impact on patient quality of life, many of them starting off with problems in infancy or adolescence and progressing into adult life, often requiring multiple surgical interventions in the process. Short, primary strictures are usually relatively easily reconstructable using oral mucosal grafts or skin flaps in a single or multi-staged approach with high rates of success. The major challenges lie with those patients having extensive LS-related strictures or "hypospadias cripples" for whom current urethroplasty techniques are not always possible or feasible. These commonly end up being managed by repeated endoscopic intervention, self-dilatation or a perineal urethrostomy, often after having undergone multiple failed attempts at urethral reconstruction.

An abundance of penile urethroplasty techniques have been described over the years bearing witness to the difficulty in dealing with this condition. All are however based on stricture aetiology, length, location and previous surgical intervention. It is up to the reconstructive surgeon to carefully evaluate the anatomy of the stricture and supporting tissues intraoperatively and only then decide which technique would give the greatest likelihood of success in any given circumstance. Hence the importance of centralisation of urethroplasty services to high volume units with expertise in a braod range of techniques.

One hopes that ongoing research will give rise to therapeutic modalities which can alter the underlying pathological processes in LS and that advances in restorative medicine would lead to the generation of novel, biocompatible and commercially viable urethral substitutes.

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Use of synthetic grafts in pelvic reconstruction: A path of continued discovery

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Abstract

Since the 1990s, mesh has been used in pelvic reconstruction to augment repairs for stress urinary incontinence and pelvic organ prolapse (POP). In 2008 and 2011, the United States Food and Drug Administration (FDA) issued Public Health Notifications ultimately informing providers and the public that complications associated with the use of synthetic mesh in the transvaginal repair of POP are not rare. In this review, we (1) examine literature characterizing surgical practice-patterns subsequent to the FDA announcements; (2) describe presentation of mesh-associated complications and outcomes of management; (3) discuss the most recent materials science research; and (4) seek to characterize whether or not mesh has lived up to the long-term efficacy promise of a permanent implant. Durability of mesh-augmented anatomical outcomes do not consistently translate into improved patient satisfaction and subjective outcomes. This, when coupled with the possibility of mesh-associated complications, emphasizes the need for continued innovation beyond the status quo of current synthetic grafts.

Key words: Pelvic organ prolapse; Mesh; Synthetic graft; Mesh-associated complications; Mesh extrusion; Mesh erosion; Host response

Core tip: While mesh-augmented prolapse repair would appear to improve anatomical outcomes, it does not consistently translate into improved patient satisfaction. The use of mesh implantation has to be balanced with the added morbidity of possible delayed mesh-associated complications over-time. We simply seek to recognize that there will be women who will suffer from adverse outcomes after these implants (just as there

can be complications after any type of surgery); it is important to recognize the need and possible benefit of effective intervention, all the while continuing to challenge ourselves to improve the techniques and materials we use in pelvic reconstruction.

Cohen SA, Raz S. Use of synthetic grafts in pelvic reconstruction: A path of continued discovery. *World J Clin Urol* 2016; 5(1): 11-17 Available from: URL: http://www.wjgnet.com/2219-2816/full/v5/i1/11.htm DOI: http://dx.doi.org/10.5410/wjcu.v5.i1.11

INTRODUCTION

Mesh was introduced into surgical reconstruction of abdominal hernias in the 1950s; it was not until the 1990s that pelvic surgeons began using mesh to augment repairs for stress urinary incontinence (SUI) and pelvic organ prolapse (POP)[1]. The United States Food and Drug Administration (FDA) issued approval for the marketing of these mesh products for such indications through a 510(k), which is a premarket submission made to the FDA demonstrating that the device in question is at least as safe and effective as another approved product (which was abdominal mesh in this instance). Synthetic midurethral slings (MUS) composed of polypropylene for SUI, in addition to transvaginal mesh kits devised for use in POP repairs, were introduced through a number of companies in the ensuing decade, with a resultant diffusion of these products. Most physicians were made aware of these new devices and kits through print advertising in professional journals, manufacturers' hospital sales force, and displays at specialty society meetings[2].

In October 2008 and July 2011, the FDA issued Public Health Notifications ultimately informing providers and the public that "serious complications" associated with the use of synthetic mesh in the transvaginal repair of POP are not rare[3,4]. The most commonly reported complications included vaginal mesh extrusion, mesh contraction associated with vaginal shortening, vaginal tightening, and vaginal pain. The FDA also made clear in this release that the warning was for transvaginal mesh placed for POP and was not inclusive of MUS procedures. In 2012, the FDA required manufacturers of transvaginal mesh POP products and single-incision mini-slings for SUI to conduct postmarket surveillance studies on these devices. In April 2014, the FDA released another update saying it was issuing a proposal to reclassify surgical mesh for transvaginal POP repair from a moderate-risk device (class Ⅱ) to a high-risk device (class Ⅲ), requiring manufacturers to submit a premarket approval application for the agency to evaluate safety and effectiveness[5]. In January 2016, this was approved[6].

Khan *et al*[7] has published work evaluating patterns in POP repair using Public Use Files from the Centers for Medicare and Medicaid Services, identifying a 5% random sample of national beneficiaries with diagnosis codes for POP from 1999 through 2009. Procedure codes were used to evaluate non-surgical and surgical management trends in this cohort. After 2005, when codes were made available, mesh/graft repairs were specifically analyzed as well. In any one year in the cohort, they found the number of women with a diagnosis of POP remained stable. There was no significant change in the rates of POP repairs over the decade. The study did note a rapid rise in mesh use, with 41% of all women undergoing surgery in 2009 having mesh or graft placed at the time of repair. In efforts to frame the impact of the national climate on mesh use, Clemons *et al*[8] utilized an electronic survey of American Urogynecologic Society (AUGS) members between December 2011 and January 2012, to determine how the 2011 FDA safety update impacted use of synthetic mesh products by pelvic surgeons. Frequency of graft use in POP (including transvaginal and transabdominal approaches) and SUI were queried. Fifty-three percent (507 of 962 members) responded; before the FDA warning 90% used synthetic mesh and 34% used biologic grafts in POP repair; 99% used synthetic mesh slings for SUI. After the FDA statement update, transvaginal mesh (for POP repair) use decreased by 40%; 12% stopped using it altogether. There was no change in transabdominal mesh POP procedures (*i.e.*, sacrocolpopexy), use of biologics, or synthetic mesh slings. Wang *et al*[9], performed another trend analysis using a 5% Medicare claims database, from 2001 to 2011, identifying POP diagnoses and related procedures with appropriate coding. The rate of mesh use increased dramatically from 2% of repairs in 2005 to 35% by 2008, at which time the initial FDA warning was issued. Subsequent to the FDA warning, the rate of sacrocolpopexy procedures (abdominally-placed mesh, as opposed to transvaginally-placed mesh) almost doubled yearly until 2011.

Anger *et al*[10] examined short-term outcomes between POP repairs with and without mesh using the national Medicare beneficiaries data set. Reoperation was higher in the POP repair/nonmesh cohort *vs* the POP repair/mesh cohort (6%-7% *vs* 4%, $P < 0.02$). The mesh removal rates were higher in the mesh *vs* nonmesh group (4% *vs* 0%-1%, $P < 0.001$). Mesh use was associated with a small decrease in early reoperation for POP; it was also associated with more dyspareunia, mesh-related complications, and urinary retention, even when controlling for concomitant sling. When examining the literature for more long-term outcomes, a retrospective review of sacrocolpopexy complications reported by Arsene *et al*[11] found median time between initial surgery and first reoperation was 3.9 ± 5.7 years. In 2013, Nygaard *et al*[12] publish long-term outcome results of the randomized, masked 2-year colpopexy and urinary reduction efforts trial. At 7 years follow-up, mesh extrusion/erosion probability estimated by Kaplan-Meier method was 10.5% (95%CI: 6.8-16.1), leading the authors to conclude that abdominal sacrocolpopexy effectiveness must be balanced with long-term risks of mesh and/or suture extrusion/erosion. Previous analysis by the same group had concluded that concomitant

Table 1 Presentation of mesh-associated adverse outcomes

Possible patient risk factors	Possible patient complaints
Prior pelvic surgery	Dyspareunia
Chronic steroid use	Hispareunia
Auto-immune disorders	Worsened urinary incontinence
Factors mitigating wound healing	*De novo* urinary urgency
Smoking	Urinary retention
Significant vaginal atrophy	Vaginal pain/scarring
Concomitant hysterectomy	Vaginal bleeding/discharge
Certain mesh types	Recurrent UTIs
Early resumption of intercourse	Secondary prolapse
	Suprapubic pain
	Groin/lower extremity pain
	Defecatory dysfunction

UTIs: Urinary tract infections.

hysterectomy, smoking, and certain mesh types appear to be modifiable risk factors associated with subsequent mesh complications after sacrocolpopexy[13].

PRESENTATION AND MANAGEMENT OF MESH-ASSOCIATED COMPLICATIONS

Mesh-associated adverse events can be viewed within the framework of immediate and late complications. Additionally, the sphere of influence of mesh-associated complications can be further understood in terms of their local, regional, and possibly systemic impacts. Mesh extrusions and erosions (mesh inside the lower urinary or gastrointestinal tract) are examples of adverse outcomes that can actually be either immediate or late complications. Vaginal mesh extrusion occurs secondary to inadequate coverage of vaginal tissue, poor vascularity, early resumption of sexual intercourse, and placement of the mesh within a thin, attenuated vaginal wall[14]. Local signs/symptoms of mesh-associated adverse outcomes can include acute urinary retention, urinary urgency, persistent vaginal bleeding/discharge, vaginal pain/scarring, and dyspareunia (if a male partner reports pain during relations, this has been described as "hispareunia"). Regional complications can include groin pain, leg pain, suprapubic pain, secondary POP, and possibly, defecatory dysfunction. In addition, further areas of ongoing research include possible systemic reactions to implanted synthetic mesh products. It should be clearly stated - there is no objective data yet to date to support a connection or etiology that would explain systemic symptoms caused by placement of synthetic mesh. A mechanism for this may or may not be an actual reality. That being said, at our tertiary referral center, approximately 20% of patients presenting with possible mesh-associated adverse outcomes report a constellation of *de novo* symptoms including but not limited to: Intermittent skin rashes, joint pain, myalgias, cough, and/or alopecia.

The management of mesh complications has developed into an emerging field, termed by some "meshology", with a need for specialized training within Female Pelvic Medicine and Reconstructive Surgery fellowships[15,16]. Methods for the management of vaginal mesh extrusion are described in the literature, ranging from observation alone, to use of topical estrogen or antiseptics, systemic or topical antibiotics, office-based trimming of the extruded material, and operative excision, at times requiring significant pelvic reconstruction[17]. When counseling patients regarding possible mesh complications, those at increased risk have vaginal atrophy, prior surgery, previous chronic steroid use, auto-immune disorders, or other factors which may mitigate wound healing (Table 1). Tijdink *et al*[18] noted differences in mesh-related symptoms, dependent upon the mesh insertion procedure, with pain and dyspareunia mainly seen after vaginal mesh insertion and vaginal bleeding and discharge after sacrocolpopexy. Protrusion of sling material or banding in the lateral fornices has been described as an etiology of persistent dyspareunia in patients with a MUS placed through the transobturator approach[19]. A retrospective review of 90 patients over a year who underwent retropubic placement of a MUS revealed 4 patients with vaginal extrusion of mesh; 2 patients were asymptomatic, with mesh extrusion identified at routine physical examination 6 wk postoperatively. Two patients had persistent vaginal discharge at 6 wk postoperatively, including 1 who complained primarily of partner discomfort during sexual intercourse[20]. Each patient was observed conservatively, without medication or surgical intervention and asked to abstain from sexual intercourse; 3 mo postoperatively all 4 had complete spontaneous epithelialization over the mesh. In a retrospective review of 73 patients who underwent complete and/or partial mesh excisions secondary to mesh-related symptoms subsequent to POP or SUI surgery, 63% failed conservative management with estrogen cream, antibiotics, and/or physiotherapy[18]. Literature supports the surgical excision of mesh if 3 mo of conservative treatment has resulted in no improvement or the erosion is more than 1 cm[21].

Multiple groups have reported outcomes of their series regarding mesh removal in the setting of mesh complications. In a multicenter, retrospective review, Unger *et al*[22] reported the results of surveys given to 101 women treated for vaginal mesh complications; 51% of women in the study underwent surgical management as treatment, and less than 10% required a second surgery. Sixty-three percent (19 of 30) of patients with pain prior to intervention reported significant improvement after treatment; however, almost a third reported worsening pain or no change after surgical management. Less than half of patients with voiding dysfunction improved after intervention[22]. In another study, validated instruments were administered to 84 women whom had experienced complications associated with vaginal mesh; each had undergone some type of treatment (surgical intervention, treatment by pelvic pain specialists, or physical therapists)[23]. The study's mean interval since presentation was 2.3 years. Twenty-two percent of reported vaginal discharge, 15% vaginal

bleeding or spotting, and 45% sexual abstinence due to problems related to mesh. Despite 2 years of tertiary care level multidisciplinary treatment, 29% were the same or worse.

Hammett *et al*[24] reported a single-center, 10-year retrospective review of patient satisfaction after surgical excision of mesh, in the setting of mesh-associated complications; a total of 57-patients (including both MUS and vaginal mesh for POP) were included with a diagnosis of mesh extrusion into the vaginal wall[24]. The International Continence Society (ICS) and International Urogynecological Association classification system was used to describe the mesh complications. The most common presenting patient complaints were chronic pelvic pain (55.9%), dyspareunia (54.4%), and vaginal discharge (30.9%). At a 6-wk post-operative visit, 57.3% of patient's symptoms were completely resolved and 14.6% were improved. Hokenstad *et al*[25] were able to analyze surveys given to 41 patients who had undergone excision of vaginal mesh placed for treatment of POP. Only 54% reported successful outcomes after mesh excision, with only 3 of 23 patients reporting resolution of dyspareunia. The authors found that patients who had complete excision of mesh, new overactive bladder symptoms after mesh placement, and a body mass index higher than 30 kg/m^2 were more likely to report improvement. Blaivas *et al*[26] reported patient improvement after surgical intervention in 47 women with associated mesh-complications. Surgical procedures included sling incision, sling excision, urethrolysis, urethral reconstruction, ureteroneocystoscomy, cystectomy and urinary diversion, and enterocystoplasty. With a median follow-up of 2 years (range 0.25 to 12, mean 3), successful outcome was achieved in 34 of 47 patients (72%) after the initial salvage surgery.

In 2015, Rogo-Gupta *et al*[27] reported outcomes of a large series of women, all of whom had undergone removal of synthetic or biological implants between 2005 and 2012. Of the 306 patients, 57% underwent removal for extrusion or erosion, 46% for pain, and 54% for urinary symptoms or incontinence. Twenty-nine percent of had previous revision. Eleven percent of had POP implants, 48% had sling implants, and 41% had both. Seventy-eight percent of the population with pain reported improvement, 14% had worsening of pain, and 9% reported no change. Overall quality of life significantly improved for those who underwent removal of POP and sling implants, and sling implants alone; however, this was not the case for those with only POP implant removal.

Over the last 5 years, our group has performed over 1200 surgical procedures to remove pelvic mesh (implanted for all indications - including urinary incontinence and POP), in the setting of vaginal bleeding, dyspareunia, and recurrent urinary tract infections with associated mesh extrusion/erosion, in addition to persistent groin and pelvic pain, which only began after mesh implantation. This has provided a robust experience in patient recovery after mesh explantation. Reflecting an oft capitulated concern of worsening incontinence in the setting of mesh removal, we sought to objectively quantify the rate of recurrent urinary incontinence and progression to another anti-incontinence surgery. A portion of this research was recently presented by Ramart *et al*[28] at the ICS 2015 Annual Meeting, entitled "Urinary Incontinence After Suburethral Mesh Removal Requiring Anti-Incontinence Procedures". The research summarizes a retrospective review of 117 continent patients who underwent mid-urethral sling removal for mesh associated complications, most commonly of which was persistent vaginal/pelvic pain [70 retropubic mid-urethral slings (RPMS) and 47 transobturator mid-urethral slings (TOMS)]. At 1-year follow-up, 38.6% of the RPMS and 34% of TOMS had recurrent SUI requiring an anti-incontinence procedure. Thus, in an initially continent population, post-mesh-removal, approximately one-third of patients progressed to an anti-incontinence procedure within 1 year.

ONGOING MATERIALS SCIENCE RESEARCH

The host response to implanted biomaterials is a series of events that could potentially impact overall tissue functionality and contribute to or even detract from clinical outcomes. As researchers look at materials design, there is now a body of research examining the ability to modulate host-response to implanted synthetic grafts in animal models. For instance, work by Nohuz *et al*[29] has investigated the use of hyaluronate carbxymethylcellulose-based bioresorbable membrane and auto-cross-linked polysaccharide hyaluronan-based solution to prevent polypropylene shrinkage in a rat model; there was significantly less shrinkage of mesh (19.12% and 17%) with the application of these materials compared to a control with a median mesh shrinkage of 29% (P-values < 0.05)[28]. The strategy of augmenting the synthetic mesh with an overlying layer or coating is not new. In 2014, Rudnicki *et al*[30] reported their outcomes after implanting collagen-coated mesh for cystocele, comparing it with a conventional anterior colporrhaphy. Although the objective cure rate was significantly improved in the collagen-coated mesh repairs, it was associated with a high exposure rate (13.3%) and no difference in quality of life or sexual function on administered questionnaires, compared to conventional repair. Lo *et al*[31] also reported a notable rate of mesh exposure, 15%, during following-up after implantation of collagen-coated mesh for anterior repair.

In 2014, Wolf *et al*[32] investigated the ability to manipulate macrophage polarization following mesh implantation. They performed spatiotemporal analysis of macrophage polarization in response to uncoated polypropylene mesh and mesh coated with hydrated and dry forms of extracellular matrix (ECM) hydrogels derived from either dermis or urinary bladder. The authors concluded that ECM coatings attenuate the pro-inflammatory M1 macrophage response and reduce the

number of foreign body giant cells to polypropylene mesh *in vivo*. With the goal of contributing to the development of synthetic implants that minimize surface area interface and increase integration with host tissue long-term, Faulk *et al*[33] investigated the effects of an ECM hydrogel coating on the long-term host tissue response to propylene mesh in a rodent model of abdominal muscle injury. At 14 d post implantation, the ECM coated polypropylene mesh devices showed a decreased inflammatory response as characterized by the number and distribution of M1 macrophages around mesh fibers when compared to the uncoated mesh devices. At 180 d, the ECM coated polypropylene showed decreased density of collagen and amount of mature type Ⅰ collagen deposited between mesh fibers when compared to the uncoated mesh devices. The authors concluded this work confirmed and extended the previous findings that an ECM coating mitigates chronic inflammatory response and associated scar tissue deposition. Dias *et al*[34] have examined the use of highly purified collagen gel coating in the immune-inflammatory response, host collagen metabolism, and angiogenesis around propylene mesh in a Wistar rat model. Using 20 Wistar rats, monofilament polypropylene mesh was implanted on one side of the abdominal wall and on the other side a mesh coated with a new highly purified collagen gel was implanted. Sacrificing the animals at 7, 14, 21, and 90 d, multiple assays were performed, including immunohistochemical analysis using interleukin 1 and surface antigen CD-31. The authors concluded that purified collagen coating can impact angiogenesis and the immune reaction of metalloproteinase around mesh implants in rats. This knowledge could contribute to the design of future synthetic grafts used in pelvic floor surgery.

At the 36th Annual Scientific Meeting of AUGS, in October 2015 in Seattle, Washington, Hachim *et al*[35] presented their paper, "Effects of Aging Upon the Host Response to Polypropylene Mesh," in which they sought to define the effects of aging upon the host response to polypropylene mesh, with particular emphasis on the participation of macrophages. After implanting mesh subcutaneously in young mice (6-8 wk old) and aged mice (18-20 mo old), implants were harvested at delayed time points and host response examined with multiple assays including histologic staining, along with subsequent *in vitro* studies to investigate the impact of ECMs on observed macrophage phenotype. The authors concluded that the results suggest differences in the character of the host macrophage response to mesh in aged animals, with possible effects upon downstream integration of implants, finding that the host response appears to be a function of at least both cell-intrinsic defects and the local ECM microenvironement.

As did Hachim *et al*[35] (previously described), Mellano *et al*[36] presented their work entitled: "The role of bacterial biofilms and chronic inflammation in the delayed development of pain following transvaginal placement of mesh slings for incontinence", in October 2015, at the 36th Annual Scientific Meeting of AUGS. The authors examined the possibility of delayed-onset pelvic pain being attributable to bacterial seeding of mesh implanted transvaginally; they described findings from a cohort of women whom reported new onset pelvic pain at least 6 mo after synthetic mesh placement. The study included 20 patients, 18 with delayed-onset pelvic pain and 2 controls (patients with urinary obstruction, no pelvic pain), whom had surgically-removed mesh examined for the presence of bacterial species by polymerase chain reaction-based amplification of bacterial ribosomal RNA (rRNA). Bacterial rRNA transcipts were present in all patients with delayed onset pelvic pain, but not present in the patients with urinary obstruction (no pain). The bacterial species identified were different from vaginal flora cultured at the time of mesh removal (reducing the likelihood the findings were secondary to a contaminated field). The authors concluded that unavoidable colonization of vaginal mesh at the time of transvaginal mesh placement may result in a bacterial biofilm that could contribute to possible delayed-onset pain, through a yet to be characterized mechanism.

CONCLUSION

When introduced into the practices of pelvic floor surgeons, the promise of synthetic mesh was outcomes more durable than biologics and native tissue repairs. Recently, Kenton *et al*[37] reported 5-year outcomes of women enrolled in an observational cohort study after having completed the Trial of Mid-urethral Slings study. The primary outcome, treatment success, was defined as no re-treatment or self-reported SUI symptoms. At 5 years, this was 51.3% in women assigned to the retropubic sling and 43.4% in women assigned to the transobturator sling; contrary to previously held beliefs, just as with biological materials, permanent mesh slings showed a progressive decrease in efficacy over time.

Thus, one has to ask - does the field of pelvic medicine and reconstructive surgery really need polypropylene mesh? Withagen *et al*[38] reported findings from their randomized control trial examining conventional vaginal repair (97 women) *vs* repair with trocar-guided tension free vaginal mesh (93 women), in a population with recurrent POP. Twelve months after surgery, anatomic treatment failure in the treated compartment was observed in 45.2% of the conventional group and 9.6% of the mesh group ($P < 0.001$); subjective improvement was reported in 80% of the conventional group and 81% in the mesh group. Mesh exposure was detected in 16.9% of the mesh repair patients. This is just an example of how important it is to understand that curing the anatomy is not the most important factor for patients' perceptions of success; the subjective outcomes are the same in both arms of this trial. However, the after-effects of mesh-associated complications (and 16.9% of this group had mesh exposure within 12 mo) can linger with patients for years potentially.

While the previously described literature represents advances in biomaterials science and the ability to impact

host-response in animal models, it is not known if this body of knowledge will translate into clinically meaningful and relevant alterations in the design of future synthetic grafts utilized (*i.e.*, would modifications ultimately impact patients long-term outcomes). While mesh augmented POP repair would appear to improve anatomical outcomes, this does not consistently translate into improved patient satisfaction and subjective outcomes. The use of mesh implantation has to be balanced with the added morbidity of possible delayed mesh extrusion/erosion over-time. The future of POP surgical repair may very well be in new, more durable biologics, completely moving beyond any continued use of synthetic materials.

In an opinion-piece in 2013, Chapple *et al*[39] noted that although mesh insertion may seem like an easy procedure, treating complications of mesh surgery may require extensive and complex procedures; even with mesh removal, it is possible that more than 30% of patients may be permanently disabled or experience long-term symptoms. The full scope of patients requiring reoperation in the setting of previous mesh placement may still be largely unknown, as the presentations can occur years later, as women age and post-menopausal status impacts on tissue quality compound. Thus, there is a subset of the patient population that will have mesh-associated complications, some of whom will benefit from surgical revision and a portion of whom will not. The work presented by Ramart *et al*[28] at the recent ICS Annual Meeting provides an objective assessment of progression to additional anti-continence surgery within 1 year of sub-urethral mesh removal (approximately 1/3 of patients). Determining what makes an individual more at-risk for any of the myriad of mesh-associated complications and ameliorating any such risk is the subject of ongoing research efforts. It should be underscored that this review is not a critique of the use of mesh in pelvic surgery. Our national organizations, AUGS and the Society of Urodynamics, Female Pelvic Medicine, and Urogenital Reconstruction, have put forth well-written statements endorsing the safety of the polypropylene mesh mid-urethral sling for SUI[40]. We simply seek to recognize that there will be women who will suffer from complications after these implants (just as there can be complications and poor outcomes after any type of surgery), and it is important to recognize the need and possible benefit of effective intervention, all the while continuing to challenge ourselves to improve the techniques and materials we use in pelvic reconstruction.

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Bladder cancer exosomes: Getting the message across

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Abstract

Bladder cancer is the seventh most common cancer in men and the seventeenth most common in women. It is also the most expensive cancer to treat over the lifetime of a patient, partially due to the necessity of frequent cystoscopy to monitor for tumor recurrence. There have also been no new developments for the treatment of bladder cancer in the last several decades. Exosomes are small, secreted, membrane-bound vesicles representative of the donor cell. Increasing understanding of the role of exosomes in cancer biology has inspired interest in their potential use as a non-invasive diagnostic tool, prognostic markers and/or indicator of recurrence of bladder cancer, and even for use in the treatment of bladder cancer. Exosomes can be readily isolated from urine. Several groups have already demonstrated differences in the protein and micro RNA content of exosomes in bladder cancer patients compared to normal healthy volunteers. Furthermore, cancer cell-derived exosomes mediate tumor progression through the delivery of their biologically active content to recipient cells. Exosomes may be useful for the delivery of targeted molecules for the treatment of bladder cancer.

Key words: Bladder cancer; Cystoscopy; Exosome; Biomarker; Urine

Core tip: Exosomes are small membrane-bound vesicles representative of their donor cell. There is growing interest in understanding the function of exosomes in diseases such as cancer. Because of their unique properties, there is developing interest in using exosomes as biomarkers, and as a therapeutic modality in cancer. There is a critical need for affordable, non-invasive methods for diagnosis and monitoring for recurrence of bladder cancer as well as novel therapeutic options. Exosomes have the potential to meet these needs. In this review, we explore what is currently known about exosomes and their role in bladder cancer.

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INTRODUCTION

The first reliable documentation of exosomes was in the 1970's with the observation of the release of membrane-bound vesicles into the extracellular space after fusion of an endosome with the plasma membrane[1,2]. For many years, exosomes were thought to be a method of disposing of cellular content. In the late 1990's, a few publications emerged demonstrating that exosomes may have a role in intercellular communication. Raposo *et al*[3] demonstrated that exosomes released by B cells could stimulate $CD4^+$ T cells *in vitro*. Zitvogel *et al*[4] found that exosomes released by human dendritic cells which were tumor peptide-pulsed could suppress or eradicate established murine tumors. These finding led to an increased interest in understanding the role of exosomes in both the normal state, and eventually disease processes.

Exosomes are formed from the endocytic pathway. Early endosomes recognize and incorporate ubiquitinated proteins[5]. This process leads to the formation of an intraluminal vesicle giving rise to multivesicular bodies (MVBs). The MVBs then fuses with the plasma membrane releasing the contents into the extracellular space. Exosomes are the resulting 30-150 nm membrane-bound extra cellular vesicles with a typical density of 1.15 to 1.19 g/mL[5]. Exosomes are secreted by many different cell types, and are found in most body fluids including blood, urine, semen, saliva and breast milk. Exosomes are representative of their cells of origin[5-8]. They contain cytoplasmic and membrane proteins, micro RNA (miRNA), messenger RNA (mRNA), long non-coding RNA (lncRNA), and even short DNA segments. Exosomes are also enriched in certain lipids including cholesterol, ceramide, sphingolipids and phosphoglycerides with long saturated fatty acids[6-8].

Exosomes have many biological functions which are dependent on their cells of origin. Examples include modulation of the immune system, programmed cell death, angiogenesis, inflammation and coagulation. Exosomes also have roles in many pathologic conditions such as infectious diseases, neurodegenerative disease, cardiovascular disease, and cancer[5,7,9].

EXOSOME ISOLATION

There are multiple isolation methods available to the exosome researcher. The investigator must decide what the downstream application of the exosome preparation is intended for in order to determine the most reasonable approach. Isolation by ultracentrifugation is considered the "gold standard" for exosomes isolation in the literature. However, due to the time-commitment associated with this method, several other approaches have been investigated and applied. Each of the following methods can be used for isolation of exosomes from several different sample sources including cell culture medium and urine.

Isolation by ultracentrifugation

Serial centrifugation with or without filtration followed by ultracentrifugation is the most widely accepted method for exosome isolation[6,10-14]. Several protocols have been used in the literature with varying speed, duration and number of low-speed centrifugation and ultra-centrifugation steps. The process begins with a series of low speed centrifugation steps to remove cells and larger vesicles. The supernatants are then collected and subjected to ultracentrifugation. This method alone is insufficient to isolate pure exosomes, but the addition of filtration and the use of a 30% sucrose cushion or 5%-30% sucrose gradient step increases the purity of the isolation. The use of a sucrose cushion or gradient allows the low-density exosomes to be separated from other higher-density vesicles, contaminating particles and protein complexes. This isolation strategy maintains the exosome structure, but is time-consuming[11,12,15-17]. If one wishes to use exosomes for functional studies, purification by ultracentrifugation with sucrose cushion or sucrose gradients yield the most purified exosomes at the lowest cost.

Immunoaffinity

In this method, antibodies to surface proteins on the exosomes are used for isolation. Antibodies are associated with beads or other matrices to immobilize them. The target exosome surface proteins bind covalently to the antibodies allowing isolation from other particles. Immunoaffinity allows for specific exosome isolation. However, it requires a clean-up procedure to remove proteins that are bound in a nonspecific manner. This process is often inefficient, yielding very few exosomes for downstream functional studies, and is very expensive[11,12,15-17].

Ultrafiltration

Ultrafiltration isolates exosomes based on their size using polytherersulfone nanomembrane concentrators. This method has a lower limit of sample volume, and is faster and easier to execute. However, because proteins in the sample can obstruct the filter, this method leads to decreased isolation efficiency[11,12,17]. Serum and urine have abundant levels of albumin and Tams-Horsfall proteins making this technique feasible only in combination with ultracentrifugation or other isolation techniques.

Size-exclusion chromatography following ultracentrifugation

Size-exclusion chromatography also uses exosome size as a principle for isolation. Heteroporous beads are constructed from a neutral, cross-linked polymeric support

placed in a column creating pores of varying sizes. As a solution passes through the column, molecules are separated by their size with the smaller molecules taking longer to pass through the pores. The major advantage of this method is that it excludes high abundant proteins. However, it is time consuming and labor-intensive[11,15-17].

Commercial kits

Several commercial kits for exosome isolation are available. The exact mechanism by which these reagents isolate exosomes is usually not disclosed by the companies. Typical steps in these protocols include incubation with a polymer, precipitation of the mixture, and centrifugation. Kits are simple, fast, and allow for processing of large volumes of sample. However, they tend to yield low quantities of exosomes and can be cost prohibitive[11,12,15-17].

QUALITY CONTROL AND QUANTIFICTION

Western blotting using known exosome marker proteins such as CD63, Alix or Tsg101 can be used to confirm the presence of exosomes in isolated samples. Commercially available Micro Bicinchoninic Acid protein assay kits can be used to quantify total exosome protein concentration[11,16,17].

Electron microscopy can be used to identify exosomes based on size and morphology. Transmission electron microscopy in combination with immune-gold staining outlines more detail and establishes the presence of specific exosome markers[11,12,16,17].

Nanoparticle tracking analysis (NTA) uses an ultramicroscope and laser illumination to calculate the mean velocity of particles suspended in a solution on the basis of Brownian motion. The velocity is then used to determine the particle size and concentration. NTA requires careful optimization and modification and setting adjustments, but is promising as a method for confirming the presence and determining the quantity of particles in the size range of exosomes after isolation by any method[12,15-17]. Western blotting and electron microscopy often accompanies this technique to provide sufficient evidence for the presence of exosomes.

BLADDER CANCER EXOSOMES

Exosomes are representative of the cells from which they originate. They contain miRNA, mRNA, lncRNA and protein. Exosomes play a role in several processes crucial for cancer progression, invasion and metastasis. Cancer cell-derived exosomes have altered content and composition which leads to altered biology. Several studies have demonstrated that exosomes from patients with bladder cancer contain discrete proteins and miRNA not found in the exosomes isolated from healthy volunteers[18,19]. The process of formation and secretion of exosomes as well as the mechanisms by which they influence tumorigenesis is not fully understood. However, there is significant evidence that cancer cell-derived exosomes influence the phenotype of recipient cells through several different mechanisms including angiogenesis, cytotoxicity, cell proliferation, migration, invasion and inhibition of apoptosis[10,13,14,19,20].

Beckham *et al*[10] previously demonstrated that bladder cancer exosomes are involved in tumor progression as exosomes isolated from bladder cancer cell lines or the urine of bladder cancer patients were shown to facilitate angiogenesis, migration and invasion. They demonstrated that exosomes isolated from bladder cancer cell lines contain hundreds of proteins such as epidermal growth factor like repeats and discoidin-1 like domains or EDIL-3. Knockdown of EDIL-3 in the high-grade bladder cancer cell line TCC-SUP resulted in exosomes that could not facilitate migration or angiogenesis, demonstrating an important role for exosome driven tumor progression in bladder cancer[10].

Yang *et al*[20] demonstrated that T24 bladder cancer cells (a high-grade bladder cancer cell line) treated with varying concentrations of exosomes have increased levels of bcl-2 and Cyclin-D1, reduced levels of Bax and caspase-3, and resulted in activation of Akt and ERK tumor cell apoptosis. Zhang *et al*[21] demonstrated that T24 bladder cancer cell exosomes can promote the antitumor effect of cytotoxic T lymphocytes *in vitro*.

A recent publication revealed that metastatic bladder cancer cells are dependent on RAB27 to secrete miR23b, miR224 and miR921 *via* exosomes. They also determined that silencing RAB27A or RAB27B halted the secretion of miR23b and miR921 and reduced cellular invasion[22].

BLADDER CANCER EXOSOMES AS BIOMARKERS

Several properties of exosomes make them desirable as biomarkers. As previously discussed, exosomes contain protein, miRNA, mRNA, lncRNA representative of the cell from which they originate. Exosomes are extremely stable, and RNA contained within exosomes is protected from degradation[23,24]. Additionally, they can be isolated from almost every body fluid, including urine. These characteristics give exosomes the potential to be used as a non-invasive biomarker for diagnosis, prognosis and recurrence of bladder cancer.

Bladder cancer tumors contain a high number of variable mutations, and tumors are frequently heterogeneous. Due to this, biomarker discovery will likely include a panel of molecules including bladder cancer specific proteins, miRNA, mRNA and lncRNA rather than a single marker. Welton *et al*[25] discovered several proteins in HT 1376 bladder cancer cell line exosomes using in-depth proteomic analysis. Jeppesen *et al*[26] completed proteomics on fractionated membranes compared to luminal contents of exosomes of metastatic and

non-metastatic bladder cancer cell lines and discovered several proteins important in epithelial-to mesenchymal transition.

Several groups have identified unique proteins and miRNA in the urine of bladder cancer patients which are not found in the urine of healthy volunteers. Chen *et al*[18] identified 22 discrete proteins in the exosomes of bladder cancer patients compared to healthy volunteers. In addition, they identified 7 proteins found differentially enriched patients. Smalley *et al*[27] found 9 exosomes proteins with differential enrichment in bladder cancer patients compared to normal healthy controls. Weber *et al*[19] identified 2 miRNA (miR-200a and miR449b) present in the urine of bladder cancer patients not present in the urine of healthy pregnant women. They also found other miRNA either enriched or reduced in bladder cancer samples compared to normal control samples. The authors speculate that the extracellular miRNA in the urine is transported in urinary exosomes. They also make the observation that quantification and normalization of miRNA is difficult due to the lack of housekeeping gene equivalents.

FUTURE DIRECTIONS

Although there are promising results for bladder cancer biomarker discovery with the use of exosome-derived proteins and miRNA, there are limitations. Microarray for miRNA has been unable to discover novel miRNA signatures for bladder cancer. High-depth RNA-sequencing may be necessary to reveal bladder cancer markers and multi-institutional cooperation may be necessary to overcome the cost barrier.

Further directions in biomarker discovery in bladder cancer may include the use of exosomal mRNA and/or lncRNA. To date, there are no published data on the function or biomarker potential of bladder cancer exosome mRNA or lncRNA. In an attempt to fill this gap, our group recently completed deep RNA-sequencing of 8 bladder cancer patient tumors, distal normal tissue and corresponding urinary exosomes, and the urinary exosomes of 7 normal healthy controls. We identified the enrichment of several mRNA and lncRNA in the bladder cancer patient exosomes compared to healthy normal controls. We used quantitative real-time reverse transcriptase polymerase chain reaction to confirm two lncRNAs enriched in the urine exosomes of bladder cancer patients compared to healthy controls. Further work in an appropriate population will be needed for validation of these transcripts for biomarker use[28].

In addition to their use as biomarkers in bladder cancer, urinary exosomes have the potential to aid in the diagnosis and monitoring of a variety of diseases. Exosome have been proposed as biomarkers for a wide-range of benign and malignant diseases. Detection of biomarker exosomes in the urine could provide a non-invasive option for the diagnosis of an assortment of conditions.

The functional roles of exosomes in cancer continue to be revealed over time. There is evidence that bladder cancer exosomes are involved in angiogenesis, cytotoxicity, cell proliferation, migration, invasion and inhibition of apoptosis. Additional functions of exosomes have been described in other cancers. For example, melanoma-derived exosomes have been shown to prime the metastatic niche[29]. There is also evidence in lung and breast cancer that exosomes may be instrumental in transferring chemotherapeutic drug resistance to chemosensitive cells[14]. There are no published data on the role of bladder cancer exosomes in priming of the metastatic niche or regulating the response to chemotherapeutics. This is another gap left to be filled in the understanding of bladder cancer exosomes.

Urinary exosomes may also be useful in predicting response of patient with bladder cancer to adjuvant therapy. Bladder cancer cells that are likely to respond to therapy may have unique (or differential expression of) proteins, mRNA, miRNA and lncRNA compared to cells that are not likely to respond to therapy. Exosomes are representative of their cells of origin in content and these differences can potentially be identified in urinary exosomes. If these differences can be identified, then urinary exosomes could potentially be used to help predict response to treatment.

There is growing interest in using exosomes in the treatment of cancer. One potential use for exosomes is as a vehicle for targeted therapy delivery in the form of cellular components of pharmaceuticals. A study by Alvarez-Erviti *et al*[30] used exosomes derived from the dendritic cells of bone marrow in mice to deliver siRNA in a targeted fashion to the brain. Another option for treatment, is in the therapeutic removal of exosomes from the circulatory system, but further work is needed to determine whether or not this method may be effective[31]. The observation that tumor-derived exosomes can activate a specific cytotoxic response has been used to initiate Phase Ⅰ and Phase Ⅱ clinical trials in the use of exosomes for the treatment of advanced stage non-small cell lung cancer[5]. There are currently no publications regarding the use of exosomes in the treatment of bladder cancer.

Exosomes show promise as a means for treatment of a variety of cancers. However, there are some limitations. Thus far, investigation into exosomes as therapeutics has been limited by technical and financial difficulties. In addition, there is concern for the safety in using exosomes for treatment. Exosomes for therapeutic use would likely be produced from cell lines grown in animal serum-containing medium. Although exosomes have been shown to be non-immunogenic, exosomes can conceivably carry theoretically harmful particles such as viruses, parasites, prions and transposons[32-34]. One potential advantage in the treatment of bladder cancer is the ability to deliver therapeutics intravesically, potentially avoiding risks associated with the treatment delivered systemically.

CONCLUSION

Exosomes are desirable as biomarker for disease because of their unique properties, including stability, protein and nucleic acid content representative of their donor cell, and presence in most body fluids. Several studies have demonstrated their potential use as biomarkers for bladder cancer. In these studies, both proteins and miRNA unique to bladder cancer patients were found in urinary exosomes. These studies use pooled data, highlighting the importance of developing a reliable panel of biomarkers for bladder cancer diagnosis and monitoring for recurrence of disease. And finally, there is some data to support the use of exosomes in cancer treatment.

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MINIREVIEWS

Cost effectiveness of robot-assisted urologic oncological surgery in the United States

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Abstract

Urology has been on the forefront of technological advances in minimally invasive surgery, from laparoscopy to robot-assisted surgeries. As with all new technological advances in medicine, the results of new advances are compared to previously established gold standards. When it comes to robot-assisted urology, morbidity, oncological outcomes, and cost between the same surgeries performed in an open fashion *vs* with robot-assistance should be assessed. Because healthcare spending is increasingly under more scrutiny, there is debate on the cost effectiveness of robot-assisted surgeries given the high acquisition and maintenance cost of robotic systems. This articles aims to critically evaluate the cost effectiveness of robot-assisted surgeries for prostatectomies, cystectomies, and partial nephrectomies in the United States.

Key words: Cost-effectiveness; Robot; Prostatectomy; Cystectomy; Partial nephrectomy

Core tip: Robot-assisted urologic oncologic surgeries offers significant amounts of benefit, with shorter length of stay, less blood loss and improved peri-operative quality of life. The high fixed cost of robot acquisition and maintenance is offset by increasing the number of robot cases per year, narrowing the gap in cost between robot-assisted surgeries and open surgeries. Cost effective analysis and cost benefit analysis of robot-assisted surgeries are difficult to assess given the difficulties with evaluating indirect costs. However, the measurable differences favor robot-assisted surgeries.

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INTRODUCTION

Healthcare spending is an important topic as current

practices are under heavy scrutiny and affected by changes in healthcare policy. The cost of medical care has come to the forefront in both the medical and political community. This places pressure on the scientific community to develop technological advances that will not only improve health outcomes but that are also more cost effective. Robot-assisted surgery is a recent technology targeted in the debate regarding cost effectiveness and added value of healthcare.

Since the approval of the Da Vinci Surgical System (Intuitive Surgical, Inc., Sunnyvale, CA) by the Food and Drug Administration (FDA) in 2000, robotic assisted surgery has been rapidly adopted, with more than 1400 systems installed in the United States by 2009, growing by 85% from 2007 to 2009[1]. As of March 2015, Intuitive has reported that 3317 base units have been installed worldwide, with 2254 units in the United States, 556 in Europe, 194 in Japan and 313 in the rest of the world[2].

The urologic community has been quick to adopt robotic assisted laparoscopic surgery especially in urologic oncology, first through embracing robotic assisted prostatectomy and more recently increasing utilization to partial nephrectomies and cystectomies. Currently, the majority of radical prostatectomies are performed robotically in the United States, with estimate in 2009 being 69% performed robotically[3].

Robotic assisted laparoscopic surgery offers several advantages. From the surgeon's perspective, robotic assisted surgery offers improved visual field, including 3-dimentional view, improved freedom of movement through "wristed" instruments, elimination of surgeon tremor and ergonomic benefits[4]. For the patient, benefits include improved cosmetics with smaller incision sites, decrease loss of blood, decreased post-procedure pain, shorter length of stay and faster recovery[4]. However, some reported disadvantages include longer operative time, lack of tactile sensation, and instrument collision resulting in injury to surrounding organs.

Currently in the United States, most patients pay for their healthcare through insurance, and ultimately only pay a small portion directly leading to poor understanding of medical costs. Many studies have demonstrated that robotic surgery can be more expensive due to the high acquisition cost[5-7].

ECONOMICS OF MEDICAL CARE

There are three types of models to assess the economics of medical care (Table 1): Cost-identification analysis, cost effective analysis, and cost-benefit analysis[8]. Cost-identification analysis simply identifies the cost without addressing outcomes. Cost effectiveness analysis is a method used to assess cost and outcomes[9]. It is often presented as an incremental cost effectiveness ratio, where the numerator is the difference of cost between two different interventions and the denominator is the difference between the health outcomes[10]. Health outcomes can be measured in several different ways (*i.e.,* quality of life, disease free survival, life years gained). Cost-benefit analysis evaluates whether the benefit is worth the cost done by measuring cost and outcomes in the same unit[8].

Direct costs are divided into two categories (Figure 1), fixed cost which would not change based off of the number of procedures and variable cost which does change based on the number of procedures done[8]. Indirect costs are measured by cost incurred by loss of livelihood or life due to morbidity or mortality such as lost wages or disability[8]. Given the difficulties in evaluating indirect costs, there has not been any study to evaluate this. Most published literature focus on the direct cost of robotic surgery.

Some of the draw backs to economic analysis are due to bias and uncertainties. It is difficult to obtain precise values for many of the components for necessary cost analysis. Insurance reimbursement also differs compared to actual cost. Currently, Medicare uses cost effective analysis for preventative services but not for treatment.

The direct costs in robotic surgery tend to be higher than open procedures predominantly due to the high acquisition cost of a robotic surgical system as well as cost of disposable instruments and terms of maintenance agreements. Currently, Intuitive Surgical is the only company on the market producing a FDA approved robotic surgical system, thus, holding a monopoly on the market. It is estimated that robotic acquisition is typically around 1.5 million dollars with an annual $150000 service contract. Per the American Hospital Association's 2008 asset life assessment guidelines, most studies amortize this cost over 7 years, dividing the total cost over the total number of robotic cases to determine the cost per case[11-14]. Thus, the cost of robotic utilization per case is lower at a large volume practice compared to a low volume practice. Other direct cost consists of cost for robotic instruments. With programmed obsolesce, robotic instruments are limited to 10 uses per instrument compared to laparoscopic and open instruments, which tend to have unlimited uses.

COST COMPARISON: PROSTATECTOMY

Out of the limited literature published on the cost of robotic assisted urologic surgery, the literature is most robust for radical prostatectomy. Bolenz *et al*[5] published their data on cost from the hospital billing department. They obtained disposable laparoscopic cost, including cost of trocars, specimen entrapment sac, suction irrigator, clip appliers, and use of adjuvant hemostatic agents. Cost specific for the robot included robotic instruments per use. They evaluated operative time to determine OR cost, including cost for anesthesia and OR overhead. The rate for room and board was included, based on length of stay. They concluded that the median direct cost for robotic assisted radical prostatectomy (RARP) was $6752, laparoscopic prostatectomy was $5687 and $4437 for open radical retropubic prostatectomy (RRP)[5]. However, they did not include acquisition cost and maintenance cost in these values, which would only raise the cost of

Table 1 Three types of models to assess the economics of medical care

Economic models of medical care	Definition
Cost identification analysis	Identifies cost without evaluating outcomes
Cost effectiveness analysis	Assess cost and outcomes; represented as an incremental cost effectiveness ratio (difference of cost between two different interventions/ the difference between the health outcomes)
Cost-benefit analysis	Evaluates whether the benefit is worth the cost done by measuring cost and outcomes in the same unit

RARP.

Bolenz *et al*[15] subsequently published a systematic review on the cost of prostatectomy using different methods, including 11 studies that reported the direct cost of the procedure in their final analysis. Out of the 11 studies included, 6 studies compared open RRP with minimally invasive prostatectomy. For minimal invasive prostatectomy, which included both laparoscopic and robotic prostatectomy, the cost ranged from $5058-$11806. For open RRP, the cost ranged from $4075-$6296. The direct cost in minimally invasive prostatectomy was higher than open in 5 out of the 6 studies.

Hyams *et al*[16] specifically evaluated the impact of surgical volume on the cost of radical prostatectomy. They used a statewide database to identify all open and robotic prostatectomies between 2008-2011 in Maryland. They found that in both the open RRP and the RARP groups, the larger the surgical volume, the lower the cost per case. However, they still note that open RRP had lower direct costs even at high volume. This study did not take into account acquisition and maintenance costs; thus, possibly increasing the difference between the cost for RARP and open RRP more.

In a retrospective study of 882 patients (294 in the robot-assisted group and 588 in the open group), Krambeck *et al*[17] demonstrated that there was significant difference in median operation time between the RARP and open RRP groups; however, by the last 100 RARP cases, there was no difference in median operation time. They included docking time of the robot in their analysis. Through their study, they demonstrated that with increased experience, the cost of OR time could be equivalent between the two groups.

There are no studies that have directly analyzed and calculated a value for the indirect cost of robotic assisted prostatectomies. However, there have been studies that indirectly address this through evaluating cancer control and side effects.

In a retrospective study of 400 patients, the overall incidence of positive surgical margin was 15% in the RARP arm compared to 35% in the open RRP arm ($P < 0.001$)[18]. When sub-stratified based on pathological stage, the positive surgical margin was lower in the RARP

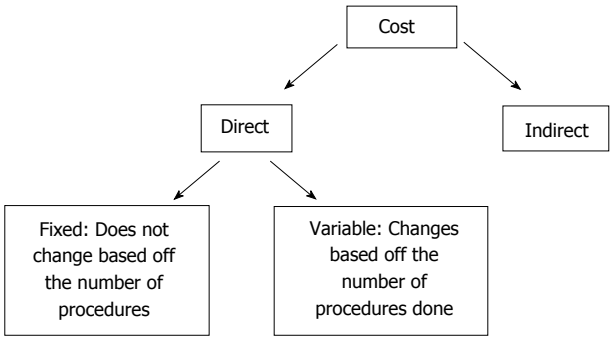

Figure 1 Direct costs two categories.

groups for both pT2 and pT3 disease[18].

Tewari *et al*[19] demonstrated in a prospective comparison between open RRP and RARP that patients in the RARP group had faster return of continence (44 d *vs* 160 d) and erections (180 d *vs* 440 d) compared to those in the open RRP group. They also report that positive margins were more frequent in the open RRP group compared to the RARP group (23% *vs* 9%).

There has only been one study published evaluating and comparing quality of life in men undergoing RARP *vs* open RRP in the peri-operative period. In a prospective study, Miller *et al*[20] had patients complete the SF-12 version 2 Physical and Mental Health Survey Acute Form preoperatively and weekly postoperatively for 6 wk. This questionnaire assesses physical functioning, role limitations due to physical health, pain, general health perceptions, vitality, social functioning, role limitations due to emotional problems, and mental health. This was broken down into a mental component score and a physical component score, which higher scores indicating better functioning. The physical component score was consistently higher in the RARP group starting from week 1 to week 6. There was no statistically difference in the mental component score except on the preoperative survey, where the RARP group scored higher than the open RRP group. Studies that have looked at long term quality of life notice no difference between different methods of RARP and open RRP[21,22].

COST COMPARISON: CYSTECTOMY

The direct cost comparison between robot-assisted radical cystectomy (RARC) and open radical cystectomy (ORC) is less clear compared to that analysis for prostatectomies. There are significantly fewer studies published for cystectomies and as a whole, the urologic community is at an earlier stage in the learning process for cystectomies compared to prostatectomies.

Yu *et al*[23] reported that RARC costs is greater than ORC cost by $3797; however, they did not elaborate on how these numbers were obtained. They report in their retrospective study using the United States Nationwide Inpatient sample no difference in length of hospital stay or transfusion rates between the RARC and ORC groups. The RARC group had lower parenteral nutrition use and

lower inpatient complications, but they were not able to classify or grade these complications.

In a retrospective study on 20 RARC and 20 ORC at a single institute, Smith *et al*[7] demonstrated that the cost of the RARC group was overall higher than the ORC by $1640. They included fixed cost, variable cost, as well as hospital cost. Fixed cost included base cost and disposable equipment cost for ORC. Robotic fixed cost included amortization of the robot as well as maintenance fees. Variable operating room cost depended on the duration of the case, which was higher in the RARC group. Hospital cost was actually higher in the ORC group because of increased transfusion rates and length of stay.

On the other hand, Martin *et al*[14] demonstrate when evaluating actual patient costs there is a 38% cost advantage favoring RARC when combining both operating room and hospital costs. The absolute cost was not given. The costs relating to the operating room was more in the RARC group because of longer procedure time and fixed cost of robot acquisition and maintenance. However, there was a significant difference in the length of stay (LOS), with the mean LOS of 5 d in the RARC group and 10 d in the ORC group. This was a relatively small study with 19 patients in the RARC group and 14 patients in the ORC group.

Lee *et al*[11] also demonstrated similar findings. In a retrospective study on 186 patients, they subdivided the patients based of the type of urinary diversion used. The cost of RARC with orthotopic neobladder was less than the cost ORC with orthotopic neobladder. They conclude that the difference in LOS is able to offset the higher cost of robotic surgery. Furthermore, the overall complication rate within the 90-d global surgery period was lower in the RARC group (49.4%) than the ORC group (61.2%).

The main limitation of cost evaluation of RARC *vs* ORC is the lack of published data on effectiveness as well as comparison of side effects. There is limited data on oncologic outcome, with the longest follow-up of 3.5 years in RARC[24].

COST COMPARISON: PARTIAL NEPHRECTOMY

There are limited studies evaluating the cost of robotic-assisted partial nephrectomy (RAPN), open partial nephrectomy (OPN) and laparoscopic partial nephrectomy (LPN). The studies that have been published are small, with the largest only evaluating 89 patients[12].

Hyams *et al*[25] evaluated 20 consecutive RAPN and OPN from 2009-2010. They calculated that RAPN was $1066.09 more than LPN. This was attributed to the high capital cost for robotic surgery specific to their center. Capital cost was estimated for the purchase and amortization of 2 robotic systems as well as maintenance cost divided by the total number of robotic cases between 2001 and 2009. They concluded that when the fixed robotic cost was calculated based off 1 robotic system with "ideal" utilization of 300 cases per year, the cost difference is only $333.85 per case.

In another study that compared RALN to OLN, Alemozaffar *et al*[13] also conclude that RALN can be cost equivalent to OPN by minimizing OR time and LOS. However, RALN was most expensive when fixed costs were factored.

CONCLUSION

Overall, robotic assisted surgery has offered significant amounts of benefit to urologic surgery, with shorter LOS, less blood loss, and improved peri-operative quality of life. Given the high fixed cost of robotic acquisition and maintenance, robotic assisted surgery is more often than not, more expensive than open procedure when evaluating direct costs. However, the gap in cost between robotic assisted and open surgery can be narrowed in high volume centers where the fixed cost can be divided between a larger number of cases. Also, if the LOS is substantially different between robotic and open groups, such as in cystectomies, the cost of robotic surgery can actually be even lower than an open procedure. Due to the difficulty of identifying indirect costs and health outcomes, it is very difficult to assess cost-benefit of robotic assisted surgery. Furthermore, these cost evaluations do not factor in patient preference and requests for procedures to be done robotically. Ultimately, more data is needed in evaluating and comparing long term surgical outcomes between robotic assisted and open surgery.

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Diagnosis of voiding dysfunction by pressure-flow study in women

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Abstract

Pressure-flow study (PFS) of micturition is the best method to quantitatively analyse voiding function. It allows us to distinguish voiding lower urinary tract symptoms and low urine flow rate caused by bladder outlet obstruction (BOO) from those caused by detrusor underactivity (DU). Voiding dynamics are significantly different in men and women and the established criteria for urodynamic diagnosis in men do not apply to women. Basic principles of voiding mechanics and voiding patterns in asymptomatic women are analyzed. Although attempts have been made to establish a consensus for diagnosis of BOO in women with pressure-flow cutoff, video-urodynamics criteria and nomograms, currently there is no consensus. There is no standard urodynamic test to diagnose and quantify DU in women for which further investigations are needed. Modified projected isovolumetric pressure (to assess detrusor contraction strength) and pressure-flow cutoff criteria have been used. The diagnosis of voiding dysfunction in women is challenging, requiring PFS with very good quality control and often involves integrating clinical and radiographic data to make the final assessment.

Key words: Bladder outlet obstruction; Pressure-flow studies; Urodynamics; Women; Detrusor underactivity

Core tip: Pressure-flow study of micturition is the best method to quantitatively analyze voiding function. Voiding dynamics differ significantly between men and women and the established criteria for urodynamic diagnosis in men do not apply to women. Although attempts have been made to establish a consensus for diagnosis of bladder outlet obstruction in women with pressure-flow cutoff, video-urodynamics criteria and nomograms, currently there is no consensus. There is no standard urodynamic test to diagnose detrusor underactivity in women for which further investigations are needed. The diagnosis of voiding dysfunction in women is challenging and often involves consideration of clinical and radiographic data to make the final assessment.

by pressure-flow study in women. *World J Clin Urol* 2016; 5(1): 29-36 Available from: URL: http://www.wjgnet.com/2219-2816/full/v5/i1/29.htm DOI: http://dx.doi.org/10.5410/wjcu.v5.i1.29

INTRODUCTION

At present, the best method for quantitative analysis of voiding function is the pressure-flow study (PFS) of micturition, with concomitant recording of intravesical, abdominal, detrusor pressures ($p_{det} = p_{ves} - p_{abd}$) and flow rate[1]. It is defined by the International Continence Society (ICS) as "the method by which the relationship between pressure in the bladder and urine flow is measured during bladder emptying"[2].

PFS is able to evaluate normal voiding as well as detrusor underactivity (DU) and bladder outlet obstruction (BOO). BOO is the term employed for defining obstruction during voiding and corresponds to increased detrusor pressure and reduced urine flow rate. DU is defined as a detrusor contraction "of reduced strength and/or duration, resulting in prolonged bladder emptying and/or failure to achieve complete bladder emptying within a normal time span"[2]. An acontractile detrusor is defined as the one "that cannot be observed to contract during a urodynamic studies resulting in prolonged bladder emptying and/or failure to achieve complete bladder emptying within a normal time span"[3]. Thus, acontractile detrusor may be considered as a more severe form of DU.

PFS is a well established diagnostic tool for evaluating voiding dysfunction in men. This is the result of extensive studies in patients with benign prostatic enlargement which has led to the development of normograms, such as de nomogram described by Abrams *et al*[4], the Passive Urethral Resistance Relation[5,6] and the ICS nomogram[1]. However, due to anatomic differences between men and women their voiding dynamics differ significantly. Women usually void at lower detrusor pressures than those observed in men. Therefore the established criteria for urodynamic diagnosis used in men are not well suited for women. Moreover, up to date there is no equivalent prevalent condition such as benign prostatic enlargement causing BOO in women, making the diagnosis more challenging.

In this article we will discuss the basic principles of voiding mechanics, the voiding patterns in asymptomatic women, the urodynamic criteria currently used to assess BOO and DU in women and some quality control issues of the pressure-flow studies in this gender.

BASIC PRINCIPLES OF VOIDING MECHANICS

The detrusor, as it occurs with other muscles, follows the Hill equation. This equation describes the relation between the muscle's force of contraction and it's shortening velocity[7]. For example, for a given muscle length and it's activation degree, a shortening speed of zero will produce that tension attains its isometric value. As the muscle's shortening speed increases, the tension falls and reaches zero at a maximum shortening velocity characteristic of that muscle (Figure 1)[7,8]. In the case of the bladder, the Hill equation becomes the bladder output relation (BOR). It relates the pressure of the detrusor to urinary flow rate (Figure 2)[8]. For a given detrusor contraction strength, given that there is no obstruction, the pressure needed to drive urine through the urethra is low meanwhile the flow rate is high. Contrarily, if outlet obstruction is present, the pressure required is high and flow rate low. If obstruction develops progressively, voiding conditions alter gradually from low pressure/high flow towards high pressure/low flow[9]. Moreover, the BOR curve is not fixed. When the detrusor decompensate and develops hipo-contractility, the curve shifts to lower pressures and flow rates and may cause urinary retention[9-11].

In other words, voiding arises from the balance between an actively contracting detrusor as source of mechanical energy and the relaxed bladder outlet as a passive conduit with special hydrodynamic characteristics. The detrusor has a specific pattern of energy release in which the outlet determines how the energy provided is converted to attain voiding. Voiding power is proportional to detrusor pressure and to urine flow rate. The detrusor does not produce a particular pressure or flow during voiding. Instead, this muscle is able to provide mechanical power and it is the bladder outlet that dictates the way this power is splited into pressure and flow rate, following an inverse relationship (BOR). The maximum detrusor power is proportional to the filling volume of the bladder. This higher detrusor power explains why, for the same voiding pressure, the peak flow rate is higher at larger voiding volumes (therefore the outlet resistance is not lower at larger volumes). Moreover, the collapsed urethra differs from a rigid pipe in that an increase in intraluminal pressure is required to open the lumen before flow can occur. This urethral opening pressure must also be supplied by detrusor contraction and cannot be converted into flow. Consequently, flow rate will be lower than it could be in a rigid conduit of the same size. A special feature of flow in collapsible and distensible tubes is that the pressure-flow relation can be controlled by a small segment acting as a "flow controlling zone". Under physiologic conditions, this zone is at the level of the pelvic floor. Under pathological outflow conditions, the obstruction itself takes over the role of the flow controlling zone[5].

VOIDING PATTERNS IN ASYMPTOMATIC WOMEN

Most of our knowledge of voiding function has been extrapolated from studies of women with lower urinary tract dysfunction. However, women with and without lower urinary tract symptoms have different voiding patterns.

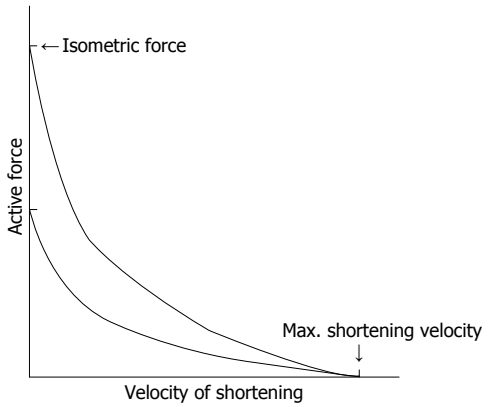

Figure 1 Hill curves relating active force to velocity of shortening at a given muscle length. Curves are shown for two different muscle lengths, corresponding to the same bladder when full (upper curve) and when nearly empty (lower curve: Volume approximately 12.5% of capacity). (From Griffiths[8]. Assessment of detrusor contraction strength or contractility. Neurourol Urodyn 1991; 10: 1; with permission).

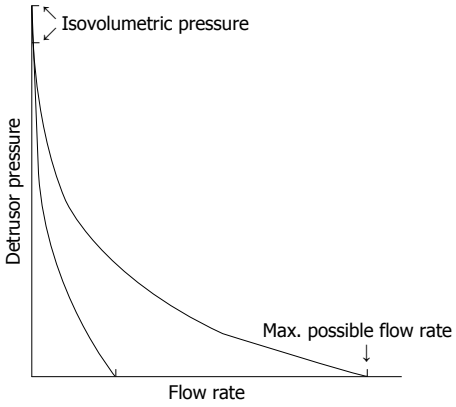

Figure 2 Bladder output relations relating active detrusor pressure to rate of urine flow at a given bladder volume. Curves show Bladder output relations for the same two situations as in Figure 1, corresponding to a full bladder (curve with higher maximum possible flow rate) and a nearly empty bladder (lower maximum possible flow rate; volume approximately 12.5% of capacity). (From Griffiths[8]. Assessment of detrusor contraction strength or contractility. Neurourol Urodyn 1991; 10: 1; with permission).

In their work, Tanagho *et al*[12] studied the initiation of voiding by simultaneously using cineradiography and recording pressures in the urethra, bladder, rectum and anal sphincter. They described 5 different voiding patterns: (1) Decrease in urethral closure pressure followed by contraction of the detrusor; (2) detrusor contraction without decrease in urethral pressure; (3) decrease in urethral closure pressure and increase of intravesical pressure due to straining; (4) increase of intravesical pressure due to straining without decrease in urethral pressure; and (5) decrease in urethral closure pressure without straining or contraction of the detrusor. They stated that only patients with low urethral closure pressure voided with negligible or no detrusor contraction. This leads to question if these types of voiding are indeed normal[12]. Of notice, from our knowledge of the BOR we can asseverate that women with very low bladder outlet resistance who do not strain to void should be using their bladder detrusor to void even if no increase in detrusor pressure is detected.

Few studies have described the voiding patterns of "healthy, continent and/or asymptomatic" women. Furthermore, definitions of what is considered detrusor contraction and straining to void vary between these studies (Table 1)[13-16]. All women included in these reports voided with a measurable detrusor contraction and variable participation of abdominal muscles (0%-73%). Backman *et al*[17] studied 15 normal women of all ages and found that they all initiated voiding by increasing abdominal pressure. However, young women did not use straining during the whole micturition as often as elderly women did. Consequently, the authors argued that the detrusor muscle tends to lose some of its power with age[17].

BOO

BOO "is the generic term for obstruction during voiding and is characterized by increased detrusor pressure and reduced urine flow rate"[2]. Women typically void at lower detrusor pressures than men. Small increases in detrusor pressure or decreases in flow rate, probably considered insignificant in men, could correspond to BOO in women. BOO in women without neurological diseases can be classified as anatomic or functional. Anatomic causes of BOO include high grade pelvic organ prolapse, previous anti-incontinence surgery and urethral disease (stricture, diverticulum). Functional causes of BOO are primary bladder neck obstruction and dysfunctional voiding (also known as learned voiding dysfunction) among other less frequent causes[18]. Currently, no consensus exists regarding urodynamic criteria to define BOO in women. Attempts have been made to establish a standard for the diagnosis of BOO in women, grouping them into one of three categories: (1) Pressure-flow cutoff criteria; (2) video-urodynamics criteria; and (3) nomograms.

The major studies of pressure-flow cutoff criteria for the diagnosis of BOO in women have been reported by the Department of Urology of the University of Texas Southwestern Medical Center. This group published three articles in which they calculated the best combination of maximum flow rate (Q_{max}) and detrusor pressure at maximum flow rate ($p_{det}Q_{max}$) using receiver operating characteristic curves in women who had a clinical diagnosis of BOO[19-21]. In two of their studies, control groups included women suffering stress urinary incontinence, whereas a third study included healthy volunteers to correct for effects of low outlet resistance. Their last study included 169 consecutive women with clinically diagnosed obstruction. That is to say, a history of urethral or bladder neck surgery, pelvic examination revealing urethral hyperelevation or high grade anterior vaginal wall prolapse and altered voiding cystourethrography and/or endorectal coil magnetic resonance imaging. The study reported high-stage anterior vaginal wall prolapse, previous anti-

Table 1 Voiding patterns of "healthy, continent or asymptomatic" women

	Rud *et al*[13]	Rud *et al*[14]	Karram *et al*[15]	Pauwels *et al*[16]
No. of patients	16	6	30	26
Patients condition	Healthy	Healthy	Asymptomatic, continent	Healthy, history free, continent
Age, yr (range)	33 (23-73)	42 (37–54)	34	26
Definitions				
Detrusor contraction	Not defined	Not defined	Increase in detrusor pressure of 5 cm H_2O above resting pressure	Increase in detrusor pressure of 15 cm H_2O above resting pressure[1]
Strain to void	Not defined	Not defined	Increase in abdominal pressure of at least 10 cm H_2O above baseline	Increase in abdominal pressure of at least 10 cm H_2O above baseline during the entire voiding phase
Voiding pattern				
Drop in urethral pressure	16/16 (100%)	6/6 (100%)	Not studied	Not studied
Detrusor contraction	16/16 (100%)	6/6 (100%)	30/30 (100%)	26/26 (100%)
Strain to void	0/16 (0%)	0/6 (0%)	22/30 (73%)	11/26 (42%)

[1]There was no definition of detrusor contraction but increase in detrusor pressures of at least 15 cm H_2O developed in all women.

incontinence surgery and documented distal urethral obstruction/periurethral fibrosis as causes of anatomic BOO. They excluded patients with neurologic conditions that could affect bladder function, patients with bladder capacity under 100 mL, abdominal strain during voiding greater than 10 cm H_2O, absence of urethral sphincter or pelvic floor relaxation during voiding (evidenced by patch electrode electromyography) together with inability to void for the PFS. Their results showed that "the $p_{det}Q_{max}$ value with a specificity of at least 60% and the greatest sensitivity for the detection of BOO was 25 cm H_2O, and that Q_{max} value resulting in equal sensitivity, specificity, and accuracy (68%) for predicting BOO was close to 12 mL/s" (cutoff criteria: $p_{det}Q_{max} \geq 25$ cm H_2O + $Q_{max} \leq 12$ mL/s)[21]. It is worth remembering that with voided volumes greater than 140 mL a $Q_{max} \leq 12$ mL/s falls under the 5th percentile of the Liverpool nomogram, and over 110 mL of voided volume a $Q_{max} \leq 12$ mL/s falls under the 10th percentile[22].

In a retrospective work, Nitti *et al*[23] described the video-urodynamic criteria used to diagnose BOO in 261 women with non-neurogenic voiding dysfunction, who were able to void during the PFS. They argued that if physological voiding in women take place at low detrusor pressure the bladder response to obstruction by producing higher voiding pressures might be difficult to notice. BOO was characterized as radiographic proof of obstruction from the bladder neck to the distal urethra when observing a sustained contraction the detrusor of any magnitude. This was generally associated with decrease or delay in urinary flow rate. The authors define radiographic obstruction at the bladder neck when it was either closed or narrow during voiding. Radiographic obstruction of the urethra was diagnosed when they detected a distinct area of narrowing with proximal dilatation. This method allows for diagnosis of the zone of obstruction. In this study 67 patients were considered obstructed and 185 patients unobstructed. Patients with BOO had anatomical (cystocele, urethral stricture, urethral diverticulum, iatrogenic obstruction from incontinence surgery, uterine prolapse and rectocele) and functional causes (dysfunctional voiding and primary bladder neck obstruction). When urodynamic parameters were compared, the obstructed cases had significantly higher mean $p_{det}Q_{max}$ (42.8 ± 22.8 cm H_2O *vs* 22.1 ± 11.3 cm H_2O), lower mean Q_{max} (9.0 ± 6.2 mL/s *vs* 20.2 ± 10 mL/s), and higher mean postvoid residual urine (157 ± 183 mL *vs* 33 ± 91 mL) than unobstructed cases. However, given that both groups presented wide intervals for each parameter, it was difficult to assign specific cutoff values[23].

Blaivas *et al*[24] developed a nomogram to asses BOO in women. They analyzed a database of 600 consecutive women referred for evaluation with urodynamic study. They found BOO in 50 patients when using the following criteria: (1) Free $Q_{max} \leq 12$ mL/s in at least two free-flow studies, combined with a maintained contraction of the detrusor and $p_{det}Q_{max} \geq 20$ cm H_2O in the PFS; (2) evident radiographic proof of BOO with a sustained detrusor contraction ≥ 20 cm H_2O and poor Q_{max}, regardless of free Q_{max}; and (3) incapacity to void using a transurethral catheter despite maintained detrusor contraction ≥ 20 cm H_2O. This group of patients was compared to 50 age-matched controls with no evidence of obstruction, 20 with normal urodynamic study and 30 patients presenting sphinteric-incontinence. They used two parameters to assess BOO: (1) Free Q_{max} (noninvasive maximum flow rate) instead of invasive Q_{max}, given that many unobstructed patients presented low Q_{max} because of the adverse effect of the transurethral catheter on Q_{max}; and (2) p_{detmax} (maximum detrusor pressure during voiding) instead of $p_{det}Q_{max}$, because isolated test of the parameters did not reveal a difference considered statistically significant. Also because $p_{det}Q_{max}$ cannot be assesed in presence of urinary retention since there is no measurable flow regardless of the possible presence of a detrusor contraction (whereas p_{detmax} may enable analysis). The analysis reported that the data was distributed in three clusters: (1) Unobstructed group of patients presenting low pressure and high flow; (2) obstructed patients presenting high pressure and low flow; and (3) a group with low-to-intermediate pressure and flow rates, which was subdivided into two categories. A four-zone nomogram was developed (Figure 3). The

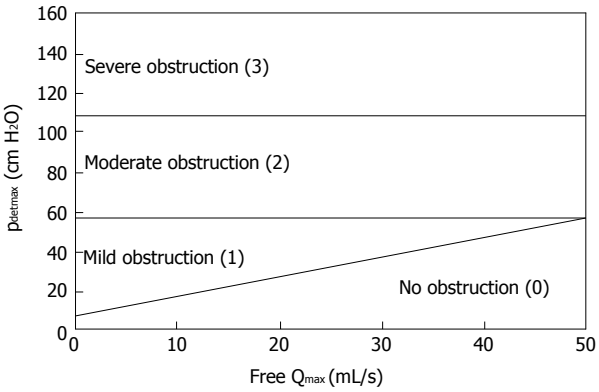

Figure 3 Bladder outlet obstruction nomogram for women. (From Blaivas *et al*[24]. Bladder outlet obstruction nomogram for women with lower urinary tract symptomatology. Neurourol Urodyn 2000; 19: 553; with permission).

boundaries between the four zones were: Between unobstructed and minimally obstructed: (1) A line with slope 1.0 and intercept 7 cm H_2O; *i.e.*, running through the point (0,7) and (50,57); (2) between minimally and moderately obstructed: A horizontal line at p_{detmax} of 57 cm H_2O; and (3) between moderately and severely obstructed: A horizontal line at p_{detmax} of 107 cm H_2O. Using this nomogram, all women with obstruction were correctly classified and further subclassified as mildly obstructed (68%), moderately obstructed (24%), and severely obstructed (8%). The authors found that subjective severity of symptoms (assessed by American Urological Association Symptom Score) was positively correlated to the zones of the nomogram. Of the patients classified as unobstructed, the nomogram correctly identified 80% as unobstructed, 8% as mildly obstructed, and 12% on the borderline between no obstruction and mild obstruction[24].

DU

DU is defined as a "detrusor contraction of reduced strength and/or duration, resulting in prolonged bladder emptying and/or a failure to achieve complete bladder emptying within a normal time span"[2]. This definition has remained unchanged through the last terminology report[3] and is based on two characteristics: (1) A weak strength of detrusor contraction; and (2) a short duration of the detrusor contraction. Both aspects of detrusor contractility seem to be independent. If the detrusor contraction is not adequately sustained, there will be postvoid residual urine[25].

The diagnosis of DU is based on pressure-flow studies and encompasses low-pressure, and poorly sustained contraction of the detrusor associated to low urinary flow[26]. There is no standard urodynamic test for diagnosing and quantifying DU and most measures only assess detrusor contraction strength and not duration[26,27]. It is challenging to make a correct diagnosis since measuring detrusor contraction strength is not easy and the criteria used for men are not applicable to women.

The presence of DU in several clinical groups suggests that its ethiopathogenesis tends to be multifactorial. Among non-neurogenic etiological factors leading to DU in women are: (1) Idiopathic cause due to physiological ageing, unknown causes in younger subjects; (2) myogenic: Long term BOO, overdistension injury, diabetes; (3) iatrogenic: Radical hysterectomy and pelvic surgery, abdominoperineal resection or anterior rectal resection; and (4) pharmacologic: Anticolinergic medication, tricyclic antidepressants[18,26].

According to the principles of voiding mechanics, detrusor contraction strength is expressed partially as pressure and partially as flow. Therefore the contraction strength is not the same as the pressure of the detrusor. In theory, the isovolumetric detrusor pressure obtained when there is interruption in flow or by continuous occluding with a balloon catheter, provides a good appraisal of detrusor contraction strength[28]. It also gives more reliable results than those obtained interrupting flow by voluntary contraction of the urethral sphincter due to reflex bladder contraction inhibition[29]. Because producing mechanical interruption of flow or continuous occlusion with a balloon catheter alters voiding, is difficult to perform and produces discomfort, other methods to estimate detrusor contraction strength have been developed based on the BOR. For example, if we know the slope and curvature of the BOR, we can estimate the isovolumetric detrusor pressure by extrapolating the pressure where it intersects the pressure axis[30].

Schafer simplified the BOR by using a straight line with a fixed slope of 5 cm H_2O/mL per second, not considering bladder volume, and obtaining the projected isovolumetric pressure (PIP) in men[5,6,30]. For a given void, PIP is assesed at the point of maximum flow rate. This was done using the following equation: $PIP = p_{det}Q_{max} + 5\ Q_{max}$. Schafer proposed that PIP values over 150 cm H_2O meant strong contractions; values from 100 to 150 cm H_2O, normal contractions; values from 50 to 100 cm H_2O, weak contractions; and values below 50 cm H_2O very weak contractions. He developed a contractility nomogram by drawing the corresponding BORs on a pressure-flow diagram, allowing the contraction strength to be classified in four groups[5,6,30]. Since 100 cm H_2O is a normal PIP value, the ratio PIP/(100 cm H_2O) is a coefficient with no dimension for which values over 1 represent normal or strong contractions, and values under 1, weak contractions. The ratio was nominated detrusor coefficient (DECO), and if it is expressed as a percentage it is numerically equal to PIP (in cm H_2O) and identical to the bladder contractility index (BCI) described later by Abrams[31].

Tan *et al*[30] compared stop-test isovolumetric pressures with approximate calculations based on pressure flow studies in a cohort of 100 women (mean age 70.1 years; range 53-89) suffering from urgency incontinence. Measurements were documented both pre- and post-treatment with placebo or oxybutynin. This allowed for investigation of test- retest reliability and

Table 2 Comparison of the reference isovolumetric pressure with estimates given by detrusor coefficient/bladder contractility index and projected isovolumetric pressure 1[1]

	Reference isovolumetric pressure (cm H_2O)	DECO/BCI ($p_{det}Q_{max}$ + 5 Q_{max})	PIP_1 ($p_{det}Q_{max}$ + Q_{max})
Mean ± SD (mean)	50 ± 25 (45)	133 ± 45 (128)	49 ± 17 (48)
5 and 95 percentiles	20/112	60/215	29/78
Mean difference (cm H_2O) from reference (95%CI: Wilcoxon signed ranks test)	-	86 (76-96; $P < 0.05$)	0.2 (-5 to 5; $P = 0.98$)
Spearman's coefficient of correlation with reference	-	0.21 ($P = 0.06$)	0.52 ($P < 0.01$)

[1]Modified from Tan *et al*[30]. DECO: Detrusor coefficient; BCI: Bladder contractility index; PIP_1: Projected isovolumetric pressure 1.

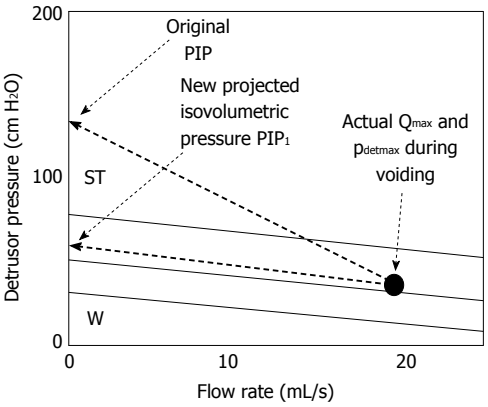

Figure 4 To determine projected isovolumetric pressure 1 the point representing the pressure and flow rate measured during uninterrupted voiding is projected back to the axis with a line of slope -1 cm H_2O/mL per second. (Note that the value of original PIP would be much larger). For this void, the value of PIP1 is about 60 cm H_2O, and the void falls in the band of typical values (unshaded). Values in the regions shaded gray would represent either ST or W contractions than those typical of the subjects in this group. (From Tan *et al*[30]. Stop test or pressure-flow study? Measuring detrusor contractility in older females. Neurourol Urodyn 2004: 23: 184 with permission). PIP: Projected isovolumetric pressure; ST: Stronger; W: Weaker.

responsiveness to small changes in contractility. They reported that the Schafer contractility nomogram and related parameters (DECO and BCI) used in men tend to greatly overestimate isovolumetric pressures in women. They suggested a modification called projected isovolumetric pressure 1 (PIP_1) which provided a more reliable estimate. This was based on the formula: $PIP_1 = p_{det}Q_{max} + Q_{max}$ (Figure 4). PIP_1 responded less to small changes in contraction strength than those observed for isovolumetric pressures measured using mechanical interference. Table 2 presents a comparison between the three variables. They concluded that in the group of elderly women with urgency incontinence, 90% of baseline PIP_1 values were observed between 29 and 78 cm H_2O. Thus, "contractions with PIP_1 smaller than about 30 cm H_2O might be considered unusually weak"[30].

Gotoh *et al*[32] studied the pathophysiology and subjective symptoms in 83 women with postvoid residual urine over 100 mL, most of whom had neurological diseases and postoperative problems after pelvic surgery. They defined impaired detrusor contraction in women who had Q_{max} less than 12 mL/s associated to $p_{det}Q_{max}$ less than 10 cm H_2O and significant rise in abdominal pressure[32]. In this study, the projected isovolumetric pressure to diagnose low detrusor contraction strength would be 20 cm H_2O, quite lower than the 30 cm H_2O proposed by Tan *et al*[30].

QUALITY CONTROL FOR PRESSURE-FLOW STUDIES IN WOMEN

The success of urodynamic studies depends on careful tuning of the equipment and strict quality control over each of the procedures. The ICS recommends using external transducers connected to fluid-filled tubings and catheters for intravesical and abdominal pressure recording. It also recommends circumspect and continuous observation of the signals as they are obtained and an ongoing assessment of their credibility to avoid artifacts which need to be corrected immediately, since they are difficult and often impossible to correct retrospectively[33]. This is especially true in women if we consider that relatively small changes in detrusor pressure (*i.e.*, 15 cm H_2O) can change the diagnosis from BOO to DU. The urodynamicists needs to avoid: (1) Damping of the abdominal pressure measurement specially during straining to void because it can create false high detrusor pressures; and (2) the use of catheter-mounted transducers or air-filled catheters, in which case the detrusor pressure measured depends on the position of the tip of the catheter within the bladder, with up to 8-10 cm H_2O differences if the tip of the catheter is at the top or at the bottom of the bladder[34,35]. Finally, it is important to remember that voluntary straining in healthy women can increase free Q_{max} by an average of 30%[36], making diagnosis of voiding dysfunction even more challenging.

Table 3 summarizes the urodynamic criteria used to define BOO and DU in women.

CONCLUSION

PFS of micturition is the best method to quantitatively analyze voiding function. Voiding dynamics differ significantly between men and women and the established criteria for urodynamic diagnosis in men do not apply to women. Although attempts have been made to standardize the diagnosis BOO in women, currently there is no consensus. There is no standard urodynamic test to

Table 3 Urodynamic criteria to define bladder outlet obstruction and detrusor underactivity in women

Bladder outlet obstruction	
Cutoff criteria[21]	$p_{det}Q_{max} \geq 25$ cm $H_2O + Q_{max} \leq 12$ mL/s
Video-urodynamic criteria[23]	Radiographic evidence of obstruction between the bladder neck and distal urethra in the presence of a sustained detrusor contraction of any magnitude, usually associated with reduced or delayed urinary flow rate
Nomogram[24]	See Figure 3
Detrusor underactivity	
Projected isovolumetric pressure 1[30]	$p_{det}Q_{max} + Q_{max} < 30$ cm H_2O
Cutoff criteria[32]	$p_{det}Q_{max} < 10$ cm $H_2O + Q_{max} < 12$ mL/s "and significant rise in abdominal pressure"

diagnose DU in women for which further investigations are needed. The diagnosis of voiding dysfunction in women is challenging and often involves consideration of clinical and radiographic data to make the final assessment.

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MINIREVIEWS

Chylous ascites in laparoscopic renal surgery: Where do we stand?

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Abstract

Postoperative chylous ascites, which is caused by the disruption of lymphatic channels and persistent lymphatic leakage, was a rare complication in the urologic field before laparoscopic surgery was introduced. Now that laparoscopic urologic surgery, especially laparoscopic nephrectomy, is widely performed, chylous ascites as a complication of laparoscopic renal surgery has been reported more frequently. With these accumulated experiences and data comes knowledge about the proper diagnosis and management of chylous ascites, although there is still some debate regarding the correct protocol for diagnosis and management. Therefore, we performed a systematic review of the current literature regarding the etiology, incidence, diagnosis, management, and prognosis of chylous ascites after laparoscopic renal surgery, as well as strategies used to prevent it, and discuss current perspectives on overcoming this complication in the laparoscopic age.

Key words: Chylous ascites; Kidney; Laparoscopy; Nephrectomy; Postoperative complications

Core tip: Now that laparoscopic renal surgery is widely performed, postoperative chylous ascites is encountered more frequently. Although most cases can be managed conservatively without any critical sequelae, severe refractory cases may cause malnutrition and immunological deficiency and require interventional treatment. To overcome this complication, early diagnosis and proper choice of management strategies are necessary. Moreover, understanding the mechanism of and postoperative chylous ascites preventing its occurrence are the most important factors. Meticulous clipping around the great vessels and the use of hemostatic agents during laparoscopic nephrectomy can reduce the incidence of postoperative chylous ascites.

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INTRODUCTION

Since Clayman *et al*[1] first reported the use of laparoscopic nephrectomy in 1991, the technique has been widely performed and includes simple, living-donor, radical, partial nephrectomy and nephroureterectomy. There are several advantages of laparoscopic nephrectomy, such as reduced blood loss and postoperative pain, faster recovery, better cosmesis, and an earlier return to normal activities compared to open nephrectomy. Although laparoscopic nephrectomy has gained popularity due to these merits, unique complications are associated with this technique[2-5].

Chylous ascites, which is the accumulation of chyle in the peritoneal cavity, is mostly caused by diseases that interfere with the abdominal or retroperitoneal lymphatic glands[6]. Postoperative chylous ascites, which is caused by the disruption of lymphatic channels and persistent chyle leakage, was a rare complication in urologic field before the introduction of laparoscopic surgery[6,7]. The reported incidence of chylous ascites after laparoscopic nephrectomy ranges from 0.013% to 5.9% and is more common after radical or donor nephrectomy[7-12]. Although most cases of chylous ascites after laparoscopic nephrectomy can be successfully managed conservatively without critical sequelae, severe refractory cases can develop even with proper medical management. These severe refractory cases can cause devastating complications such as malnutrition, infection, and immunological deficiency and often require invasive and aggressive treatment, because chyle is rich in fat, lymphyocytes and immunoglobulins, therefore, loss of chyle means a loss of nutritional energy and immunocompetence[6].

To our knowledge, the first case of chylous ascites after laparoscopic nephrectomy was reported by Shafizadeh *et al*[13] in 2002. It occurred after laparoscopic donor nephrectomy, and the patient was conservatively managed with an elemental diet and diuretics for 2 wk. Since that time, many case reports as well as large population-based studies have reported chylous ascites after laparoscopic nephrectomy. Although many studies demonstrated that chylous ascites after laparoscopic nephrectomy is rare, it seems this complication occurs more frequently after laparoscopic renal surgery than after open procedures.

Because laparoscopic renal surgery is becoming more common, urologists need to know how to properly diagnose and manage postoperative chylous ascites. Here, we review the current literature related to chylous ascites after laparoscopic renal surgeries as well as open procedures and discuss current perspectives on the development, management, and prevention of this complication.

LITERATURE SEARCH

We performed a PubMed search of the literature on chylous ascites after laparoscopic renal surgery using "chylous ascites" or "chyloperitoneum" and "nephrectomy" as the subject heading. The search yielded 58 articles, 46 of which were related to chylous ascites after renal surgery. Most (31 articles) were case reports, and of the studies with results distinguished by type of surgery, 20 studies involved donor nephrectomy, 17 involved radical nephrectomy, 7 involved simple nephrectomy, 4 involved nephroureterectomy, and 2 involved partial nephrectomy. Among these, 28 articles were associated with laparoscopic nephrectomy, including 4 retroperitoneoscopic procedures.

ETIOLOGY AND INCIDENCE

Chylous ascites can be caused by several pathological conditions, such as congenital defects of the lymphatic system, malignant neoplasm, liver cirrhosis, blunt or surgical trauma, surgical injury to the lymphatic channels, and peritoneal infections caused by nonspecific bacteria, parasite and tuberculosis[6]. Abdominal malignancy in adults and congenital lymphatic abnormalities in children are the most common causes of chylous ascites[14]. Meanwhile, postoperative chylous ascites was a rare complication, especially in the urologic field. The mechanism of postoperative chylous ascites is operative damage to the thoracic duct, cisterna chili, or other major retroperitoneal lymphatic channel that results in lymphoperitoneal fistula formation and accumulation of chyle in the peritoneal cavity[6,7]. Thus, abdominal aortic surgery is the most common cause of postoperative chylous ascites, accounting for more than 80% of postoperative chylous complications[15]. Although the main cause of postoperative chylous ascites is abdominal aortic surgery, spinal surgeries that use a transabdominal approach or gynecologic and urologic surgeries have also been reported to cause this complication. Postoperative chylous ascites in the urologic field has traditionally been reported after retroperitoneal surgery involving extensive lymphadenectomy for testicular or kidney cancer[16-25].

Since the introduction of laparoscopy to the field of urologic surgery, reports of chylous ascites following laparoscopic nephrectomy have become more frequent[7-9,11-13,26-46]. The reported incidence of chylous ascites after laparoscopic nephrectomy ranges from 0.6% to 5.9%[7-11]. The proposed cause for this increased incidence of chylous ascites after laparoscopic nephrectomy is that lymphatics are not routinely ligated during laparoscopic surgery, even though they are usually burned with energy-based sealing devices such as monopolar or bipolar electrocautery and ultrasonic shears[9,11,47,48]. Although chylous ascites after laparoscopic nephrectomy

is frequently reported, reported incidence of chylous ascites was quite different. These differences in incidence may be due to the differences in surgical technique among surgeons and the placement and indwelling time of the drainage catheter. If a surgeon prefers wide dissection and extensive lymphadenectomy during laparoscopic radical nephrectomy and usually performs extensive dissection around the hilar area and skeletonizing renal pedicle, aorta, and/or inferior vena cava during any type of laparoscopic nephrectomy, the incidence of postoperative chylous ascites may increase. In addition, many milder cases of chyle leak due to minor lymphatic channel disruption can improve spontaneously, without the need for any additional treatment. However, routine placement of the drainage catheter and indwelling it until oral intake is resumed may lead to early diagnosis of these milder cases of chylous ascites, which can spontaneously improve and may not be diagnosed if a drainage catheter is not placed[7]. This may be another reason for the variation in the reported incidence of chylous ascites after laparoscopic nephrectomy.

DIAGNOSIS

Chylous ascites is defined by the presence of chylomicrones, which are however difficult to measure, so that triglycerides are usually taken as surrogate parameters. Use of an indwelling drainage catheter is the easiest and earliest means by which to diagnose postoperative chylous ascites. If the color of the drainage fluid changes to milky white, chylous ascites can be suspected. However, if a drainage catheter is not placed, early diagnosis is difficult. Moreover, the milky aspect may be misleading if the patient is fasting (in the absence of fat absorption, no triglycerides are transported) or if the ascites is chylous and bloody, which may resemble pus. Clinical diagnosis can be made by physical signs and symptoms of peritoneal fluid accumulation, similar to those of ascites due to other causes, including abdominal distention, dyspnea due to limitations of diaphragmatic movement, and weight gain. Nonspecific gastrointestinal symptoms such as nausea, vomiting, dyspepsia, and rarely wound site ascites leakage can be present. Most studies did not mention the time to presentation of these symptoms, but it is generally variable, ranging from several days to months after surgery[6].

When patients present these symptoms and accumulation of ascitic fluid is found by physical examination and/or imaging studies, such as abdominal ultrasound or computed tomography (CT), chylous ascites can be confirmed by analyzing the ascites obtained by diagnostic paracentesis. It is typically milky in color, odorless, and sterile, and it has a high triglyceride content (usually 2- to 8-fold that of plasma or greater than 150-200 mg/dL)[6,7]. However, sterility is not necessary for the diagnosis of chylous ascites, which may become superinfected.

Several imaging techniques can be used to diagnose chylous ascites. CT can be used to confirm the accumulation of ascitic fluid in the peritoneal cavity, but CT findings are not specific to chylous ascites, and it is indistinguishable from urine, bile, bowel secretions, and simple ascites[6,49]. Lymphangiography is useful for the diagnosis of chylous ascites, enabling localization of the exact site of injury to the lymphatic channels[50]. However, an invasive procedure must be performed to find the exact site of chyle leakage, which is not necessary for cases that can be managed conservatively. Thus, lymphangiography should be considered for patients in whom conservative treatment fails and for whom surgical repair is planned to localize the exact site of chyle leakage[7]. Lymphoscintigraphy and radionuclide scans, such as a simple diaminetriamine-pentaacetic acid renal scan, can also be used as noninvasive, physiological radiologic diagnostic tools for the diagnosis of chylous ascites. Lymphoscintigraphy may be especially useful when lymphangiography is contraindicated[51], and it can also be used during patient follow-up to confirm a decrease or cessation of chyle leakage[52]. These imaging techniques may indicate the cause of chylous ascites, but are not adequate to diagnose chylous ascites.

MANAGEMENT

Although the severity of chylous ascites varies, several cases may spontaneously resolve without any specific treatment, because a small amount of ascitic fluid can be absorbed in the peritoneal cavity and a small leakage site of the lymphatic channel can close spontaneously. Therefore, many clinically insignificant cases might not be detected if a drain tube is not routinely placed after surgery. This may explain why the incidence of chylous ascites after laparoscopic nephrectomy is lower in most studies than in those conducted by Kim *et al*[7] and Capocasale *et al*[9].

Several strategies have been used to treat postoperative chylous ascites, and some investigators have reported their own management protocol[6,11]. Although there is still some debate over the correct approach, most authors advocate conservative treatment as an initial treatment modality[6,7,9,11,28]. Conservative treatment aims to decrease mesenteric lymphatic flow and consequently limit the leakage of chyle into the peritoneum. Moreover, other goals of conservative treatment are relief of the mechanical symptoms, such as abdominal distention, and restoration of nutritional losses. The success rate of conservative treatment ranges from 67% to 100%[6,10,11].

Conservative treatment includes therapeutic paracentesis, dietary modification, total parenteral nutrition, and the use of somatostatin analogs. If the drainage tube is placed when chylous ascites is detected, natural continuous drainage of ascitic fluid can be expected and accumulation of ascites in the peritoneal cavity can be prevented. However, in cases of delayed suspicion of chylous ascites without a drainage tube, paracentesis may be necessary to confirm the diagnosis of chylous ascites and relieve abdominal fullness. Nevertheless,

there are some concerns that repeat paracentesis or permanent drainage catheter placement may cause prolonged leakage, increasing both nutritional and immunological depletion and the risk of infection[6,17,53,54]. Intravenous reinfusion of ascitic fluid may prevent the nutritional losses associated with paracentesis or percutaneous drainage, but this carries the risk of serious complications, such as fat embolism and infection[55].

Dietary intervention, which includes medium-chain triglycerides and high-protein and low-fat intake, is normally used as a first-line treatment. It can reduce the lymphatic flow in the major lymphatic channels and facilitate the closure of chylous leakage[6,9]. Approximately 50% of mild cases of chylous ascites can be resolved using dietary intervention alone, and this treatment should be continued for several weeks or months to prevent recurrences[6,11].

Total parenteral nutrition is also an effective conservative management modality for postoperative chylous ascites. It can reduce the production and flow of lymph by allowing the bowels to rest[6]. The success rate of total parenteral nutrition alone or combined with a medium-chain triglyceride, high-protein, and low-fat diet for several weeks ranges from 60% to 100%[6,7,9,11]. Many investigators recommend total parenteral nutrition as a second-line treatment when conservative management with dietary modification fails. However, several studies, including our previous study, demonstrated that an early trial of total parenteral nutrition in patients with postoperative chylous ascites may be more effective and facilitate earlier improvement[7,53]. Total parenteral nutrition can also be used as a last treatment regimen when interventional or surgical treatment fails[6]. More recently, Jairath *et al*[11] suggested that if the daily drainage output of chylous ascites is less than 500 mL, dietary modification should be tried first, but if the drain output is greater than 500 mL per day, total parenteral nutrition should be used as a first-line treatment.

Since Ulíbarri *et al*[56] reported the effectiveness of continuous intravenous high-dose somatostatin for the closure of postoperative lymphatic drainage in 1990, somatostatin and its analogs are widely used, although their exact mechanism of action is not clearly understood[11]. Somatostatin is known to decrease the intestinal absorption of fats and attenuate lymphatic flow in the major lymphatic channels. Moreover, it reduces gastric, pancreatic, and intestinal secretions, inhibits intestinal activity and slows intestinal absorption, and decreases splanchnic blood flow, which may contribute to reduced lymphatic production[6]. Based on these data and clinical experience, earlier use of somatostatin and its analogue are highly recommended in combination with dietary intervention[6,11].

Although many cases of postoperative chylous ascites can be successfully managed using conservative treatment, there are severe refractory cases that require surgical repair. The purpose of surgical repair is direct ligation of the chyle leakage site. It was historically performed using an open procedure, but with the development of laparoscopic techniques, successful management can be expected using a laparoscopic approach[34,38,57]. Although the exact timing of surgical intervention remains controversial, previous studies recommend 4 to 12 wk of conservative treatment before surgery[6,7,9,11]. However, some authors have recommended early interventional treatment to provide a better chance of direct visualization of the injured lymphatics and definite repair, thus preventing nutritional and immunological deficiency and prolonged hospitalization[6,58,59]. Since the most important step in surgical repair is to identify the chylous leakage point, several authors have suggested milk ingestion or a high-fat diet before surgery or intravenous indigo carmine injection during surgery[34,60]. If a leakage point cannot be identified, nonselective suturing of the periaortic or pericaval tissues can resolve chyle leakage. In addition, application of a hemostatic agent, such as fibrin glue, can also effectively occlude disrupted lymphatic channels[6,9].

Alternatively, peritoneovenous shunting and percutaneous transabdominal embolization can be performed, especially in patients with poor performance status and persistent severe chyle leakage[6,61-63]. Although peritoneovenous shunting does not cause nutritional deficiency, as ascitic fluid is recirculated, and has a lower risk of infection compared to repeat paracentesis, it can also carry the risk of serious complications, such as fat embolism, disseminated intravascular coagulation, and sepsis[6,11,53]. Cope *et al*[62] reported successful embolization of the lymphatic ducts using a transabdominal percutaneous puncture, but there are limited data related to percutaneous embolization, and more studies are needed to validate the efficacy and safety of this procedure.

PROGNOSIS

Chylous ascites after laparoscopic nephrectomy is most commonly reported after living-donor nephrectomy, although it can occur after any type of laparoscopic nephrectomy (radical, partial, simple, nephroureterectomy, or donor) (Table 1). The success rate of conservative treatment in published studies of laparoscopic nephrectomy ranges from 50% to 100%, except in case reports or original articles involving only 1 or 2 cases of chylous ascites[7,9,11,12,44]. In this review, 89 patients of chylous ascites after laparoscopic nephrectomy were included from original articles and case reports. Of these patients, 70 cases (78.7%) were success fully managed by conservative treatment (Table 1).

The prognosis of chylous ascites depends on the underlying pathological disease and can be poor, as mortality rates can be as high as 43% to 83%[6,55,64]. However, the prognosis of postoperative chylous ascites is generally favorable, with a significantly lower mortality rate[6,53]. Although it is likely that published reports of chylous ascites after laparoscopic nephrectomy contain more severe cases, most of these cases were successfully

Table 1 Previously reported cases of chylous ascites after laparoscopoic nephrectomy

Ref.	Type of laparoscopic nephrectomy	Success rate of conservative treatment (%)	Interventional treatment
Original articles			
Jairath *et al*[11]	Radical, donor, simple	67.7 (6/9)	Surgery
Tiong *et al*[12]	Donor	50 (5/10)	Surgery
Wan *et al*[44]	Partial	100 (5/5)	
Capocasale *et al*[9]	Donor	100 (8/8)	
He *et al*[31]	Donor	0 (0/1)	Surgery
Kim *et al*[3]	Radical, donor, simple, partial, nephroureterectomy	96.9 (31/32)	Surgery
Breda *et al*[8]	Donor	100 (2/2)	
Wadström[43]	Donor	0 (0/1)	Surgery
Ramani *et al*[39]	Donor	0 (0/1)	Surgery
Wu *et al*[45]	Donor	100 (1/1)	
Seo *et al*[46]	Donor	100 (2/2)	
Case reports			
Monge Mirallas *et al*[35]	Radical	100 (1/1)	
Itou *et al*[65]	Radical	0 (0/1)	Percutaneous obliteration
Fariña *et al*[29]	Radical	100 (1/1)	
Nishizawa *et al*[38]	Radical	0 (0/1)	Surgery
Meulen *et al*[33]	Donor	100 (1/1)	
Gagliano *et al*[30]	Donor	100 (1/1)	
Sinha *et al*[41]	Donor	0 (0/1)	Surgery
Aerts *et al*[26]	Donor	0 (0/1)	Surgery
Caumartin *et al*[28]	Donor	0 (0/1)	Surgery
Bachmann *et al*[27]	Donor	100 (1/1)	
Sharma *et al*[40]	Donor	100 (1/1)	
Molina *et al*[34]	Donor	0 (0/1)	Surgery
Shafizadeh *et al*[13]	Donor	100 (1/1)	
von Rundstedt *et al*[42]	Nephroureterectomy	100 (1/1)	
Negoro *et al*[37]	Nephroureterectomy	50 (1/2)	Sclerotherapy
Jensen *et al*[32]	Simple	100 (1/1)	

managed using conservative treatment. Moreover, even cases managed using interventional therapy successfully improved without any critical sequelae. Thus, one can expect a good prognosis if early diagnosis and proper management are achieved, although some severe cases will need to be managed using interventional therapy.

PREVENTION

With accumulated experience and understanding of the mechanisms of occurrence, early diagnosis and proper management of postoperative chylous ascites can be facilitated. However, although the incidence of postoperative chylous ascites is not very high, this complication can decrease a patient's quality of life and prolong hospitalization. Thus, the best treatment strategy is obviously the prevention of postoperative chylous ascites during the initial surgery. In our experience, appropriate lymphostasis cannot be achieved with monopolar, bipolar, or ultrasound devices, which are the most commonly used for hemostasis in laparoscopic nephrectomy[7]. Therefore, lymphatic channels should be identified and carefully divided during surgery (Figure 1A). In addition, if disruption of the lymphatic channels occurs and extravasation of lymphatic fluid is recognized intraoperatively, careful ligation of the lymphatic duct using hemoclips should be performed (Figure 1B). Moreover, empirical application of hemostatic agents over the dissected area, such as biological tissue adhesive and fibrin glue, can also be helpful, regardless of whether lymphatic disruption or extravasation is identified[9] (Figure 1C). Furthermore, the placement of a drainage tube in patients who are suspected to be at high risk of postoperative chylous ascites, such as obese patients, those undergoing extensive lymphadenectomy, or patients with obvious lymphatic leakage during surgery, can be useful for the early diagnosis of chylous ascites.

CONCLUSION

As laparoscopic nephrectomy has gained popularity, postoperative chylous ascites is no longer a very rare complication. Although many studies have reported a good prognosis for postoperative chylous ascites, it can become a highly morbid complication of laparoscopic renal surgery that requires early diagnosis and proper management. The treatment strategy should be individualized according to the severity of chylous ascites and its consequences. Initial management should be conservative treatment using high-protein, low-fat dietary modification with medium-chain triglycerides, total parenteral nutrition, and somatostatin or its analogs for several weeks. Depending on the severity of chylous ascites and the response to conservative treatment, interventional therapy including surgery, sclerotherapy, and peritoneovenous shunting should be considered. The prevention of postoperative chylous ascites is the most important factor. Therefore, careful dissection of the

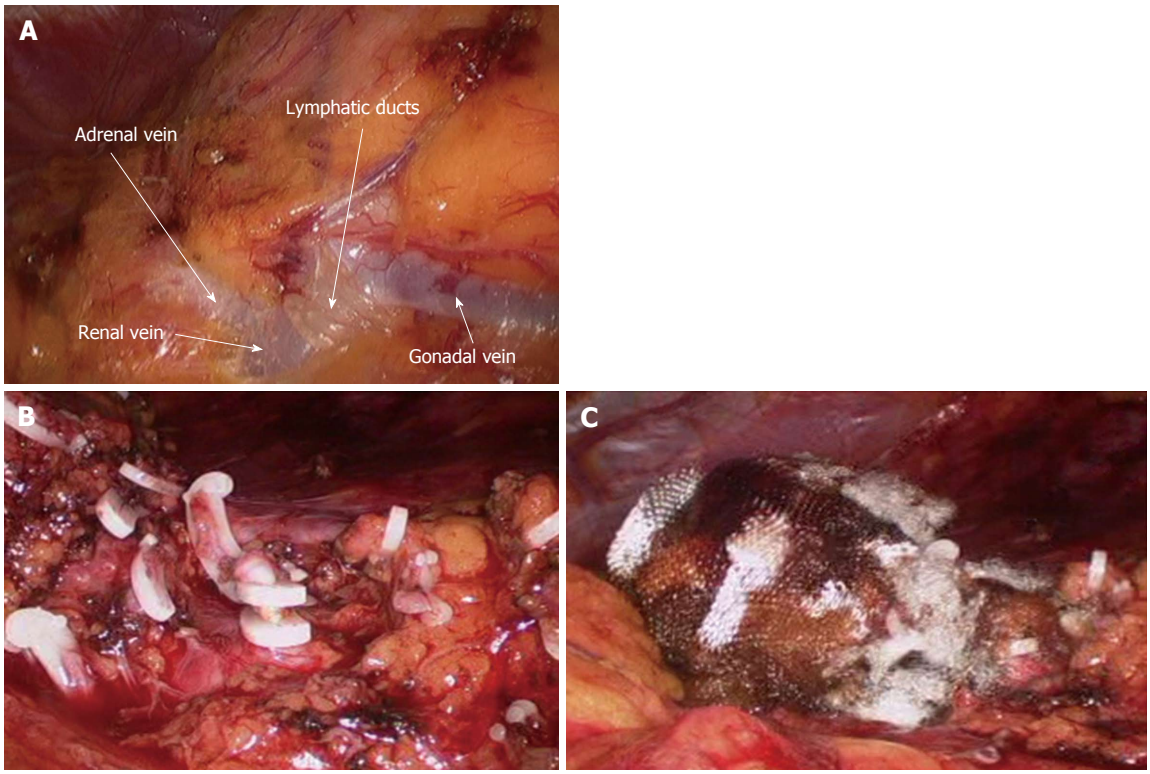

Figure 1 Intraoperative image of the hilar area during left-sided laparoscopic donor nephrectomy. A: Prominent lymphatic ducts cross the renal vein; B: The perihilar and retroperitoneal fatty tissue is meticulously clipped; C: The hilar area is completely sealed using surgicel and fibrin glue.

great vessels and renal pedicle, meticulous clipping and application of hemostatic agents to the area of perihilar and retroperitoneal fatty tissue, and placement of a drainage tube is highly recommended in patients at high risk of chylous ascites.

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ORIGINAL ARTICLE

Retrospective Cohort Study

Adjuvant radiotherapy for pathologically advanced prostate cancer improves biochemical recurrence free survival compared to salvage radiotherapy

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Abstract

AIM: To evaluate the long-term outcomes of patients receiving adjuvant and salvage radiotherapy following prostatectomy with adverse pathologic features and an undetectable prostate specific antigen (PSA).

METHODS: A retrospective review was performed of patients who received post-prostatectomy radiation at Loyola University Medical Center between 1992 and 2013. Adverse pathologic features (Gleason score ≥ 8, seminal vesicle invasion, extracapsular extension, pathologic T4 disease, and/or positive surgical margins) and an undetectable PSA following prostatectomy were required for inclusion. Adjuvant patients received therapy with an undetectable PSA, salvage patients following biochemical recurrence (BCR). Post-radiation BCR, overall survival, bone metastases, and initiation of hormonal therapy were assessed. Kaplan-Meier time-to-event analyses and stepwise Cox proportional hazards regression (HR) were performed.

RESULTS: Post-prostatectomy patients (n = 134) received either adjuvant (n = 47) or salvage (n = 87) radiation. Median age at radiotherapy (RT) was 63

years, and median follow-up was 53 mo. Five-year post-radiation BCR-free survival was 78% for adjuvant *vs* 50% salvage radiotherapy (SRT) (Logrank P = 0.001). Patients with radiation administered following a detectable PSA had an increased risk of BCR compared to undetectable: PSA > 0.0-0.2: HR = 4.1 (95%CI: 1.5-11.2; P = 0.005); PSA > 0.2-1.0: HR = 4.4 (95%CI: 1.6-11.9; P = 0.003); and PSA > 1.0: HR = 52 (95%CI: 12.9-210; P < 0.001). There was no demonstrable difference in rates of overall survival, bone metastases or utilization of hormonal therapy between adjuvant and SRT patients.

CONCLUSION: Adjuvant RT improves BCR-free survival compared to SRT in patients with adverse pathologic features and an undetectable post-prostatectomy PSA.

Key words: Radiotherapy; Adjuvant; Radiotherapy; Salvage therapy; Recurrence; Prostatic neoplasms

Core tip: We evaluated the outcomes of patients who received post-prostatectomy radiotherapy (RT) who had adverse features on the pathologic specimen and an immediately undetectable prostate specific antigen (PSA) postoperatively. In this cohort of patients, those who received RT in the adjuvant therapy (*e.g.*, while PSA remains undetectable) had an improved 5-year biochemical recurrence (BCR)-free survival of 78%, compared to 50% for patients receiving RT in the salvage setting (*e.g.*, after the postoperative PSA has again become detectable). As such, adjuvant RT improves BCR free survival in post-prostatectomy patients with adverse pathologic features and an undetectable PSA compared to salvage RT.

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INTRODUCTION

An estimated 233000 men in the United States will be diagnosed with prostate cancer (PCa) in 2014[1]. While radical prostatectomy (RP) is a curative treatment for many patients, approximately one-third of patients will experience recurrence of disease within 10 years of surgery[2-4]. Pathological features such as positive surgical margins (PSM), seminal vesicle invasion (SVI), extracapsular extension (ECE), Gleason score ≥ 8, and/or pathologic adjacent organ invasion are associated with a higher risk of biochemical recurrence (BCR)[5-8]. In these high risk patients adjuvant radiotherapy (ART) can be offered, however this leads to overtreatment of approximately 55% of patients who may never experience a BCR[4,9]. Patients who defer initial adjuvant therapy are closely monitored and offered salvage radiotherapy (SRT) if and when they experience BCR.

Three randomized controlled trials (SWOG 8794, EORTC 22911, and ARO 96-02) have been conducted comparing ART with observation following RP in patients with adverse pathologic features and an undetectable prostate specific antigen (PSA). These have demonstrated improved BCR-free survival with ART compared with observation (patients may or may not have received SRT)[5,6,10,11]. Despite these convincing data, only approximately 11.7% of patients with pT3-4N0 disease undergo ART according to an analysis of the Surveillance Epidemiology and End Results database[12]. Investigation into SRT in this same patient population (adverse pathologic features with undetectable PSA) has not been as purposefully studied in randomized controlled trials, although several retrospective studies[9,13-18], including two matched-control analyses[17,18], have been performed in this area.

In this study, we present our experience with the outcomes of ART and SRT in post-RP patients at a high risk for recurrence, with adverse pathologic features and an initial post-RP undetectable PSA.

MATERIALS AND METHODS

Patient selection

Following institutional review board approval a retrospective chart review was performed. All patients who were counseled for RT for PCa between 1992 and 2013 were identified. Of the 886 patients who subsequently received RT at our institution, 248 had a history of prior RP.

The patient demographic and pathologic PCa information listed in Table 1 was abstracted from *via* a comprehensive review of physician notes and laboratory reports (bloodwork, pathology reports, *etc.*).

Post-prostatectomy RT patients were grouped according to pathologic characteristics, postoperative PSA nadir level, and the timing of administration of post-prostatectomy RT (before/after BCR). Adjuvant therapy candidates were defined as patients with one or more adverse pathologic features (total Gleason score ≥ 8, SVI, PSM, ECE, and/or adjacent organ invasion) and an undetectable post-RP nadir PSA level. For this study, an undetectable PSA was defined as a PSA with a value of < 0.05 ng/mL. Patients with a detectable post-RP PSA (n = 54, 21.8%), the absence of adverse pathologic features (n = 50, 20.2%), or both of the aforementioned criteria (n = 10, 4.0%) were not considered to be adjuvant therapy candidates and excluded from analysis. Adjuvant therapy candidates who received RT with an

Table 1 Patient characteristics

		Received adjuvant therapy	Adjuvant candidate and received salvage radiotherapy	*P* value
Age at RT (median, IQR), mo		60 (54-65)	63 (59-68)	0.2
Follow-up (mo)		53 (19-83)	50 (22-854)	0.1
Time from RP to RT, mo	0-12	43 (93%)	12 (14%)	< 0.001
	> 12-24	3 (7%)	18 (21%)	
	> 24-48	0 (0%)	29 (33%)	
	> 48	0 (0%)	28 (32%)	
Pre-RT PSA	Undetectable	46 (100%)	0 (0%)	< 0.001
	> 0-0.2	0 (0%)	39 (46%)	
	> 0.2-1.0	0 (0%)	38 (45%)	
	> 1.0	0 (0%)	7 (8%)	
Received	No	37 (79%)	67 (77%)	0.8
Peri-RT ADT	Yes	10 (21%)	20 (23%)	
Coronary artery disease	No	36 (86%)	64 (84%)	0.8
	Yes	6 (14%)	12 (16%)	
Diabetes mellitus, type Ⅱ	No	37 (88%)	58 (76%)	0.1
	Yes	5 (12%)	18 (24%)	
Hypertension	No	19 (45%)	37 (49%)	0.6
	Yes	23 (55%)	39 (51%)	
Obesity	No	31 (74%)	51 (67%)	0.4
	Yes	11 (26%)	25 (33%)	
Peripheral vascular disease	No	39 (93%)	73 (96%)	0.4
	Yes	3 (7%)	3 (4%)	
Smoking history	No	37 (88%)	70 (92%)	0.5
	Yes	5 (12%)	6 (8%)	
Pathologic	2-6	9 (20%)	18 (21%)	0.4
Gleason score	7	21 (48%)	48 (57%)	
	8-10	14 (32%)	18 (21%)	
Pathologic	T1	0 (0%)	0 (0%)	0.08
Tumor stage	T2	11 (25%)	35 (41%)	
	T3/T4	33 (75%)	51 (59%)	
Positive surgical margin	Absent	12 (25%)	28 (32%)	0.4
	Present	35 (75%)	59 (68%)	
Extracapsular extension	Absent	20 (43%)	41 (47%)	0.6
	Present	27 (57%)	46 (53%)	
Seminal vesicle invasion	Absent	37 (79%)	80 (92%)	0.03
	Present	10 (21%)	7 (8%)	

RP: Radical prostatectomy; RT: Radiotherapy; IQR: Interquartile range; ADT: Androgen deprivation therapy; PSA: Prostate specific antigen.

undetectable PSA were classified as having received ART. Salvage therapy candidates were defined as those who following an undetectable postoperative PSA level, who later developed a detectable PSA level. Phoenix criteria of post-RP BCR were utilized (a PSA of ≥ 0.2 ng/mL, with a second consecutive test at or above this level) to define BCR following RT[19].

Treatment

Standard post-prostatectomy RT was provided to patients as either adjuvant or SRT (as above) and administered at 66.6 Gy fractionated over approximately 37 doses to the prostatic fossa and seminal vesicle remnants, if present.

Endpoints

The outcomes of interest that were evaluated include time to BCR, overall survival (OS), bone metastasis (BMet), and hormonal therapy (HT). BCR was considered to take place on the date of the first of two or more successive PSA values ≥ 0.2 ng/mL after RT. OS was defined as death from any cause. BMet was defined as any radiologic, pathologic, or clinical evidence of bony metastasis. HT was defined the initiation of androgen deprivation therapy following post-RT BCR.

Statistical analysis

Kaplan-Meier method was utilized to analyze BCR-, OS-. BMet, and HT-free survival functions. The time span between the event of interest and the final day of RT was analyzed. Patients entered the model at the date of completion of RT. If an event did not occur, the patient was considered to be right-censored for that event with the time between the day of the last follow-up and the final day of RT. A stepwise Cox proportion hazard regression was modelled to evaluate the independent effect of the categorical variables and treatment modalities in Table 1. Variables were selected in a forward fashion, with P = 0.05 meeting the standard for inclusion into the model. Variables with $P \geq 0.10$ were deemed insignificant and removed from the model.

SPSS® version 20 (SPSS, Chicago, IL), was utilized, with all comparisons 2-sided and a P-value < 0.05 was

considered statistically significant.

RESULTS

Between 1992 and 2013 our institution treated 886 patients with RT for PCa, of whom 248 received post-prostatectomy RT. Patients with adverse pathologic features, an undetectable nadir PSA, and who received post-RP RT accounted for 134 patients. Of these, 47 (35%) received ART and 87 (65%) received SRT. The median follow-up after RT was 53 (22-96) mo, and median age at RT was 63 (58-68) years old (Table 1).

For patients receiving ART *vs* SRT, pre-RT patient characteristics differed only in time from RP to RT (93% ART patients received therapy within 12 mo, compared with 14% SRT, $P < 0.001$), pre-RT PSA level (undetectable in 100% ART and 0% SRT, $P < 0.001$), and a higher rate of SVI in the ART cohort (12% *vs* 8%, $P = 0.028$). Medical comorbidities were comparable between the groups. There were no statistical differences in total Gleason score or frequency of PSM, ECE, or pathologic T4 disease between the two treatment groups.

BCR free survival

Kaplan-Meier 5-year BCR-free survival were 78% and 50% for ART and SRT, respectively (Logrank, $P = 0.001$) (Figure 1). On univariate analysis, receipt of RT at an undetectable level, and pathologic Gleason score < 8 were associated with improved BCR-free survival. On multivariate analysis, the predominant factor associated with BCR was PSA level at time of RT. Compared with RT administered with an undetectable PSA (ART), BCR was more likely when RT was administered as SRT with detectable pre-RT PSA levels as follows: > 0.0 to 0.2 ng/mL (HR = 4.1; $P = 0.005$), > 0.2-1.0 ng/mL (HR = 5.5; $P = 0.003$), and ≥ 1.0 ng/mL (HR = 52, $P < 0.001$) (Table 2). A sensitivity analysis was performed with pre-RT cutoff of PSA ≤ 0.5 ng/mL compared to undetectable, which demonstrated a similar improved BCR-free survival with adjuvant therapy (data not shown). Pathologic Gleason score of ≥ 8 also increases risk of BCR in the multivariate model (HR = 3.1; $P = 0.02$).

OS

Kaplan-Meier estimates of 5-year OS were 97% for both ART and SRT patients. A total of 3 (6%) ART and 8 (9%) SRT patients have died since RT (Logrank, $P = 0.5$). No variables contributed to OS on multivariate analysis (Table 2).

Bone metastasis

Five-year actuarial risks of bone metastasis were 0% and 6% for ART and SRT, respectively (Logrank, $P = 0.9$). Three ART patients (6%) and five SRT patients (6%) developed metastatic disease to the bone over the course of follow-up. On univariate analysis, patients who received ART had improved bone metastasis-free survival (Logrank $P = 0.004$). On multivariate analysis, patients who received SRT with a PSA ≥ 1.0 had an increased risk of bone metastases (HR = 39.806; $P = 0.02$) compared to patients who received ART (undetectable PSA) (Table 2).

Time to hormonal therapy

There was trend toward decreased utilization of hormonal therapy at 5 years post-RT in ART (6%) compared with SRT (21%) patients (Logrank, $P = 0.08$). Median time from RT to additional treatment was 218 mo for ART and 142 mo for SRT. Based on pre-RT PSA level, there was a worse HT-free survival in patients receiving RT with a PSA > 1.0, which remained true on multivariate analysis (HR = 67.841; $P < 0.001$) (Table 2). A sensitivity analysis run with pre-RT PSA ≤ 0.5 ng/mL compared to undetectable demonstrated a similar risk of progression to HT. With a PSA >0.5 ng/mL, there was an increased risk of receipt of HT (data not shown). Further, a pathologic Gleason score of 8-10 was associated with an increased risk for receipt of HT on univariate and multivariate analyses (Table 2).

DISCUSSION

Our results demonstrate that patients with adverse pathologic features (Gleason 8-10, SVI, ECE, PSM, and/or pathologic T4 disease) and an undetectable PSA have improved oncologic results with ART compared to SRT. When patients were observed until PSA became detectable and then received SRT there was an increased risk of post-RT BCR, even in the early RT (PSA < 0.2) setting. When SRT was administered with a pre-RT PSA level > 1.0, the risk of BCR, BMet and HT increased dramatically. While pathologic Gleason score 8-10 was also associated with BCR, and both pathologic Gleason 8-10 and SVI were associated with progression to HT, the receipt of RT prior to detectable PSA was shown to be the only modifiable risk factor available to the treating clinician to impact BCR-free survival.

Three randomized controlled trials (SWOG 8794, EORTC22911, and ARO 96-02) have definitely demonstrated that ART in this high-risk patient population results in improved BCR-free survival compared to RP and observation alone[5,6,10,11]. Two of these studies (SWOG 8794 and EORTC 22911) have demonstrated reduced need for salvage therapy for RT failure when patients were administered ART compared to RP and observation[5,10]. The benefit of an observational approach would be to spare men exposure to RT until they experience a BCR, which would never occur for an as of yet unspecified population. The question of whether there is a benefit to administration of ART compared with SRT at the time of BCR, as assessed in this study, has yet to be reported in a randomized controlled trial. Three trials which will address this question are currently enrolling patients in Australia/New Zealand (RAVES)[20], France (GETUG-17)[21], and in the United Kingdom and Canada (RADICALS)[22], although results are pending.

Table 2 Stepwise cox regression multivariate analysis

		Biochemical recurrence		Overall survival		Bone metastases		Hormonal therapy	
		HR (95%CI)	*P* value	HR (95%CI)	*P* value	HR (95%CI)	*P* value	HR (95%CI)	*P* value
Pathologic gleason score	2-6	Referent	0.01	Referent	0.4	Referent	0.3	Referent	0.005
	7	1.2 (0.4-3.1)	0.8		0.7		0.9	1.2 (0.3-4.6)	0.8
	8-10	3.1 (1.2-8.1)	0.02		0.2		0.1	4.9 (1.4-16.7)	0.01
Pre-RT PSA	Undetectable	Referent	< 0.001	Referent	0.8	Referent	0.045	Referent	< 0.001
	> 0.0-0.2	4.1 (1.5 -11.2)	0.005		0.8	3.3 (0.2-54.2)	0.4	2.6 (0.8-9.1)	0.1
	> 0.2-1.0	4.4 (1.6-11.9)	0.003		0.6	0.6 (0.04-8.6)	0.7	1.7 (0.5-5.8)	0.4
	> 1.0	52 (12.9-210)	< 0.001		0.7	39.8 (1.8-868)	0.02	67.8 (13.7-336)	< 0.001
Received peri-RT ADT			0.7		0.2		0.1		0.6
Seminal vesicle invasion		2.2 (0.99-4.8)	0.053		0.9		0.2	2.7 (1.1-6.6)	0.036
Positive surgical margin			0.056		0.08		0.08		0.09
Extracapsular extension			0.3		0.1		0.6		0.6
Pathologic stage	T2	Referent	0.9	Referent	0.1	Referent	0.9	Referent	0.8
	T3/4								

RT: Radiotherapy; PSA: Prostate specific antigen; ADT: Androgen deprivation therapy; CI: Confidence interval.

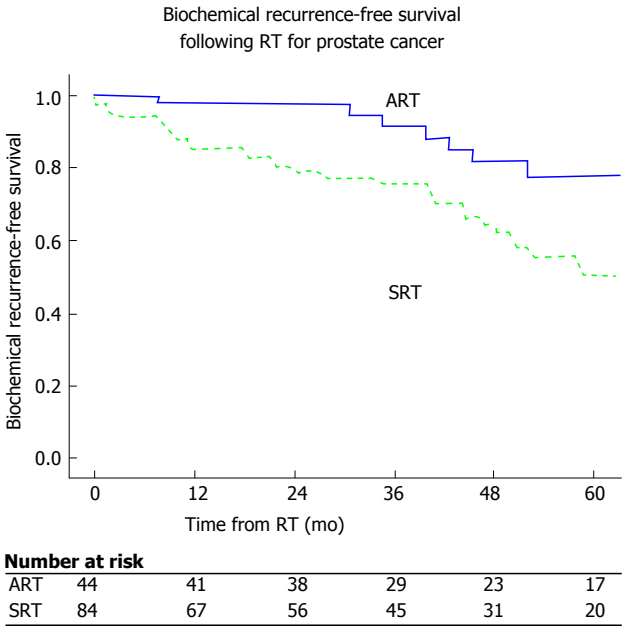

Figure 1 Biochemical recurrence-free survival for adjuvant candidates receiving adjuvant *vs* salvage radiotherapy for prostate cancer. RT: Radiotherapy; SRT: Salvage radiotherapy; ART: Adjuvant radiotherapy.

Until these trials meet accrual and have sufficient follow-up to produce meaningful conclusion, the literature remains sparse. A recent review and meta-analysis has been performed on the available, retrospective data, demonstrating an improved BCR-free survival in ART-treated patients compared to those treated with SRT[23]. While this analysis is in agreement with our findings, caution is necessary when interpreting a review of this topic. The current literature has markedly variability of the definitions of both ART and SRT, which confound generalizability and interpretation. Our study included strict inclusion criteria for analysis, including only patients with adverse pathologic features following RP and an undetectable post-RP PSA. Of the 18 studies included in the review above, eight did not require an undetectable post-RP PSA for SRT patients and four allowed ART patients to have a detectable post-RP PSA. While SRT may be administered in a different settings (*e.g.*, detectable PSA immediately post-RP, rising PSA from undetectable post-RP), ART should be administered within 6-12 mo post-operatively with an undetectable PSA. It is important to strictly define these criteria prior to analysis in order to compare treatment effects on comparable baseline patient cohorts.

Of the retrospective studies available, three deserve special mention and represent the best evidence to date regarding ART *vs* SRT in post-RP patients with adverse pathologic features and an undetectable PSA. Trabulsi *et al*[18] reported on 449 patients received postoperative RT for adverse pathologic features with an undetectable postoperative nadir PSA. After propensity score matching, 96 patients remained in each treatment group (ART and SRT). With a median follow-up of 73 mo from RT, there was improvement in five-year BCR-free survival in the ART group (73% *vs* 50%; HR = 2.3; $P = 0.007$). Comparable to the present study, pathologic Gleason score 8-10 was found to be associated with BCR (HR = 2.5; $P = 0.005$).

Ost *et al*[17] and coworkers reported a comparable match-controlled analysis of 178 patients, with 89 in each group. Three-year BCR-free survival was improved for ART *vs* SRT (90% and 65%, $P < 0.05$) in this analysis as well. Further, patients with Gleason score ≥ 4 + 3, preoperative PSA > 10 ng/mL, and omission of concomitant androgen deprivation therapy had an increase in risk for BCR.

Briganti *et al*[9] performed a multi-institutional retrospective review of 390 patients who received ART. These patients were matched in a one-to-one fashion based on pathologic Gleason score, pathologic stage and surgical margin status, with patients who underwent initial observation and SRT as needed for BCR. Kaplan-Meier analysis indicated comparable BCR-free survival between the ART and observation/SRT matched cohorts. While this analysis does examine optimal patient management with

post-RP SRT prior to PSA 0.5 ng/mL, exclusion of patients who may have presented with a recurrence PSA of ≥ 0.5 ng/mL may omit more aggressive cases, and artificially improve BCR-free survival rates in the observation/SRT cohort. Further, Briganti's study assesses time to BCR following RP, while Ost, Trabulsi, and the present study assess time to BCR following RT, limiting the ability to make comparisons between the studies.

Taken together with the present studies, it appears that when patients are compared following the receipt of RT, there is improvement in BCR-free survival with ART compared to SRT. The randomized, controlled trials above will hopefully provide definitive evidence regarding the timing of RT following RP, as well as define the patients who are adjuvant therapy candidates (adverse pathologic features with an undetectable post-RP PSA) who will or will not ultimately experience a BCR necessitating RT.

The primary limitation of our study is selection bias, specifically how patients arrived at the decision to pursue ART *vs* SRT. This decision is not solely dependent on pathologic and laboratory values, and patients may have been counseled to either of these treatment strategies based on personal preference, physician preference, their recovery from surgery, and convenience of therapy availability. Further, the potential side-effects of RT (including urethral stricture disease, hematuria, proctitis, cystitis, secondary malignancy, *etc.*) are well documented[24-30], and play an integral role in the decision making process for both the patient and provider. These subjective choices are not reflected in our analysis. This analysis also does not have the denominator for how many patients elected for observational follow-up and did not recur. Avoiding overtreatment of patients with RT is a commendable goal, however until prospective trials are completed it is difficult to characterize which patients will or will not experience BCR. Finally, there was greater SVI in the ART compared to the SRT group. While this difference between treatment groups does exist, it should not influence the reported results as the greater SVI should have negatively impacted outcomes in the ART cohort, which was not seen.

COMMENTS

Background

Radiotherapy (RT) for prostate cancer (PCa) following RT is a treatment option available for patients with adverse pathologic features (positive surgical margins, seminal vesicle invasion, extracapsular extension, a Gleason score ≥ 8, and/or pathologic adjacent organ invasion. While prior prospective, randomized trials have shown improved biochemical recurrence (BCR) free survival following adjuvant radiotherapy (ART) (immediately following recovery from prostatectomy) compared to observation, the comparison of adjuvant compared to salvage radiotherapy (SRT) [after postoperative prostate specific antigen (PSA) has risen from an undetectable level] has yet to be as rigorously studied.

Research frontiers

While adjuvant post-prostatectomy RT is known to improve BCR free survival, the optimal timing of administration RT is yet to be determined. Given the additional morbidity of RT and potential overtreatment of patients who may never recur with adjuvant radiation, the results of this study contribute to the understanding of outcomes between early (adjuvant) RT compared to delayed (salvage) RT in the post-prostatectomy population.

Innovations and breakthroughs

In this study, patients who received either adjuvant or SRT following radical prostatectomy with the presence of adverse pathologic features and an undetectable PSA were identified. This was a well-matched group when comparing baseline and pathologic characteristics. It is clear that patients who received ART had an improved BCR free survival at 5 years (78%) compared to those who received SRT (50%).

Applications

This study suggests that the receipt of ART for post-prostatectomy adverse pathologic features improved BCR free survival compared to patients who receive salvage radiation following a rise in PSA from undetectable.

Terminology

PSA: Prostate specific antigen, a serum marker produced only by prostate and PCa cells. Adverse pathologic features: Poor prognostic findings on the prostate specimen including positive surgical margins, seminal vesicle invasion, extracapsular extension, a Gleason score ≥ 8, and/or pathologic adjacent organ invasion. ART: The administration of radiation to the prostatectomy surgical bed following recovery of surgery, while the patient has an undetectable PSA. SRT: The administration of radiation to the prostatectomy surgical bed following recovery of surgery, following an increase in PSA from undetectable to a detectable value.

Peer-review

This is an interesting retrospective study comparing the effects of adjuvant *vs* SRT on BCR free survival of high risk PCa pts with initially undetectable post-op PSA. This is well-written work and both the results and limitations of the study are adequately documented.

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ORIGINAL ARTICLE

Retrospective Study

Perioperative outcomes and survival of radical cystectomy as a function of body mass index

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Author contributions: Burge BK conceived of the study, carried out data acquisition and analysis, and helped to draft the final manuscript; Blackwell RH performed statistical analysis and helped to draft the final manuscript; Wilson A participated in data acquisition and initial drafting of the manuscript; Flanigan RC, Gupta GN, and Quek ML helped with data acquisition and carried out critical revision of the manuscript; all authors read and approved the final manuscript.

Institutional review board statement: This study was reviewed and approved by the Loyola University Medical Center Institutional Review Board.

Informed consent statement: This is a retrospective study of a chart review nature and is therefore exempt from informed consent.

Conflict-of-interest statement: The authors have no conflicts of interest to report.

Data sharing statement: Technical appendix, statistical code, and dataset available from the corresponding author at Bethany.burge@luhs.org. This study was exempt from informed consent given its retrospective, chart review nature. The presented data are anonymized and risk of identification if low.

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Abstract

AIM: To evaluate the perioperative and long term outcomes of cystectomy in obese patients.

METHODS: This is a retrospective review of 580 patients for whom radical cystectomy (RC) was performed for primary urothelial bladder cancer between November 1996-April 2013 at a single institution. Body mass index (BMI) was available for 424 patients who were categorized as underweight (< 18.5), normal (18.5-24.9), overweight (25.0-29.9), and obese (≥ 30). Baseline demographics, perioperative outcomes, and survival were assessed. Overall survival (OS) and disease specific survival (DSS) was estimated by Kaplan-Meier method. Medians were compared using the Mann-Whitney U Test. Categorical variables were compared using the χ^2 test. A *P*-value of < 0.05 was considered statistically significant. Statistical analyses were performed using the Software Package for the Social Sciences (SPSS), Version 20 (International Business Machines SPSS, Chicago, IL, United States).

RESULTS: The median age of all patients was 69 years (inter-quartile range 60-75) and median follow-up was 23.4 mo (8.7-55.1). Patients were characterized as underweight [9, (2.1%)], normal [113, (26.7%)],

overweight [160, (37.8%)], or obese [142, (33.5%)]. Estimated blood loss during RC was higher in the obese group (800 mL) as compared to the normal weight group (500 mL). However, need for transfusion (47.7% *vs* 52.1%), number of lymph nodes resected (32 *vs* 30), length of stay (9 d *vs* 8 d), and 30-d readmission (29.7% *vs* 25.2%) between obese and normal BMI patients were similar. Obese patients underwent ileal neobladder diversion in 42% of cases, compared to 24% of normal BMI patients (0.003). Normal BMI and obese patients had comparable urinary incontinence (21.4% *vs* 25.6%, $P = 0.343$), and need for intermittent catheterization (14.3% *vs* 5.2%, $P = 0.685$) at 2 years follow-up. Overall survival was better in obese compared to normal BMI patients on univariate analysis, with median survival of 67 mo *vs* 37 mo, respectively ($P = 0.031$). Disease specific survival in these populations followed the same Kaplan Meier curve, with the obese group having a significantly improved OS, $P = 0.016$. Underweight patients had a significantly worse prognosis, with a median overall survival of 19 mo ($P = 0.018$). Disease specific survival was significantly worse in the underweight group compared to the obese group, $P = 0.007$. On multivariate analysis underweight patients remained at increased risk for death (HR = 3.1, $P = 0.006$), as were older patients (HR = 1.6, $P = 0.006$), those with multiple nodal metastases (HR = 3.7, $P = 0.007$), and those who had received neoadjuvant chemotherapy (HR = 2.0, $P = 0.015$).

CONCLUSION: Perioperative outcomes and survival following RC in obese patients is comparable with non-obese patients. Underweight patients have the worst OS and DSS.

Key words: Urinary bladder neoplasms; Body mass index; Obesity; Cystectomy; Underweight

Core tip: As obesity rates increase, more obese patients will require radical cystectomy for muscle invasive bladder cancer. Anecdotally, obesity increases the technical difficulty of an operation. Literature regarding outcomes of obese patients undergoing radical cystectomy is limited. This study shows obese patients do better than their non-obese counterparts in terms of perioperative outcomes and overall and disease specific survival. However, we found that underweight patients have a significantly decreased overall and disease specific survival compared with obese and patients.

Burge BK, Blackwell RH, Wilson A, Flanigan RC, Gupta GN, Quek ML. Perioperative outcomes and survival of radical cystectomy as a function of body mass index. *World J Clin Urol* 2016; 5(1): 53-59 Available from: URL: http://www.wjgnet.com/2219-2816/full/v5/i1/53.htm DOI: http://dx.doi.org/10.5410/wjcu.v5.i1.53

INTRODUCTION

The prevalence of obesity in the United States continues to rise on a yearly basis[1]. Defined as a body mass index (BMI) > 30, it is estimated that 27.2% of the American population in 2013 was obese, increased from 25.5% in 2008. The estimated population that is overweight, defined as a BMI of 25 to < 30, accounted for 35.5%, making greater than half of the population heavier than their ideal body weight[1]. These rates may be underestimated, as the National Center for Health Sciences estimated in 2009-2010 that obesity was present in 35.7% in adults and 16.9% in children[2].

Regardless of the discrepancies, it is clear that an ever growing percentage of our population is overweight or obese. It follows then that an increasing number of patients presenting for surgical management of invasive bladder cancer will be subject to this trend. Anecdotally, increasing body habitus negatively impacts technical ease of surgery. For example, in the general surgery literature, obesity has been correlated with longer operating times during cholecystectomy, mastectomy, and colectomy[3]. Similar findings were demonstrated by Maurer *et al*[4] in 2009 for radical cystectomy, with increased operative time in obese compared with non-obese patients.

The current literature regarding other surgical outcomes of radical cystectomy in obese patients is limited. Furthermore, to our knowledge, studies evaluating the impact of BMI on surgical outcomes do not differentiate underweight patients from the normal weight cohort. Herein we examine the impact of BMI on perioperative and long term outcomes of radical cystectomy.

MATERIALS AND METHODS

A retrospective chart review was performed for 580 patients who underwent radical cystectomy at a single institution for urothelial cell carcinoma of the bladder between November 1996 and April 2013. Baseline patient demographics, comorbidities, and clinical cancer characteristics were recorded (Table 1). Surgical technique (open *vs* robotic-assisted laparoscopic) was chosen at the discretion of the primary surgeon (557 *vs* 23, respectively). BMI was calculated from height and weight data recorded prior to cystectomy (kg/m^2). BMI information was available for 424 patients, who were used in the final analysis. Patients were categorized into underweight (BMI < 18.5), normal weight (BMI 18.5-24.9), overweight (BMI 25-29.9), and obese (BMI ≥ 30) using World Health Organization BMI criteria[5].

BMI subgroups were evaluated for perioperative, pathologic, and long term outcomes including estimated blood loss, need for blood product transfusion, number of lymph nodes resected, admission length of stay, 30-d readmission rate, rate of continent diversions (ileal neobladder or continent catheterizable stoma), rate of node positive disease, and overall and disease specific survival (months). Follow-up was computed from the

Table 1 Preoperative patient characteristics

		Normal Weight (BMI 18.5-24.9)	Underweight (BMI < 18.5)	Overweight (BMI 25.0-29.9)	Obese (BMI > 30)	*P* value
Age at surgery (median, IQR), yr		70 (63-76)	78 (68-79)	70 (61-76)	67 (58-72)	0.126
Gender	Male	74 (66%)	4 (44%)	130 (81%)	106 (75%)	0.005
	Female	39 (35%)	5 (56%)	30 (19%)	36 (25%)	
Clinical tumor stage	cT0	1 (1%)	0 (0%)	1 (1%)	1 (1%)	0.05
	cTis	0 (0%)	0 (0%)	8 (5%)	11 (8%)	
	cTa	7 (7%)	1 (11%)	9 (6%)	10 (8%)	
	cT1	30 (28%)	2 (22%)	26 (17%)	35 (26%)	
	cT2	65 (61%)	4 (44%)	103 (67%)	67 (50%)	
	cT3	3 (3%)	2 (22%)	4 (3%)	5 (4%)	
	cT4	1 (1%)	0 (0%)	3 (2%)	4 (3%)	
Prior intravesical therapy	No	86 (78%)	6 (67%)	113 (71%)	83 (59%)	0.018
	Yes	25 (22%)	3 (33%)	47 (29%)	57 (41%)	
Prior neoadjuvant chemotherapy	No	100 (90%)	9 (100%)	150 (94%)	129 (92%)	0.478
	Yes	11 (10%)	0 (0%)	9 (6%)	11 (8%)	
Race	Caucasian	105 (92%)	9 (100%)	151 (94%)	134 (94%)	0.492
	Hispanic	3 (3%)	0 (0%)	0 (0%)	0 (0%)	
	Black	3 (3%)	0 (0%)	6 (4%)	7 (5%)	
	Asian	1 (1%)	0 (0%)	2 (1%)	0 (0%)	
	Unknown	1 (1%)	0 (0%)	1 (1%)	1 (1%)	
Hypertension	No	52 (46%)	2 (22%)	73 (46%)	33 (23%)	< 0.001
	Yes	60 (54%)	7 (78%)	87 (54%)	108 (77%)	
Diabetes mellitus, type Ⅱ	No	99 (88%)	8 (89%)	132 (82%)	100 (71%)	0.006
	Yes	13 (12%)	1 (11%)	28 (18%)	40 (29%)	
Coronary artery disease	No	89 (80%)	9 (100%)	125 (78%)	103 (74%)	0.248
	Yes	23 (20%)	0 (0%)	35 (22%)	37 (26%)	
Cardiac arrhythmia	No	102 (91%)	7 (78%)	143 (89%)	129 (92%)	0.491
	Yes	10 (9%)	2 (22%)	17 (11%)	11 (8%)	
History of coronary vascular accident	No	106 (95%)	8 (89%)	156 (97%)	139 (99%)	0.068
	Yes	6 (5%)	1 (11%)	4 (3%)	1 (1%)	
Pulmonary disease	No	94 (84%)	7 (78%)	147 (92%)	115 (82%)	0.063
	Yes	18 (16%)	2 (22%)	13 (8%)	25 (18%)	
Liver disease	No	110 (98%)	8 (89%)	159 (99%)	138 (99%)	0.077
	Yes	2 (2%)	1 (11%)	1 (1%)	1 (1%)	
Nephrolithiasis	No	101 (91%)	9 (100%)	149 (93%)	126 (90%)	0.606
	Yes	10 (9%)	0 (0%)	11 (7%)	14 (10%)	
Preoperative renal function	Normal	58 (72%)	7 (88%)	79 (70%)	70 (71%)	0.652
	CKD stage 3	19 (24%)	1 (12%)	31 (28%)	26 (27%)	
	CKD stage 4	2 (2%)	0 (0%)	2 (2%)	2 (2%)	
	CKD stage 5	2 (2%)	0 (0%)	0 (0%)	0 (0%)	
Smoking history	No	27 (24%)	1 (11%)	42 (27%)	36 (26%)	0.76
	Yes	84 (76%)	8 (89%)	116 (73%)	103 (74%)	

BMI: Body mass index; CKD: Chronic kidney disease; IQR: Inter-quartile range.

date of surgery to last clinic appointment with urologic or medical oncologist. Dates of death were confirmed by the Social Security Death Index[6].

Overall and disease specific survival was estimated by Kaplan-Meier method. Medians were compared using the Mann-Whitney U Test and categorical variables were compared using the χ^2 test. A *P*-value of < 0.05 was considered statistically significant. Statistical analyses were performed using the Software Package for the Social Sciences (SPSS), Version 20 (International Business Machines SPSS, Chicago, IL USA).

RESULTS

Perioperative and pathologic characteristics are demonstrated in Table 2. Of the 424 patients who underwent radical cystectomy for urothelial carcinoma and for whom BMI data was available, the median age was 69 years (range 60-75 years). There was a median follow-up of 23.4 mo (8.7-55.1). Of these 424 patients, there were 9 (2.1%) underweight, 113 (26.7%) normal BMI, 160 (37.8%) overweight, and 142 (33.5%) obese.

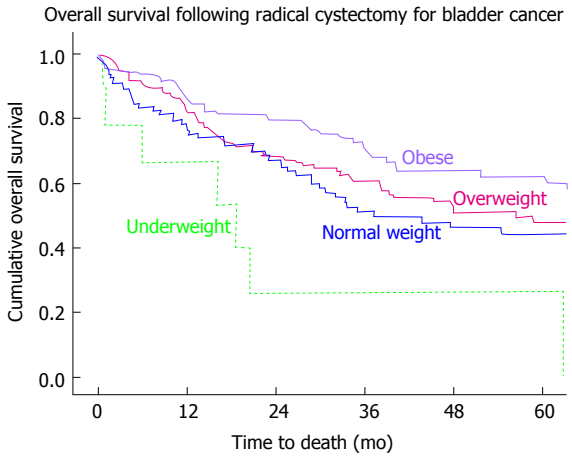
The median estimated blood loss was higher in the obese patients compared with the normal BMI group (500 mL and 800 mL, respectively). The median number of lymph nodes resected was comparable between the normal BMI and obese, at 30 and 32, respectively. The need for transfusion (52.1% and 47.7%), admission length of stay [8 d (7-10) and 9 d (7-14)], and 30 d readmissions (25.2% and 29.7%) also showed no significant differences.

Rates of orthotopic ileal neobladder urinary diversion were higher in obese patients than in normal weight and obese patients (41.5% *vs* 23.9%, respectively, *P* = 0.003). At 2 years follow-up, there was no statistical differences in rates of urinary incontinence (21.4% *vs*

Table 2 Postoperative patient characteristics

		Normal weight (BMI 18.5-24.9)	Underweight (BMI < 18.5)	Overweight (BMI 25.0-29.9)	Obese (BMI > 30)	*P* value
Length of stay (median, IQR), d		8 (7-10)	13 (10-16)	8 (7-11)	9 (7-14)	0.054
Prolonged length of stay (> 7 d)	No	39 (35%)	0 (0%)	61 (38%)	49 (35%)	0.137
	Yes	73 (65%)	9 (100%)	99 (62%)	93 (65%)	
Estimated blood loss (median, IQR), mL		500 (400-700)	600 (450-925)	700 (500-1000)	800 (600-1100)	< 0.001
Urinary diversion	Ileal conduit	70 (61.9%)	8 (88.9%)	88 (55%)	68 (47.9%)	0.160
	Orthotopic ileal neobladder	27 (23.9%)	1 (11.1%)	58 (26.2%)	59 (41.5%)	
	Continent cutaneous diversion	14 (12.3%)	0 (0%)	12 (7.4%)	11 (7.7%)	
	Cutaneous ureterostomy	0 (0%)	0 (0%)	1 (0.6%)	0 (0%)	
	None	4 (3.5%)	0 (0%)	2 (1.2%)	1 (0.7%)	
Pathologic tumor/nodal stage	No evidence of disease (pT0)	8 (7%)	0 (0%)	2 (1%)	9 (6%)	0.01
	Localized disease (pT0-2bN0)	45 (40%)	2 (22%)	73 (46%)	76 (53%)	
	Locally advanced disease (pT3-4bN0)	25 (22%)	6 (67%)	49 (30%)	33 (23%)	
	Solitary nodal metastasis (pT × N1)	12 (11%)	0 (0%)	14 (9%)	12 (9%)	
	Multiple nodal metastases (pT × N2-3)	23 (20%)	1 (11%)	22 (14%)	12 (9%)	
Readmission within 30 d	No	83 (75%)	6 (67%)	113 (71%)	97 (70%)	0.85
	Yes	28 (25%)	3 (33%)	46 (29%)	41 (30%)	
Adjuvant chemotherapy	No	74 (67%)	7 (78%)	105 (66%)	93 (67%)	0.907
	Yes	36 (33%)	2 (22%)	54 (34%)	45 (33%)	
Recurrence of disease	No	81 (72%)	5 (56%)	113 (71%)	97 (69%)	0.031
	Yes	31 (28%)	4 (44%)	47 (29%)	44 (31%)	
Deceased	No	59 (52%)	2 (22%)	95 (59%)	91 (64%)	0.727
	Yes	54 (48%)	7 (78%)	65 (41%)	50 (36%)	

BMI: Body mass index; IQR: Inter-quartile range.



Number at risk						
Normal weight BMI 18.5-24.9	113	74	56	34	26	18
Underweight BMI ≤ 18.5	9	5	3	1	1	1
Overweight BMI 25-29.9	158	113	79	60	45	31
Obese BMI ≥ 30	139	102	78	58	38	35

Figure 1 Improved overall survival in obese patients compared with normal body mass index patients. BMI: Body mass index.

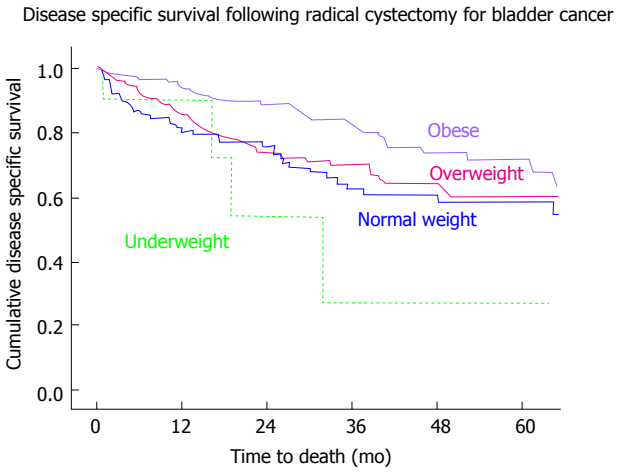


Figure 2 Decreased disease specific survival of patients in the underweight group compared with other weight groups.

25.6%, *P* = 0.343) or need for intermittent catheterization (14.3% *vs* 5.2%, *P* = 0.685) between normal BMI and obese patients with an ileal neobladder urinary diversion.

While overall survival was improved in obese patients when compared with normal BMI patients [median survival of 67 mo (57-77) and 37 mo (16-58), respectively], it was significantly decreased in the underweight population with a median survival of 19 mo (2-35), *P* < 0.001 (Figure 1). A similar trend was seen in disease specific survival, with patients in the underweight group having a decreased DSS when compared with other weight groups. DSS in the underweight group, when compared to the obese group was significantly lower, *P* = 0.007 (Figure 2, Table 3).

On multivariate analysis (Table 4) underweight patients had an increased risk of death (HR = 3.129, *P* = 0.006) compared to normal BMI patients, as did older

Table 3 Pairwise comparison of disease specific survival according to body mass index

	BMI	0		1		2		3	
		χ^2	Sig.	χ^2	Sig.	χ^2	Sig.	χ^2	Sig.
Log rank (Mantel-cox)	0			1.204	0.272	2.144	0.143	7.160	0.007
	1	1.204	0.272			0.961	0.327	5.838	0.016[2]
	2	2.144	0.143	0.961	0.327			2.189	0.139
	3	7.160	0.007[1]	5.838	0.016	2.189	0.139		

[1]DSS for underweight *vs* obese: 0.007. [2]DSS for obese *vs* normal: 0.016. BMI: Body mass index; DSS: Disease specific survival; 0: Underweight; 1: Normal; 2: Overweight; 3: Obese.

Table 4 Cox stepwise multivariate regression

		HR (95%CI)	*P* value
Age at surgery ≥ 65 yr		1.62 (1.15-2.29)	0.006
Gender			0.330
BMI	Normal weight (BMI 18.5-24.9)	Referent	0.015
	Underweight (BMI ≤ 18.5)	3.13 (1.39-7.07)	0.006
	Overweight (BMI 25.0-29.9)	0.94 (0.64-1.38)	0.764
	Obese (BMI ≥ 30)	0.83 (0.56-1.24)	0.370
Coronary artery disease			0.808
Cardiac arrhythmia			0.722
Pulmonary disease			0.192
Hypertension			0.110
Diabetes mellitus, type Ⅱ			0.217
Smoking history			0.657
Intravesical therapy			0.560
Neoadjuvant chemotherapy		2.02 (1.14-3.56)	0.015
Adjuvant chemotherapy			0.251
Pathologic stage	pT0	Referent	< 0.001
	pT1-2N0	0.78 (0.30-1.99)	0.602
	pT3-4N0	1.47 (0.56-3.80)	0.430
	pT × N1	2.48 (0.91-6.77)	0.076
	pT × N2-3	3.73 (1.43-9.74)	0.007

BMI: Body mass index.

patients (age ≥ 65 years) (HR = 1.622, *P* = 0.006), patients with > 1 nodal metastasis (HR = 3.730, *P* = 0.007), and patients who had received neoadjuvant chemotherapy (HR = 2.017, *P* = 0.015).

DISCUSSION

Radical cystectomy appears to be safe in the obese population, with perioperative and overall survival outcomes comparable to the normal BMI population. We find no clinically or statistically significant differences in rate of blood product transfusion, length of hospital stay, or 30-d readmission. This echoes a NSQIP population-based comparison between these groups, which demonstrated no increase in 30-d mortality or in perioperative complications[7]. Other prior studies have demonstrated an increase in operative time in the obese[4,7].

Further, 59 (42%) obese patients in our series received orthotopic ileal neobladder urinary diversion. While there is a theoretical concern for increased urinary incontinence given the increased intra-abdominal pressure, this was not demonstrated (26.7% *vs* 26.3%, obese *vs* normal BMI). Compared to normal BMI patients with orthotopic neobladder, obese patients had a trend toward a lower rate of intermittent catheterization (2% *vs* 11%, *P* = NS). Given that orthotopic neobladder patients have been shown to have improved physical functioning[8] without the same body image concerns present in patients with ileal conduits[9], orthotopic neobladder stands out as an appropriate option in the obese population.

An unexpected finding was the significant decrease in overall and disease specific survival in the underweight group. We hypothesize that this tendency toward a worse outcome is the result of a systemic manifestation of cancer-related nutritional deficiency and sarcopenia, resulting in a lower physiologic reserve in the underweight patients. This group did notably have a high proportion of pT3-4N0 disease compared to patients in other BMI distributions, however less incidence of nodal involvement. On multivariate analysis underweight patients had an increased risk of death compared to normal BMI patients (HR = 3.1, *P* = 0.006). As such, underweight BMI may serve as a surrogate marker for poor outcome following radical cystectomy.

Radical cystectomy patients are known to be nutritionally deficient. Jensen *et al*[8] reported that 26% of

patients are at a preoperative nutritional risk prior to cystectomy. Further, Gregg *et al*[9] demonstrated that in 538 patients, 19% were nutritionally deficient (defined as BMI < 18.5, albumin < 3.5, pre-surgical weight loss > 5% of body weight). The 90-d mortality in this population was 16.5%, and their 3-year overall survival was decreased compared to nutritionally normal patients (44% *vs* 68%, respectively)[10].

Radical cystectomy patients are also at increased risk for nutritional deficiency postoperatively. Following surgery these patients are in a catabolic state secondary to the stress response to surgery and wound healing. They may develop ileus and also suffer a loss of lymphatic fluid intra- and post-operatively that can contribute further to their nutritional deficiency[11]. In a case series reported by Mathur *et al*[12], it was demonstrated that there are significant decreases in mean protein levels and water in the first 2 wk following cystectomy. What is most striking is that it required greater than 6 mo to regain 67% of the protein lost following surgery. In a prospective, randomized trial, Roth *et al*[10] demonstrated that while patients who received parenteral nutrition had earlier improvements in serum prealbumin (mg/L) and total protein (g/L), there was no improvement in time to gastrointestinal recovery or length of stay. Furthermore, there were increased postoperative infectious complications in this group.

All of the above data suggest that preoperatively underweight and nutritionally deficient patients are at a disadvantage following radical cystectomy. A recent review of the colorectal surgery literature found that the use of preoperative nutritional supplements improved time to return of gastrointestinal function, and decreased time to discharge and postoperative muscle mass loss. It follows that preoperative nutritional intervention may lead to improved outcomes. More will be known in the radical cystectomy population following the results of a pilot study that is currently in enrollment to assess the impact of an enriched oral nutritional shake to improve preoperative nutritional status on patient's outcomes following radical cystectomy.

Limitations of our study include retrospective design with its inherent bias, as well as small sample size, particularly in the underweight patient group.

While obesity may increase the technical difficulty of surgical management of invasive bladder cancer, perioperative outcomes and survival following radical cystectomy appear better than non-obese patients. Obese patients with orthotopic neobladders have comparable urinary function to patients with a normal BMI, making continent diversion a reasonable option in this population. A paradigm shift may be warranted to incorporate preoperative nutritional assessment and supplementation, particularly in underwent patients, to improve radical cystectomy outcomes. Prospective studies evaluating the effect of nutritional supplementation or hyperalimentation prior to radical cystectomy are necessary to determine how to best improve the nutritional status and outcomes in this nutritionally compromised population.

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COMMENTS

Background

Radical cystectomy is the gold standard for treatment of muscle invasive bladder cancer. As obesity rates in the Unites States increase, so will the rates of obese patients that require radical cystectomy. Currently, literature in other surgical fields note increased operating times in the obese population. However, these studies did not evaluate how these patients tolerated the surgery and how well they did postoperatively. In this study the authors evaluated perioperative outcomes and survival, both overall and disease specific, of patients undergoing radical cystectomy according to their body mass index (BMI). The authors' hypothesis was that obese patients would have more technically difficult operations leading to increased need for transfusion, less complete oncologic outcomes (specifically evaluated by number of lymph nodes resected), longer hospital stay, and increased 30-d readmissions. However, no significant difference was found between obese and normal weight patient groups with regards to these perioperative factors. An unexpected finding was underweight patients had a significantly decreased overall and disease specific survival when compared with other weight groups.

Research frontiers

Given the high complication rate of radical cystectomy of up to 30% in the literature, increased hospital length of stay, and high rate of readmission there is a need for information on preoperative optimization for these patients. The finding that underweight patients have a decreased survival could point to the fact that they are nutritionally deficient prior to surgery. Further studies are necessary to determine if, and by what method, preoperative nutritional supplementation would benefit this patient group.

Innovations and breakthroughs

This study provides information on perioperative factors and survival. Other studies that have looked at BMI and its relation to surgical outcomes have focused on the technical aspects of the surgery alone. Those that have evaluated perioperative outcomes and survival as a function of BMI did not specifically evaluate how underweight patients fared, as this study does.

Applications

This study highlights the need for future prospective studies evaluating preoperative nutritional optimization for patients undergoing radical cystectomy.

Peer-review

This study is the first and most extensive study. The presented article is well written and can contribute to current data. The paper describes the relationship between preoperative BMI and long-term outcome. The results are very interesting, showing a substantially decreased overall survival in the underweight group. Separate analysis of cancer-specific survival would improve the manuscript.

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ORIGINAL ARTICLE

Retrospective Study

Robotic-assisted laparoscopic partial nephrectomy: A comparison of approaches to the posterior renal mass

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Author contributions: Wetterlin JJ, Blackwell RH, Capodice S, Quek ML and Gupta GN performed the research; Wetterlin JJ, Blackwell RH, Capodice S and Gupta GN wrote the paper; Wetterlin JJ, Gupta GN designed the research study; Kliethermes S contributed analytic tools.

Institutional review board statement: Our project was performed with institutional IRB approval LU#280388 at Loyola University Medical Center.

Informed consent statement: Our study does not involve human subjects research so there was no need for informed consent.

Conflict-of-interest statement: We have no financial relationships to disclose.

Data sharing statement: No additional data are available.

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Abstract

AIM: To evaluate outcomes of robotic-assisted laparoscopic partial nephrectomy performed for posterior renal tumors *via* a transperitoneal or retroperitoneal approach.

METHODS: Retrospective review was performed for patients who underwent robotic-assisted laparoscopic partial nephrectomy (RALPN) for a posterior renal tumor between 2009-2015. Patient demographic characteristics, operative factors, pathology, oncologic outcomes, renal function, and tumor complexity were obtained. Radius of the tumor, exophytic/endophytic properties of the tumor, nearness of tumor to the collecting system, anterior/posterior position, location relative to the polar line (RENAL) nephrometry scores were calculated. nephrometry scores were calculated. The operative approach was determined by the primary surgeon.

RESULTS: A total of 91 patients were identified who underwent RALPN for a posterior renal tumor. Fifty-four procedures were performed *via* the retroperitoneal (RP) approach, and 37 *via* the transperitoneal (TP) approach. There were no significant differences in patient factors (race, sex, age and body mass index), RENAL nephrometry scores, tumor size, conversion rates, or margin status. Among procedures performed on-clamp, there

was no significant difference in warm ischemia times. Total operative time (180.7 min for RP *vs* 227.8 min for TP, $P < 0.001$), robotic console time (126.9 min for RP *vs* 164.3 min for TP, $P < 0.001$), and median estimated blood loss (32.5 mL for RP *vs* 150 mL for TP, $P < 0.001$) were significantly lower *via* the RP approach. Off-clamp RALPN was performed for 31 (57.4%) of RP procedures *vs* 9 (24.3%) of TP procedures. Oncologic and renal functional outcomes were equivalent.

CONCLUSION: The RP approach to RALPN for posterior renal tumors is superior with regard to operative time and blood loss and the ability to be performed off-clamp.

Key words: Retroperitoneal; Transperitoneal; Robotic-assisted laparoscopic partial nephrectomy; Posterior renal masses

Core tip: A retrospective review was completed to evaluate perioperative outcomes of robotic-assisted laparoscopic partial nephrectomy (RALPN) performed for posterior renal tumors performed *via* a transperitoneal or retroperitoneal (RP) approach. Ninety-one patients underwent RALPN for a posterior renal tumor. Fifty-four procedures were performed *via* the RP approach. Total operative time, robotic console time, and median estimated blood loss were significantly lower *via* the RP approach. Fifty-seven percent of RP procedures were performed off-clamp. The RP approach to RALPN for posterior renal tumors is superior with regard to operative time and blood loss and the ability to perform the procedure off-clamp.

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INTRODUCTION

Robotic-assisted laparoscopic partial nephrectomy (RALPN) is increasingly utilized as an alternative to laparoscopic or open partial nephrectomy for surgical extirpation of renal masses. RALPN can be performed *via* a transperitoneal (TP) or retroperitoneal (RP) approach, but the majority of the literature describes the TP approach as it has been more widely adopted and provides a larger working space with more familiar anatomical landmarks[1]. The RP approach, however, has specific advantages including direct access to posterior and lateral tumors without whole kidney mobilization, direct access to the renal artery, and does not require bowel mobilization[1,2]. Additionally, several recent studies have indicated that the RP approach for RALPN is associated with decreased operative time, decreased length of hospital stay, decreased estimated blood loss (EBL), decreased warm ischemia time (WIT), decreased narcotic use, and permitted quicker return of bowel function with comparable oncologic outcomes[1-11].

While the current literature suggests the RP approach to RALPN provides an acceptable alternative to the TP approach, there are no studies that compare these two methods for posteriorly located tumors. The current study evaluates the use of RALPN for posterior renal tumors *via* the TP and RP approaches in regards to perioperative, renal functional, and oncological outcomes.

MATERIALS AND METHODS

A retrospective review was performed in our prospectively-maintained RALPN institutional database to identify patients who underwent RALPN for a posteriorly-located renal tumor from September 2009 to January 2015. Tumor characteristics, including posterior location, were based on radius of the tumor, exophytic/endophytic properties of the tumor, nearness of tumor to the collecting system, anterior/posterior position, location relative to the polar line (RENAL) nephrometry scores. Information regarding patient demographic characteristics, operative factors, renal function, tumor histology, and oncological outcomes were obtained by chart review. Surgical approach was determined by the primary surgeon based on tumor location and characteristics.

Surgical technique

The RP approach to RALPN has been previously described, and our technique had little variation[12]. In brief, patients were instructed to hold anticoagulation and antiplatelet agents prior to surgery. No bowel preparation was administered. Patients were placed in a full flank position over a beanbag, secured and appropriately padded, with the table flexed. The flank and abdomen were prepped and bony landmarks identified. An incision was made at the level of the tip of the 12th rib, one centimeter superior to the anterior superior iliac spine. Blunt dissection was then used to enter the retroperitoneum. A balloon trocar was placed to dilate the RP space, after which pneumoretroperitoneum was established. Under direct visualization, two 8 mm robotic ports and a single 12 mm assistant port were placed. The robot was docked over the ipsilateral shoulder at a 15 degree angle towards the spine. Arterial vascular dissection was immediately performed by elevating the kidney off the psoas muscle to identify the renal hilum. For RALPN performed with WIT, only the artery was clamped with bulldog clamps. Intraoperative ultrasound was used to correctly identify the tumor, Gerota's fat overlying the tumor was removed and sent for pathological analysis, and the tumor was excised using sharp dissection. The decision to perform the procedure with or without clamping of the renal hilum was made by

the primary surgeon. Renorrhaphy and placement of hemostatic agents was performed as deemed necessary.

Alternatively, patients undergoing the TP approach were placed in a modified flank position with the table maximally flexed to provide optimal exposure. Insufflation was obtained with the Veress needle. Ports were placed in the supraumbilical area, lateral to the rectus sheath, one 8 mm port superior in the midline, and one inferiorly in the midclavicular line. A 12 mm assistant port was placed inferiorly, and a 5 mm assistant port superiorly. For right-sided procedures, an additional 5 mm assistant port was occasionally placed along the contralateral margin for liver retraction. The robot was docked over the ipsilateral shoulder, after which the kidney and renal hilum were identified in a standard fashion. During the TP approach, the kidney required complete mobilized to facilitate visualization of the posterior tumor.

Outcomes

The patient characteristics that were evaluated included age at time of procedure, gender, race, and body mass index (BMI). Operative factors examined included length of total procedure, robotic console time, conversion to open, EBL and WIT. Renal function was evaluated by comparing preoperative creatinine to postoperative creatinine; postoperative creatinine was measured at an average of 4.5 (1.7-15.3) mo after surgery. Postoperative creatinine levels were routinely measured on postoperative day one, and daily throughout patient's hospital stay. There was no standardization of postoperative creatinine measurement after patient discharge, and was performed on an individual basis. Tumor characteristics evaluated included RENAL nephrometry scores, tumor histology, size, laterality, and surgical margin status. Patients were followed postoperatively for radiographic evidence of tumor recurrence and or metastasis.

The RENAL nephrometry score is a scoring system to objectively describe anatomic characteristics of renal tumors including tumor radius, amount of tumor that is exophytic, nearness of deepest portion of the tumor to the collecting system or renal sinus, anterior or posterior location, and location relative to the polar line[13].

Statistical analysis

Standard statistical methods were used to describe characteristics of individuals in both groups. Continuous variables were primarily represented as means and standard deviations, whereas categorical variables were represented as frequencies and percentages. Univariable analyses were conducted to compare differences in patient characteristics, tumor characteristics and operative outcomes between the two groups. Independent *t*-tests were used for continuous variables and Pearson c^2 or Fisher's exact tests were used for categorical comparisons. Due to the non-normality of WIT and EBL, medians and interquartile ranges were presented and Wilcoxon rank sum tests used.

RESULTS

All procedures were performed by 5 surgeons at a single institution from September 2009 to January 2015. A total of 91 patients underwent RALPN for a posterior renal tumor. Fifty-four procedures were performed *via* the RP approach, and 37 *via* the TP approach. There were no significant differences in patient factors including race, sex, age, and BMI (Table 1). The only significant difference with regard to tumor characteristics was laterality of the tumor. A majority of patients with left-sided tumors underwent resection *via* the TP approach (59.5%), whereas a majority of patients with right-sided tumors were *via* the RP approach (63%, P = 0.04). There were no significant differences in tumor size or RENAL nephrometry scores, including individual components (Table 2).

Off-clamp RALPN was performed for 57.4% of RP procedures *vs* 24.3% of TP procedures. Among procedures performed on-clamp, there was no significant difference in warm ischemia times. There were no significant differences in conversion rates or surgical margin status between the two groups. One patient in the RP group had a positive surgical margin *vs* three in the TP group. Total operative time (180.7 min for RP *vs* 227.8 min for TP, $P < 0.001$), robotic console time (126.9 min for RP *vs* 164.3 min for TP, $P < 0.001$), and median EBL (32.5 mL for RP *vs* 150 mL for TP, $P < 0.001$) were significantly lower *via* the RP approach (Table 3). There was no significant difference in postoperative renal function between both groups, measured at an average of 4.5 (1.7-15.3) mo postoperatively (Table 4).

Patients in both groups were followed postoperatively for evidence of radiographic recurrence or metastasis. No patients in either group had evidence of disease recurrence or metastasis after median follow-up of 187 d for the TP group, 104 d for the RP group. Tumor histology was assessed in all patients that underwent RALPN, with the majority of patients in both groups being diagnosed with clear cell renal cell carcinoma (Figure 1).

DISCUSSION

Minimally invasive techniques and nephron sparing surgery for the management of renal masses are increasingly utilized and have comparable oncologic outcomes to the open approach. Partial nephrectomy remains the standard of care for small renal masses in appropriately selected patients according to current guidelines[14]. Minimally invasive techniques have demonstrated the added advantage of faster postoperative convalescence and shorter hospital stay[7]. In comparison to the TP approach, the RP approach has been less commonly used, even for posteriorly located tumors. This may be attributed to less operative familiarity, a smaller working space, and less familiarity with surgical landmarks[7]. Despite these obstacles, an increasing amount of data supports the use of the RP approach for RALPN. To our knowledge, no prior studies have examined the use of the

Table 1 Patient characteristics

	RP (n = 54)	TP (n = 37)	P
Age at time of surgery, mean (SD)	56.5 (13)	57.2 (11.6)	0.80[1]
BMI (SD)	31.1 (5.8)	32.1 (7.0)	0.51[1]
Race			
Asian	1 (1.9%)	0	0.45[2]
Black	3 (5.6%)	3 (8.1%)	
Hispanic	7 (13.0%)	2 (5.4%)	
Other	0	1 (2.7%)	
White	43 (79.6%)	31 (83.8%)	
Sex			
Female	17 (31.5%)	17 (46.0%)	0.16[3]
Male	37 (68.5%)	20 (54.1%)	
Preoperative creatinine, mean (SD)	0.95 (0.21) n = 53	0.90 (0.17) n = 36	0.27[1]

P = Significance based on: [1]Independent samples t-test; [2]Fisher exact test; [3]Pearson χ^2 test. RP: Retroperitoneal; TP: Transperitoneal; BMI: Body mass index; SD: Standard deviation.

Table 2 Tumor characteristics

	RP (n = 54)	TP (n = 37)	P
Renal location			
Left	20 (37.0%)	22 (59.5%)	0.04[3]
Right	34 (63.0%)	15 (40.5%)	
Pathologic tumor size (cm), mean (SD)	3.1 (1.6) n = 53	2.9 (1.2) n = 36	0.54[1]
Surgical margin			
Negative	50 (98.0%)	32 (91.4%)	0.30[2]
Positive	1 (2.0%)	3 (8.6%)	
RENAL score, mean (SD)	6.5 (1.9)	6.6 (1.8)	0.71[1]
Radius			
1	42 (77.8%)	33 (89.2%)	0.41[2]
2	10 (18.5%)	4 (10.8%)	
3	2 (3.7%)	0	
Exophytic			
1	29 (53.7%)	15 (40.5%)	0.41[2]
2	20 (37.0%)	19 (51.4%)	
3	5 (9.3%)	3 (8.1%)	
Nearness			
1	23 (42.6%)	15 (40.5%)	0.94[3]
2	8 (14.8%)	5 (13.5%)	
3	23 (42.6%)	17 (46.0%)	
Location relative to polar line			
1	30 (55.6%)	19 (51.4%)	0.51[3]
2	12 (22.2%)	6 (16.2%)	
3	12 (22.2%)	12 (32.4%)	

P = Significance based on: [1]Independent samples t-test; [2]Fisher exact test; [3]Pearson χ^2 test. RP: Retroperitoneal; TP: Transperitoneal; SD: Standard deviation; RENAL: Radius of the tumor, exophytic/endophytic properties of the tumor, nearness of tumor to the collecting system, anterior/posterior position, location relative to the polar line.

RP *vs* TP approach exclusively for posterior renal tumors.

RENAL nephrometry score has been widely used to objectively describe anatomic characteristics of renal tumors including tumor radius, amount of tumor that is exophytic, nearness of the tumor to the collecting system or renal sinus, anterior or posterior location, and location relative to the polar line[13]. Prior studies have evaluated the impact of RENAL nephrometry scores on outcomes of partial nephrectomy and have demonstrated that higher

Table 3 Operative factors

	RP (n = 54)	TP (n = 37)	P
Total operative time (SD)	180.7 (62.3)	227.8 (59.0)	< 0.001[1]
Robot console time, mean (SD)	126.9 (40.0)	164.3 (51.3)	< 0.001[1]
WIT, median (IQR)[4]	28.0 (20-31) n = 23	27.0 (21-31) n = 28	0.96[3]
Conversion			
No	52 (96.3%)	32 (86.5%)	0.12[2]
Yes	2 (3.7%)	5 (13.5%)	
EBL, median (IQR)	32.5 (20-100)	150.0 (50-250)	< 0.001[3]

P = Significance based on: [1]Independent samples t-test; [2]Fisher exact test; [3]Wilcoxon-Rank Sum test; [4]Excludes patients with WIT = 0. RP: Retroperitoneal; TP: Transperitoneal; SD: Standard deviation; IQR: Interquartile range; WIT: Warm ischemia time; EBL: Estimated blood loss.

Table 4 Renal function

	RP (n = 54)	TP (n = 37)	P
Preoperative creatinine, mean (SD)	0.95 (0.21) n = 53	0.90 (0.17) n = 36	0.27[1]
Postop creatinine, mean (SD)	1.0 (0.21) n = 46	1.0 (0.18) n = 28	0.67[1]

P = Significance based on: [1]Independent samples t-test. RP: Retroperitoneal; TP: Transperitoneal; SD: Standard deviation.

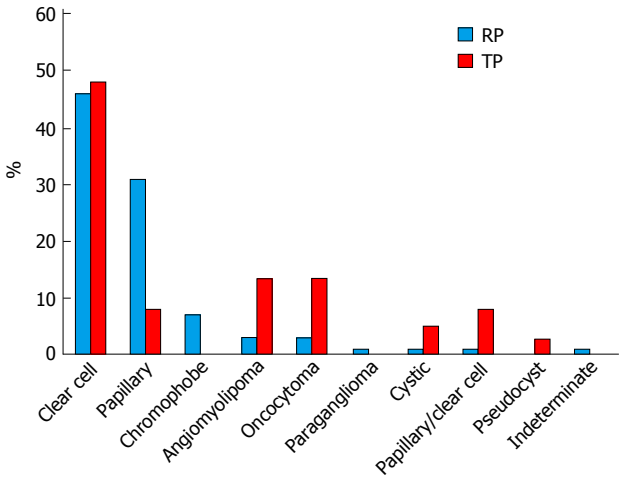

Figure 1 Tumor histology. RP: Retroperitoneal; TP: Transperitoneal.

nephrometry scores were associated with more EBL, and longer hospital stay and warm ischemia times[10,13]. Ellison *et al*[10] found that the nearness of the tumor to the renal sinus had the greatest impact on perioperative outcomes. Hayn *et al*[13] found that nephrometry score did not impact overall operative times, transfusion rate, complication rate, or pre- and post-operative creatinine clearance. Similarly, our study demonstrated no significant difference in outcomes between RP *vs* TP approaches with regard to RENAL nephrometry score. In our study, the nephrometry score was only useful to classify the tumor as anterior or posterior.

In a study comparing perioperative outcomes of all

renal tumors regardless of anterior or posterior location that underwent RALPN *via* TP or RP approach, Gin *et al*[7] found that after adjusting for tumor complexity that less complex tumors based on RENAL nephrometry score were more likely to undergo RP RALPN. They demonstrated that more patients (69%) with posterior renal tumors underwent excision *via* the RP approach, and this was associated with lower EBL and lower rates of readmission[7].

Further, benefits to the RP approach have been shown with regard to multiple perioperative factors including operative time, EBL, length of hospital stay, and return of bowel function[3,9,15]. A meta-analysis by Ren *et al*[5], including eight retrospective studies evaluating the use of TP *vs* RP laparoscopic partial nephrectomy found that RP partial nephrectomy was associated with shorter operative times, lower EBL, and a shorter hospital stay. A similar meta-analysis by Fan *et al*[2], comparing TP *vs* RP laparoscopic and robotic partial nephrectomy demonstrated that the RP approach was associated with shorter time to renal hilum control, shorter operative time, shorter length of hospital stay, and a lower overall complication rate.

The RP approach eliminates the need for bowel mobilization thus limiting the potential for injury to abdominal organs and the development of intra-abdominal adhesions and intestinal obstruction[16]. The literature supports the fact that lack of bowel mobilization and faster access to the renal hilum contributes to the shorter operative times and results in earlier return of bowel function postoperatively[9,15]. We also believe that lack of total renal mobilization to access the posterior surface of the kidney contributes to shorter operative times and a lower EBL.

The ability to perform more procedures off-clamp *via* the RP approach was likely due to the simplicity and speed at which the renal hilum could be identified, thereby also allowing for easy identification of the renal hilum to place a bulldog clamp if necessary during tumor excision. Conversion to an open procedure was performed more commonly during the TP approach at 13.5% *vs* 3.7% in *via* the RP group. Although not statistically significant, this is likely due to the ease at which the renal hilum can be accessed and lack of bowel mobilization required for the RP approach. Regarding the differences in laterality of tumors, specifically that a majority of patients with left-sided tumors underwent resection *via* the TP approach (59.5%), whereas a majority of patients with right-sided tumors were *via* the RP approach (63%, $P = 0.04$), remains unclear. This difference is possibly due to anatomical reasons, such that there is no need for liver retraction and placement of an additional port for RALPN for right-sided tumors when performed *via* the RP approach.

Most patients were discharged on postoperative day one or two after RP or TP RALPN, and therefore length of hospital stay was not evaluated in our study.

Partial nephrectomy remains the standard of care for small renal masses in appropriately selected patients[14]. The RP approach to RALPN has proven an effective approach for posterior renal masses with acceptable oncologic and morbidity outcomes, including preservation of postoperative renal function[6]. In our study, more RP procedures were performed off-clamp. Despite the fact that there was no significant difference in postoperative renal function, we believe in the importance of performing RALPN off-clamp if it is deemed safe and possible, in an attempt to maximally preserve renal function.

The oncological outcomes after RP partial nephrectomy have proven similar to those of competing approaches including rate of recurrence and positive margins. The literature demonstrates positive margin rates of 0%-5.6% for RP RALPN, and recurrence rates of 1.5%-6%. Of note, positive margin rates for open partial nephrectomy and laparoscopic RP partial nephrectomy are similar at 1.3%-1.5% and 2%-7.1%, respectively[6]. Our incidence of positive margins was lower *via* the RP approach (2%) when compared to the TP approach (8.6%), however this was not statistically significant. We believe that it is important to note the dramatic difference, which may be due to better tumor visualization during excision *via* the RP approach. Our recurrence rate was low for both approaches, with only one recurrence in the RP group.

Our results support existing literature demonstrating the superiority of the RP approach to RALPN with regard to operative time, blood loss, preservation of renal function, and oncologic outcomes[2,5]. The current study, however, was the first to evaluate outcomes of RP RALPN exclusively for posterior renal masses. With an increasing body of data to support its use, increased familiarity with the RP approach to RALPN may lead to widespread adaptation of this technique, particularly for posterior renal tumors.

The limitations of our study include the retrospective design and lack of randomization. A selection bias likely existed as the surgical approach was determined by the primary surgeon based on the tumor location and characteristics. Patients with posterior renal tumors were more likely to be selected to undergo the RP approach to RALPN. Despite this, however, the findings of decreased total operative time, robotic console time, and EBL remain significant. A prospective, randomized trial is necessary to remedy this selection bias. Randomization should include both right- and left-sided posterior renal tumors performed *via* the RP and TP approaches. Another limitation includes the short follow-up interval for assessment of postoperative renal function, which was measured at an average of only 4.5 mo. Long-term assessment of oncological outcomes is needed, as our study included radiographic follow-up at an average of less than 1 year postoperatively.

In conclusion, the TP and RP approach to RALPN are feasible approaches for posterior renal masses. The RP approach to RALPN, however, is superior with regard to operative time and blood loss when compared to the more familiar TP approach.

COMMENTS

Background

Robotic-assisted laparoscopic partial nephrectomy (RALPN) is increasingly utilized as an alternative to laparoscopic or open partial nephrectomy for surgical extirpation of renal masses, and can be performed *via* a transperitoneal (TP) or retroperitoneal (RP) approach. The majority of the literature describes the TP approach as it has been more widely adopted, however the RP approach has been shown to have specific advantages. No study has evaluated the use of the RP approach to RALPN specifically for posteriorly located renal tumors.

Research frontiers

The literature suggests that the RP approach to RALPN is an acceptable alternative to the TP approach, however no studies have compared these methods specifically for posteriorly located tumors. The current study evaluates the use of RALPN for posterior renal tumors *via* the TP and RP approaches in regards to perioperative, renal functional, and oncological outcomes.

Innovations and breakthroughs

The RP approach to RALPN has been proven to have specific advantages over the TP approach including direct access to posterior and lateral tumors without whole kidney mobilization, direct access to the renal artery, and lack of need for bowel mobilization. This study was the first study to examine the use of the RP approach to RALPN specifically for posteriorly located renal tumors. The authors concluded that the RP approach to RALPN for posterior renal tumors is associated with decreased total operative time, robotic console time, and estimated blood loss, and is more likely to be performed off-clamp when compared to the TP approach.

Applications

This study suggests that the RP approach to RALPN is a safe alternative to the more familiar TP approach for surgical extirpation of posterior renal tumors, and is associated with decreased total operative time, robotic console time, and estimated blood loss. The RP approach to RALPN is also more likely to be performed off-clamp, and is associated with similar oncological outcomes and postoperative renal function. The authors' findings support the use of the RP approach to RALPN for posteriorly located renal tumors.

Terminology

The RENAL nephrometry score is a scoring system to objectively describe anatomic characteristics of renal tumors including tumor radius, amount of tumor that is exophytic, nearness of deepest portion of the tumor to the collecting system or renal sinus, anterior or posterior location, and location relative to the polar line.

Peer-review

The study is interesting.

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Pre-transplant treatment of large polycystic kidney

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Abstract

AIM: To evaluate the indications, optimal timing and outcomes of native nephrectomy and other techniques in pretransplant treatment of autosomal dominant polycystic kidney disease (PKD).

METHODS: A literature review was conducted using the PubMed and Epistemonikos databases. Keywords for pre-transplant surgical management of polycystic kidneys were: Transplant, treatment and PKD. Keywords for pre-treatment embolization of PKD were: Embolization, transplant and polycystic kidney disease. The inclusion criterions were all articles found using this search method. The exclusion criterions were articles found to include bias and not attending pre-transplant treatment options. Fifteen articles were included in our final analysis. Ten articles were found regarding embolization of PKD of which three reviews were selected for final analysis. The reviews were divided into pre transplant and intra transplant treatment for the surgical treatment of PKD. All articles meeting inclusion criteria were thoroughly analyzed by two independent reviewers. A third independent reviewer was consulted if the reviewers did not agree upon the inclusion or exclusion of a specific article. No statistical analysis was performed.

RESULTS: Studies vary regarding the technique used (open or laparoscopic), laterality (single or bilateral) and temporality of nephrectomy with respect to renal transplant (pre-transplant or simultaneous to transplant). Several groups argue in favor of simultaneous nephrectomy and kidney transplant since it avoids the deleterious effects of being anefric. Long-term results and patient satisfaction are acceptable. However, it is associated with increased operative time, transfusion rate, morbidity and length of hospital stay. Based on small sample studies, bilateral nephrectomy prior to transplant has been associated with a higher risk of morbidity and mortality. Studies on laparoscopic approach report it as a feasible and safe alternative to the open surgery approach, highlighting its lower complication rate, transfusions and shorter hospital stay. Arterial embolization of the kidney appears as an effective

and low morbid alternative for the management of large native kidneys. The reduction in renal size allow transplant in a significant number of patients, which makes it an appealing alternative to surgery.

CONCLUSION: There is limited evidence regarding best pretrasnplant treatment of large PKD but to date embolization seems an appealing alternative to augment space for renal graft allocation.

Key words: Polycystic Kidneys; Kidney transplant; End stage renal disease; Kidney embolization

Core tip: Pre-transplant management of polycystic kidneys for patients with end-stage renal disease is unclear. A number of studies have advocated in favor of bilateral nephrectomy prior to transplant, others promote simultaneous nephrectomy and kidney transplant. Arterial embolization to reduce native kidney volume appears as an effective and attractive alternative.

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INTRODUCTION

Autosomal dominant polycystic kidney disease (ADPKD) is responsible for approximately 10% of all cases of end stage renal disease[1] and is the leading cause of inherited kidney failure in the United States and Europe[2-7].

For patients with ADPKD who reach end stage renal disease, the preferred treatment is kidney transplant, which permits an improved survival and lower morbidity rate compared to other forms of renal replacement therapy[8-13].

The indications for native nephrectomy in patients with ADPKD are: (1) Very large kidneys, causing lack of space for the transplant; (2) chronic and severe abdominal or lumbar pain attributable to the mass; (3) recurrent UTI or urosepsis due to cyst infection, especially in those not responding to medical treatment; (4) hematuria requiring recurrent or persistent blood transfusions; (5) gastrointestinal symptoms (early satiety) secondary to mass compression; and (6) suspicious of malignancy on preoperative diagnostic images.

These indications and timing of nephrectomy in ADPKD patients remains controversial for those undergoing renal transplant. While most ADPKD patients do not require either a unilateral or bilateral nephrectomy to facilitate kidney transplant, the size of the kidneys and associated symptoms in some cases provide sufficient indications for surgery. Some authors advocate for native unilateral or bilateral nephrectomy prior to transplant; others promote unilateral or bilateral native nephrectomy at the time of transplant, and others suggest doing the native nephrectomy following the transplant[14]. Another method described is the "sandwich technique", where the most severely affected native kidney is removed prior to transplant and the other native kidney is removed subsequently[15]. All these approaches have been described with open surgical techniques, but lately, some centers have published their experience with laparoscopy showing promising results[16].

Arterial embolization and secondary shrinkage of very enlarged kidneys has been proposed as an alternative to nephrectomy in selected cases, with the sole objective of making anatomical space for transplant or treating symptoms related to kidney volume [17].

All of the above methods show advantages and disadvantages.

The aim of this review is to evaluate the indications, optimal timing and outcomes of native nephrectomy and other techniques in patients with ADPKD as related to kidney transplant.

MATERIALS AND METHODS

A literature review was conducted using the PubMed and Epistemonikos databases. Keywords for pre-transplant surgical management of polycystic kidneys were: Transplant, treatment and polycystic kidney disease. Keywords for pre-treatment embolization of PKD were: Embolization, transplant and polycystic kidney disease. The inclusion criterion was all articles found using this search method. The exclusion criterions were articles found to include bias and not attending pre-transplant treatment options. As a result of our search, 15 articles were found for surgical treatment and included in our final analysis. Ten articles were found in the embolization search with 3 reviews subject for final analysis. The reviews were divided into pre transplant and intra transplant treatment for the surgical treatment of PKD. All articles meeting inclusion criteria were thoroughly analyzed by 2 independent reviewers. A third independent reviewer was consulted if the reviewers did not agree about the inclusion or exclusion of a specific article. No statistical analysis was carried out.

RESULTS

Fifteen articles present results of surgical treatment in ADPKD and renal transplant. They vary with regard to the technique used (open or laparoscopic), laterality (single or bilateral) and temporality with respect to renal transplant (pre-transplant or simultaneous to transplant). Table 1 shows the results of these series.

Unilateral or bilateral nephrectomy simultaneous to renal transplant

The majority of series incorporate this modality. This

Table 1 Summary of the nephrectomy series results

Author	Year	*n*	Technique Open/ laparoscopic	Side Uni/Bilateral	Relation with trasplant Pre-trasplant/ simultaneous/posttrasplant	Transfusion (units)	Complications (%)	Mortality
Song	2011	31	Open	Bilateral	Simultaneous	4.68 ± 1.51	32	No
Glassman	2000	10	Open	Bilateral	Simultaneous	2.3	20	No
Tabibi	2005	13	Open	7 UI/6 bilat	Simultaneous	ND	ND	No
Skauby	2012	78	Open	Bilateral	Simultaneous	1.6 (0-11)	30	No
Kramer	2009	20	Laparoscopic	Bilateral	Simultaneous	3.3 (0 - 8)	20	No
Dunn	1999	11	Laparoscopic	7 UI/2 bilateral	Pre-trasplant	ND	55	No
Nunes	2007	16	Open	Unilateral	Simultaneous	1.81	6.3	No
Lucas	2010	42	Laparoscopic	18 UI/24 bilateral	Pre/posttrasplant	ND	25	No
Desai	2007	13	Laparoscopic	5 UI/7 bilateral	Pre/postrasplant	0.9	60	No
Krol	2006	20	Open	Bilateral	Pretrasplant	3.2	45	No
Neeff	2012	100	Open	Unilateral	Simultaneous	ND	22	No
Wagner	2006	32	Open	Bilateral	17 simultaneous/15 pretrasplant	2.2	70 (simultaneous) 75 (pretrasplant)	No
Kirkman	2010	35	Open	10 UI/10 bilateral	Pretrasplant	ND	35	Yes (2 patients, bilateral group)
Tyson	2013	2368	Open	Bilateral	271 simultaneous/2097 pretrasplant	ND	ND	Yes (1.1% simultaneous-15.8% pretrasplant)

procedure does not show major risks when compared to renal transplant exclusively[18-25].

These series have longer surgical times, higher transfusion and complication rates when compared to renal transplant alone. However, they all coincide on favorable long-term results of renal graft function and global survival. These series do not show mortality rates.

Song *et al*[18] reports that 32 patients with ADPKD who were transplanted without nephrectomy had a greater incidence of hypertension (91% *vs* 66%) and urinary tract infection (31% *vs* 6.4%) compared to a similar group where simultaneous bilateral nephrectomy and renal transplant was performed.

Glassman reports that in nine transplanted patients, postoperative creatinine was 2.2 *vs* 1.6 in the simultaneous nephrectomy and transplant group. This study incorporates a non-validated user satisfaction survey: 70% of patients submitted to the double procedure were satisfied. In patients submitted to transplant exclusively, 7 out of 9 would have preferred simultaneous nephrectomy[19].

Neeff *et al*[24] presents a series of 100 patients with ADPKD submitted to nephrectomy with a prolonged unilateral midline Gibson incision. Only 12% of patients presented postoperative complications (linfocele, hernia, hematoma, haemorrhage). Four percent of patients had to be operated due to one of these complications. Overall renal graft survival was of 96% and 80% in years 1 and 5, respectively. Graft survival rates are similar to series without nephrectomy. This study does not present a control group.

Fuller at UCLA presents 32 patients submitted to nephrectomy at all times. Seven patients underwent nephrectomy before transplant, 16 simultaneous with renal transplant and nine post-transplant. There were no differences in terms of complications. This study suggests performing unilateral or bilateral nephrectomy simultaneous to transplant, especially in the live donor setting[25].

Other authors study results in patients submitted to bilateral nephrectomy; some patients were also transplanted simultaneously. In these series, surgical times and complications rates in the compared groups were similar[16,26,27].

Wagner *et al*[26] reports shorter hospitalization stay in patients with simultaneous nephrectomy and transplant (6.9 d) *vs* differed nephrectomy and transplant (11.8 d for both hospitalization periods).

Tyson *et al*[27] presents the analysis of the Nationwide Inpatient Sample Database, demonstrating lesser mortality in the nephrectomy and transplant (OR = 0.06) compared with the bilateral nephrectomy without transplant group. This difference is not found when analyzing high volume centers only.

Martin *et al*[16] reports better postoperative creatinine values in patients submitted to laparoscopic bilateral nephrectomy and simultaneous transplant compared to differed transplant (1.6 *vs* 2.3 mg/dL).

Pre-transplant bilateral nephrectomy

Two authors present very small series with pre-transplant nephrectomy with differed transplant. Both show the highest postoperative complications rate and mortality.

Kirkman analyzes outcomes of patients submitted to unilateral or bilateral nephrectomy before or after transplant. Mortality is present in this series. In the pre transplant bilateral nephrectomy group 2 of 10 patients died, while in the bilateral differed nephrectomy group 1 of 10 patients died. All deaths were due to colonic ischemia leading to multiorgan failure. There is no statistical analysis for this difference[14].

Król *et al*[28] presents 20 patients in hemodialysis submitted to open bilateral nephrectomy. Postoperative complications were present in 9 of 20 patients (45%).

Table 2 Serum creatinin at discharge in transplant and nephrectomy series

Author	Year	Creatinin at discharge	
		Transplant	Transplant + nephrectomy
Wagner	2006	2	1.6
Lucas	2010	1.6	1.5
Nunes	2007	1.79	1.6
Kramer	2009	2	1.6
Tabibi	2005	1.2	1.3
Glassman	2000	2.2	1.6
Wagner	2007	2	1.6
Martin	2012	2.3	1.6

Complications described include hernia, chronic abdominal pain, peptic ulcer and ileum. This series does not present mortality.

Laparoscopic nephrectomy

Two authors present small laparoscopic nephrectomy series, with no control group. There is a lesser complication, transfusion, pain and hospital stay rate as compared to cohorts with open surgery. There is no mention of graft function or survival with this technique[29,30].

Pre-transplant embolization of polycystic kidneys

There are few cohorts that show the effect of embolization of renal arteries to reduce the size of polycystic kidneys for graft space. In 2010, Cornelis *et al*[17] published their experience of 25 patients with ADPKD awaiting renal transplant treated with embolization. Renal size was evaluated with computed tomography scan pre embolization and at 3 and 6 mo post procedure. Thirty-six percent and 84% of patients had a reduction of renal size at 3 and 6 mo, allowing renal transplant. Mean reduction in renal size at these times was 42% and 54%. The main complication reported was post embolization syndrome in five patients. This syndrome is characterized by low fever and severe lumbar pain. Pain was managed with opioid derivatives, disappearing in 2 wk post procedure. One patient developed a pseudo-aneurism at the puncture site, managed with manual compression. These authors conclude that trans-arterial embolization prior to renal transplant is an option to nephrectomy and suggest a post-therapy pain management protocol[17].

This same group published their results in 2014, presenting now a series of 73 patients in which 82 procedures were performed in 76 rental units. Renal artery embolization was successful in diminishing renal size by 89.5% at 5.6 mo after treatment (range 2.8 to 24.3 mo). Mean renal size reduction was 59% 3 mo post embolization. Post embolization syndrome was present in 15 procedures (18.3%). Complications described in this series include one pulmonary embolism, one iliac artery thrombosis, a pseudo aneurysm of the femoral artery and an infection of a renal cyst, all categorized as grade Ⅱ complications according to the Clavien Dindo classification. This group describes 43 successful transplants with previous renal embolization[31].

DISCUSSION

All published series present small patient cohorts. This does not allow categorical conclusions regarding pre-treatment options of very large ADPKD. The largest series, presented by Skauby *et al*[21] and Tyson *et al*[27], coincide in that there is a longer surgery time and complication rate in nephrectomy with concomitant transplant than in transplant alone. Tyson also refers to the possible better prognosis for patients that receive transplant with simultaneous nephrectomy. However, this difference could be accounted for by technical experience more than a graft-related determinant factor.

Another factor to consider is the function of the graft at the moment of hospital discharge. Reports seem to indicate that the function of the graft may be better when it is done with simultaneous nephrectomy as compared to transplant and differed nephrectomy (Table 2).

It seems that the worst moment for nephrectomy is before or after the transplant. Although these series are small, Kirkman *et al*[14] and Król *et al*[28] report higher rates of complications and mortality -up to 20%- in patients with bilateral nephrectomy without immediate transplant. The factors that may explain this are anephric time and permanence in dialysis.

Post-transplant nephrectomy, though not a central objective of our study, seems to have a greater rate of urinary tract infection due to cyst infection. This greater infection rate may be due to immune-suppression in the transplanted patient. This argument is frequently employed to perform nephrectomy pre or intra transplant.

There are few reports studying renal embolization for volume management of ADPKD. There is only one group actively working on this subject, with excellent results in terms of reduction of renal size and pain control[17,31].

While our experience in embolization previous to transplant is limited, our results coincide with those shown previously in diminishing renal size and augmenting space for renal graft allocation. If we could suggest something it would be to use an epidural catheter for pain control after embolization. Another suggestion would be to embolize using not only coils but also ethanol to attain an adequate level of ischemia and posterior renal atrophy. We strongly believe that embolization of polycystic kidneys will have a leading role in the near future.

COMMENTS

Background

Autosomal dominant polycystic kidney disease plays a key role in chronic kidney disease. So far, the timing of the surgical procedure remains unclear, especially related to kidney transplantation.

Research frontiers

To find the best timing for kidney transplantation (before, concomitant, or after nephrectomy), comparing both living and cadaveric donors. Strong evidence supported by collaborative multi centric trials is necessary. The authors believe embolization of polycystic kidney disease plays an important role in this setting,

especially in low volume centers.

Innovations and breakthroughs

Embolization only requires an interventional radiologist that allows adequate management with a minimally invasive approach. This technique should be considered as a first line treatment instead of nephrectomy.

Applications

End stage and complicated autosomal dominant polycystic kidney disease (ADPKD).

Peer-review

The authors reviewed the literature regarding surgical approach and timing for the native nephrectomy for patients with ADPKD being scheduled kidney transplantation. The paper is well-written and provides important information regarding this aspect.

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CASE REPORT

Case of intramedullary spinal cord metastasis of renal cell carcinoma

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Abstract

Intramedullary spinal cord tumors are rare. The improved survival resulting from more effective treatments for many cancers has led to an increased number of publications concerning intramedullary spinal cord metastasis (ISCM), including case reports and literature reviews; however, ISCM remains extremely rare in renal cancer. A 69-year-old man with a medical history of renal cell carcinoma (RCC) presented with urinary retention and bilateral paralysis of the lower extremities. A neurological examination revealed bilateral paraparesis below L1. Although brain magnetic resonance imaging (MRI), bone scintigraphy, and abdominal contrast-enhanced computed tomography revealed no abdominal findings, the thracolumbar MRI indicated a spot on the spinal cord at the Th12 level that exhibited hyperintensity on T2-weighted imaging and gadolinium diethylenetriaminepentaacetic acid enhancement on T1-weighted imaging. Accordingly, an ISCM of RCC was diagnosed. The patient rejected all treatments for these metastases except the steroid therapy. The patient's condition deteriorated owing to metastatic progression, and he died 3 mo after the appearance of ISCM symptoms. The prognosis of this condition was poor. The mean survival durations were 8 mo with surgical treatment, 4 mo with irradiation, and 2 mo with palliative treatments. In cases involving neurological features and if brain or bone metastasis or spinal cord compression is not clearly observed, gadolinium-enhanced MRI should be performed to determine the existence of ISCM. Recently, some authors have reported the efficacy of ISCM resection. Surgical treatment could potentially yield improvements in the nervous symptoms or a longer survival after treatment. Although the prognosis was poor in most cases of ISCM, surgical treatment may improve the patient's quality of life.

Key words: Renal cancer; Intramedullary spinal cord metastasis; Magnetic resonance imaging

Core tip: Intramedullary spinal cord metastasis (ISCM)

is extremely rare in renal cancer. A 69-year-old man with a medical history of renal cell carcinoma presented with urinary retention and bilateral paralysis of the lower extremities. A neurological examination revealed bilateral paraparesis below L1. ISCM of renal cell carcinoma was diagnosed *via* thracolumbar gadolinium-enhanced magnetic resonance imaging (MRI). In a case involving neurological features and if brain or bone metastasis or spinal cord compression is not clearly observed, gadolinium-enhanced MRI should be performed to reveal the existence of ISCM.

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INTRODUCTION

Intramedullary spinal cord tumors are rare. The improved survival resulting from more effective treatments for many cancers has led to an increased number of publications concerning intramedullary spinal cord metastasis (ISCM), including case reports and literature reviews; however, it is still extremely rare in renal cancer. Lung cancer and breast cancer are the most common primary tumors associated with ISCM[1,2]. In the present case, a 69-year-old man with a medical history of renal cell carcinoma (RCC) presented with urinary retention and bilateral paralysis of lower extremities. Magnetic resonance imaging (MRI) revealed an ISCM of RCC.

CASE REPORT

A 69-year-old man presented with cough since the previous month. The patient was diagnosed with stage Ⅳ renal cancer and multiple pulmonary metastases following a radical left nephrectomy and right segmental lung resection. A histopathological examination confirmed clear cell carcinoma, grade 2, pT1b, pM1-pul. Immunotherapy was initiated, with interferon alpha as an adjuvant therapy. Three months after adjuvant therapy initiation, the patient observed urinary retention after experiencing gait unsteadiness. The results of serum biochemical and hematological evaluations were normal. A neurological examination revealed bilateral paraparesis below L1. Deep tendon reflexes were absent in both legs. Brain MRI and bone scintigraphy revealed no abnormal findings. An abdominal contrast-enhanced computed tomography did not reveal a lymphatic mass or liver metastasis; however thracolumbar MRI indicated a spot on the spinal cord at the level of the Th12 level that exhibited hyperintensity on T2-weighted imaging and gadolinium diethylenetriaminepentaacetic acid enhancement on T1-weighted imaging (Figure 1). According to the radiographic findings and clinical history, the patient was diagnosed with an ISCM of RCC. The patient rejected all treatment for these metastases except steroid therapy. His condition deteriorated due to metastatic progression, and he died 3 mo after the appearance of ISCM symptoms.

DISCUSSION

Intramedullary spinal cord tumor is rare. Clinically, intramedullary metastatic disease affects only 0.1%-0.4% of all cancer patients and comprises only 1%-3% of all intramedullary spinal cord neoplasms[3]. Furthermore, intramedullary metastatic disease clinically affects only 4%-8.5% of all cancer patients with central nervous system metastases[4,5]. In a study of 1096 autopsy cases with neoplasms, 200 cases (18%) were found to harbor central nerves system metastases, and ISCMs were found in 10 cases (0.9%) of those cases. In that report, 199 of the 200 metastatic cases had lung tumors. ISCM might result from venous dissemination *via* the Batson's plexus or direct nerve root invasion[6]. Most cases of ISCM might have additional metastases with various clinical features that cause unique symptoms such as gait disturbance or leg weakness; however, Rykken *et al*[1] reported that the clinical presentation of the ISCM preceded the primary tumor diagnosis in 20% of patients. Those authors suggested that the lack of a known primary malignancy should not dissuade clinicians from considering an ISCM when faced with a spinal cord mass[1]. MRI is generally a useful modality for the diagnosis of ISCM; furthermore, gadolinium-enhanced MRI is recommended as the most efficient diagnostic method, because unenhanced MRI dose not routinely yield critical findings.

Based on an understanding of the mechanism underlying RCC initiation and progression, several clinical trials evaluated the molecular targeting of RCC and observed efficacy against metastatic RCC[7]. However, no reports described the efficacy of the molecular targeting therapies against ISCM, possibly because some metastases already existed at the time of ISCM diagnosis. Several therapies, such as laminectomy, tumor reduction surgery, irradiation therapy, or steroid therapy, are used for ISCM treatment. The mean survival durations were 8 mo with surgical treatment, 4 mo with irradiation, and 2 mo with palliative treatment. Recently, some authors reported the efficacy of surgical ISCM removal[2,8]. Despite the poor prognosis of most cases, surgical treatment could potentially yield improvements in the nervous symptoms or survival duration one of more than 1 year after treatment[8]. Therefore, surgical treatment might be considered to effectively improve the patient's quality of life. In the present case, we selected palliative steroid treatment because of the rapid lung metastasis growth and patient's wishes. Steroid therapy significantly reduced the edematous infiltration observed

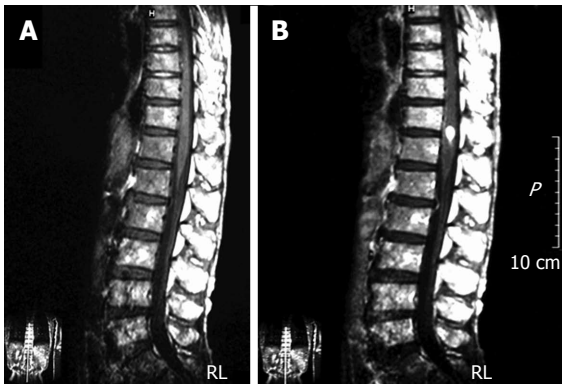

Figure 1 The thracolumbar T1-wighted magnetic resonance imaging. Though unenhanced magnetic resonance imaging (MRI) revealed no abnormal finding (A), gadolinium diethylenetriaminepentaacetic acid enhanced MRI indicated a spot on the spinal cord at the Th12 level (B).

on MRI, but did not improve the patient's symptoms in our case.

In a case involving neurological features and if brain or bone metastasis or spinal cord compression is not evident, gadolinium-enhanced MRI should be performed to reveal the existence of ISCM. Depending on the patient's condition, surgical treatment may be selected to improve the patient's quality of life.

COMMENTS

Case characteristics

A 69-year-old man with a medical history of renal cell carcinoma presented with urinary retention and paralysis of bilateral lower extremities.

Clinical diagnosis

Neurological examination revealed bilateral paraparesis below L1.

Differential diagnosis

Bone metastasis, brain metastasis, and pathological compression fracture.

Laboratory diagnosis

The results of serum biochemical and hematological evaluations were normal.

Imaging diagnosis

The thracolumbar magnetic resonance imaging (MRI) indicated a spot on the spinal cord at the Th12 level that exhibited gadolinium diethylenetriaminepentaacetic acid (DTPA) enhancement on T1-weighted imaging.

Pathological diagnosis

Although histopathological examination of renal tumor confirmed renal cell carcinoma (clear cell carcinoma, grade 2, pT1b), pathologic examination of tumor in spinal cord was not performed.

Treatment

The patient rejected all treatments for metastases except the steroid therapy.

Related reports

According to some reviews concerning intramedullary spinal cord metastasis (ISCM), lung cancer was the most frequent primary malignant disease, followed by brain and breast cancers.

Term explanation

ISCM is rare, which comprises only 1%-3% of all intramedullary spinal cord neoplasms.

Experiences and lessons

The gadolinium DTPA enhanced MRI is the most efficient diagnostic method, and early diagnosis and surgical treatment might improve the patient's quality of life.

Peer-review

The paper describes an unusual metastasis in renal carcinoma and also provides information concerning the frequency of this rare spinal cord metastasis by other neoplasm.

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