Review of the current management of radiation-induced ureteral strictures of the pelvis

Pooja Srikanth[1]^, Hannah E. Kay[1]^, Adan N. Tijerina[1]^, Arjun V. Srivastava[1]^, Aaron A. Laviana[1,2]^, J. Stuart Wolf Jr[1,2]^, E. Charles Osterberg[1,2]^

[1]University of Texas Dell Medical School, Austin, TX, USA; [2]Dell Medical School Department of Surgery and Perioperative Care, and Ascension Seton Hospital Network, Austin, TX, USA

Contributions: (I) Conception and design: EC Osterberg, P Srikanth; (II) Administrative support: EC Osterberg, AA Laviana, JS Wolf Jr; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: P Srikanth, HE Kay, AN Tijerina, AV Srivastava; (V) Data analysis and interpretation: P Srikanth, HE Kay, AN Tijerina, AV Srivastava; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Pooja Srikanth. University of Texas Dell Medical School, 1501 Red River St., Austin, TX 78712, USA. Email: pooja_srikanth@utexas.edu.

Abstract: Radiation therapy to the pelvis is indicated for cervical, prostate, rectal, and gastrointestinal (GI) malignancies. A rare, but known adverse effect of this treatment is radiation-induced ureteral stricture (RIUS). RIUS can cause infection, hydronephrosis, kidney stone formation, and ultimately, renal failure. Management of RIUS is a challenge to urologists as the strictures tend to be long, bilateral, and ischemic in etiology. Management of RIUS is divided into endoscopic, open, and minimally invasive techniques. Stents and percutaneous nephrostomy (PCN) tubes are generally used as temporizing measures until definitive repair, but they may be a long-term option for patients unfit for surgery. Balloon dilatation and endoureterotomy have shown efficacy between 60–80% but are less effective in radiation-induced stricture due to the ischemic nature of the insult. Ureteroureterostomy (UU) is best suited for short strictures in the mid-to-proximal ureter. Ureteroneocystostomy is better suited for longer strictures in the distal ureter and may be paired with psoas hitch or Boari flap to increase coverage length. Importantly, for radiation patients, bladder fibrosis may be a contraindication to these procedures. Buccal graft ureteroplasty is increasingly being used with success rates between 80–90%, although this number decreases to around 30% in longer strictures. Finally, bowel substitutes are suitable for longer strictures and bilateral disease. Most recently, appendiceal interposition has been studied for both right- and left-sided strictures around 3–5 cm, with success rates around 70%. More invasive and potentially morbid techniques like transureteroureterostomy (TUU) and renal autotransplantation are reserved for extremely long or pan-ureteral strictures and are usually unsuitable for cancer patients who have undergone radiotherapy. In general, minimally invasive approaches, while less studied, have demonstrated similar clinical outcomes and complication rates, with less pain and shorter hospital stays. In this review, we will summarize the most up-to-date literature in this field, detailing the current management of RIUS.

Keywords: Radiation; radiotherapy; ureteral stricture; stricture; radiation-induced ureteral stricture (RIUS)

^ ORCID: Pooja Srikanth, 0000-0002-5188-0234; Hannah E. Kay, 0000-0003-2085-9202; Adan N. Tijerina, 0000-0001-6647-5525; Arjun V. Srivastava, 0000-0002-6169-8209; Aaron A. Laviana, 0000-0002-8301-6344; J. Stuart Wolf Jr, 0000-0003-2102-6085; E. Charles Osterberg, 0000-0002-9752-8914.

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Introduction

By definition, a ureteral stricture is a narrowing of the muscular tube connecting the kidneys to the bladder coursing through the retroperitoneum, causing a functional obstruction that can lead to urinary tract dilatation, infection, hydronephrosis, development of kidney stones, and, if persistent, renal failure (1).

Strictures of the ureter can be caused by a multitude of benign and malignant etiologies. Benign causes include congenital malformation, secondary injury after endoscopic or open surgery, stone impaction, infection, retroperitoneal fibrosis, extrinsic compression from adjacent vessel aneurysm, and ischemic injury and fibrosis secondary to radiation therapy. Malignant causes include both intrinsic obstruction from urothelial carcinoma, local invasion, or metastasis to the ureter, and extrinsic compression due to mass effect from adjacent malignancy (2). Strictures may also arise post-renal transplant or urinary diversion where the ureteral anastomosis is made to the bladder or bowel segment (3-5).

Strictures can also be stratified by location (proximal, mid, and distal ureter). The proximal third of the ureter extends from the ureteropelvic junction (UPJ) to the upper border of the sacroiliac joint, and is involved in 2% of strictures. The middle third courses over the bony sacrum and is involved in 7% of strictures. The distal third extends from the inferior border of the sacroiliac joint to the ureterovesical junction (UVJ) within the bladder and is by far the most commonly affected by stricture disease, with 91% of stricture pathology occurring in that region (6,7).

Radiation-induced strictures have an incidence of approximately 2% to 3%, with 0.15% added risk per year for 25 years or more post-radiation (8). It is most commonly seen in radiotherapy for prostate cancer, cervical cancer, and retroperitoneal sarcoma, and the risk of ureteral obstruction increases with dose in all instances (9). Radiation-induced injury is thought to originate from damage to the basement membrane of capillaries providing blood supply to the ureter. This leads to occlusion, thrombosis, and a compromised blood supply, which in turn triggers the proliferation of fibroblasts and the development of obstructive fibrosis (10). Tissue that has undergone radiation damage has considerably less regenerative capacity because of these cellular changes, and it can impact the mobility of the tissue which may limit the range of therapeutic options (11).

Aim

This article will focus on the management of ureteral strictures secondary to pelvic radiation treatment. We will discuss the roles of endoscopic and surgical management in radiation-related strictures, as well as review the most up-to-date evidence on minimally invasive approaches to surgical repair. Our discussion will also include specific concerns relevant to handling irradiated tissue. Because pelvic radiation predominantly affects the distal ureter, the emphasis on management strategies will be focused on the distal ureter.

Radiation and ureteral injury

History of radiation

Radiation therapy is a widely-used treatment for a variety of pelvic and genitourinary cancers (12,13). First discovered in the late 19th century, radiotherapy was initially utilized to treat skin cancers, given the relatively shallow depth of penetration of X-rays. Then in the 1910's, William D. Coolidge developed a device which emitted external rays that penetrated further into tissue, allowing for treatment of deeper cancers (14). Over time, scientists began to better understand the impact of radiation on tissues, as well as benefits of fractionated doses over multiple treatment sessions in treating disease while balancing the adverse effects (15). From 1930 to 1950, two new techniques were refined-brachytherapy, which did not require an external beam source, and electron beam therapy, which offered higher energy and more targeted treatment to deeper tissues (16). At the close of the 20th century, as radiotherapy coalesced into a recognized medical specialty, more techniques were refined, including the use of computer-assisted accelerators to deliver high-energy ion beams and the development of stereotactic radiation therapy, utilizing computer-generated 3D models (17,18). Image-guided radiotherapy has continued to progress in the new millennium, offering patients and providers new options for effective and targeted therapy, improving outcomes and minimizing adverse effects to non-diseased tissue.

Pelvic radiotherapy and radiation-induced ureteral stricture (RIUS)

Pelvic radiotherapy has traditionally been utilized in the treatment of colorectal, cervical, and prostate cancers, especially in higher-grade disease for which surgical intervention is not an option. Over time, whole pelvis radiation has dwindled in popularity, giving way to more targeted therapies. Despite this, pelvic radiation is associated with a high risk of morbidity, often causing a constellation of symptoms including gastrointestinal (GI) symptoms, radiation enteritis/proctitis, radiation cystitis, and the development of stricture and scar tissue in the GI and urinary tracts, termed collectively as "pelvic radiation disease" (19). Ureteral stricture was first reported as a complication of radiation treatment in 1920 by Dr. Henry Schmitz and has since become a well-described complication of radiation to the pelvis. Ureteral stenosis has been reported as a consequence of external beam radiation therapy (EBRT) [including intensity-modulated radiation therapy (IMRT) and proton therapy], brachytherapy, photon beam therapy, and intraoperative electron-beam radiotherapy (IOERT) (20).

Malignancies most associated with RIUS include cervical cancer, prostate cancer, and retroperitoneal sarcoma. The incidence of RIUS varies, depending on the mode of radiation delivery and the type of cancer being treated. Prostate cancer patients traditionally receive a dose of 60–64 Gy radiation therapy and have a much lower incidence of ureteral stenosis than patients receiving radiotherapy for cervical cancer. However, prostate cancer patients receiving upwards of 70 Gy have been reported to experience RIUS (21). The overall 10-year propensity-weighted cumulative incidence of ureteral stenosis following EBRT for prostate cancer is reported as 2.7% (22). While a rare complication of radiation for prostate cancer, ureteral stenosis is most common after radical prostatectomy with salvage EBRT, suggesting that ureteral manipulation once again is a risk factor for stenosis (23).

The incidence of severe ureteral stenosis for stage IB cervical cancer patients receiving the standard radiation dose is 1.0%, 1.2%, 2.2%, and 2.5% at 5, 10, 15, and 20 years, respectively. Patients with cervical cancer may receive radiation in the form of centrally-blocked external fields or transvaginally, which both come with an increased risk of developing ureteral stenosis (20). The incidence of ureteral stenosis does not significantly differ between patients who receive therapeutic hysterectomy and those who do not (24).

Colorectal cancer patients may receive pelvic radiation as part of their treatment modality. In one study of patients with recurrent rectal cancer receiving EBRT (45 Gy) and surgical management ± IOERT (10–20 Gy), 7% of the patients receiving IOERT developed ureteral obstruction versus 3% of the patients who did not receive concurrent IOERT (25). In another report, patients with locally recurrent colorectal cancer who received IOERT showed ureteral toxicity in 12 of 33 (36%) patients whose ureter was within the radiation field versus 7 of the 90 (8%) patients in whom the ureter was not within the IOERT field (26). This suggests that, regardless of malignancy being treated, IOERT is a risk factor for ureteral obstruction whether or not the ureter is directly irradiated.

Most recently, the EMBRACE trial described the incidence of ureteral stricture in a patient cohort treated with 3D image-guided adaptive brachytherapy (IGABT) delivered either through intracavitary or interstitial techniques for locally advanced cervical cancer. They found that the actuarial 3- and 5-year risk for ureteral stricture was 1.7%. The EMBRACE and similar RetroEMBRACE trials found that IGABT was not a significant predictor of ureteral stenosis, and only that hydronephrosis at diagnosis was the only significant risk factor for ureteral stricture (P=0.01) (27,28).

Finally, one study investigated the rate of ureteral stricture following radiation therapy for retroperitoneal sarcoma and indicated that dose was not a predictive variable, only concomitant surgical manipulation of the ureter reliably predicted stenosis following radiation therapy. Protocols within this particular study limited ureteral radiation to 50.4 Gy (29).

Endoscopic management

The two main goals of intervention in RIUS are to preserve renal function and relieve ureteral obstruction (30). Endoscopic management for RIUS offers a low-cost, low-morbidity alternative to formal ureteral reconstruction in carefully selected patients (5). The highest rates of success are in patients with short (<2 cm) strictures that are benign in etiology, nonischemic, and located in the proximal or distal ureter (5). Patients who are poor surgical candidates can potentially be treated successfully with an endoscopic treatment. However, endoscopic treatments are generally less effective in radiation-induced strictures because of the ischemic nature of the stricture and the decreased regenerative capacity of irradiated tissue (30).

Ureteral stents

Ureteral stents in the setting of RIUS can be used as a temporary treatment until a more definitive treatment option can be planned, especially in patients with an acute need for decompression. Use of stents for decompression is not restricted by length of ureteral stricture and ureteral stents can generally be placed either in a retrograde or anterograde fashion quickly and safely.

Multiple studies have demonstrated that stents have a higher rate of success in maintaining ureteral patency and urinary drainage in intrinsic causes of ureteral obstruction, which includes radiation-induced stricture, as opposed to external compression (31,32). Yossepowitch *et al*. [2001] reported on a population of 92 patients in whom retrograde stent placement was attempted in the setting of ureteral obstruction. Stent placement was successful in 94% of patients with intrinsic obstruction and 73% of patients with extrinsic obstruction, with the remainder of patients undergoing drainage via percutaneous nephrostomy (PCN). Notably, at 3-month follow-up, 100% of the stents in patients with intrinsic obstruction remained patent, compared to only 56% in patients with extrinsic obstruction. However, only 4/61 patients (7%) had obstruction due to ureteral stricture, with the majority of cases associated with stone disease (32).

Long-term ureteral stenting may be appropriate in patients with major contraindications to or no desire for operative management, including concurrent cancer diagnoses that may have required radiotherapy. Polymer stents require exchange every 3–6 months (33). Metallic stents, which are less prone to encrustation, are more resistant to external compression, and require exchange every 12 months, have grown in popularity to treat patients who require long-term stenting (11). Forbes *et al*. [2019] reviewed technological advances in ureteral stent design including metallic stents. Two metallic stents in a double J configuration, the Silhouette stent and the Resonance stent, are currently available. The Silhouette has been shown to have superior resistance to kinking and external compression to polymer stents in *in vitro* studies. However, to our knowledge, *in vivo* studies have not yet been performed. The Resonance stent has been examined in more studies and is approved for a maximum dwell time of 12 months. In a retrospective case series review of 42 patients with malignant ureteral obstruction, the Resonance stent's dwell time was 4 months longer than polymeric stents (5.3 *vs*. 1.7 months; $P<0.0001$) and renal function was maintained in 90% of patients throughout dwell time without major complications (34).

The use of metallic stents in radiation-induced strictures has been noted in studies, with varying results. Wang *et al*. [2011] reported on 19 patients who underwent metallic stent placement for intrinsic and extrinsic ureteral obstruction. In their study, patients with a history of radiation therapy had a lower ureter patency rate in comparison with non-irradiated patients (50% *vs*. 92%, $P=0.039$) (35). Similarly, Li *et al*. [2011] reported on use of metallic stents in the treatment of ureteral obstruction at a single institution. They found that stent patency was significantly lower in the radiotherapy group (4/8; 50%) compared to the non-radiotherapy group (15/15; 100%) (36). However, Kadlec *et al*. [2013] reported on 5 years of follow-up data for 47 patients who underwent metallic stent placement and found no association between previous radiation therapy and long-term success of stenting to manage obstruction (37).

Possible complications of ureteral stents include insertional failure, inadequate relief of obstruction, malposition, urinary tract infection, migration, encrustation, erosion, and fistulization (38). Urinary tract infection can develop as a result of stent placement or can be due to underlying pathology (39). The incidence of stent colonization evidenced by positive culture is 42–92%, but only a small subset of patients develop symptoms. Stent encrustation is related to indwelling time (75.9% at more than 12 weeks) and heavily encrusted stents may necessitate an additional procedure for removal (40). Ureteroiliac fistula is a rare but potentially life-threatening ureteral stent complication that develops between poorly vascularized distal segments of the ureter and adjacent iliac vessels (41). Additionally, stent pain and bothersome urinary symptoms occur in approximately 80% of patients likely secondary to irritation of the bladder by the distal curl of the stent and reflux of urine into the renal pelvis (42).

In summary, ureteral stents are a good option but should be considered temporary except in patients who are poor surgical candidates or have contraindications to surgical management. Success rates of maintaining renal function and patency in patients who have RIUS is between 50–100%.

PCN

The primary indication for PCN tube placement is decompression of the urinary tract due to obstruction, which can be benign or malignant in nature including ureteral radiation injury. PCN is usually performed under ultrasound or fluoroscopy guidance with the patient in a prone position. It is considered a safe intervention with a success rate >90% and low risk of major complications (43). Catheter dislodgement and obstruction by encrustation are the most common technical complications of nephrostomy tubes. Risk for both dislodgement and obstruction increases the longer the nephrostomy tube is in. The rates of these complications can be reduced by scheduled nephrostomy tube exchange every 2–3 months (44). However, for most patients, nephrostomy tubes are not a long-term treatment option due to the need for external drainage leading to decreased quality of life and more definitive surgical management is required (45).

The use of PCN in ureteral obstruction due to malignant causes has been associated with a small improvement in survival in the following months after diversion. However, external diversion did not confer any additional benefit to quality of life (46), most likely due to the presence of an external tube which often requires analgesia for somatic pain at the insertion site (47). It is important to note, however, that most studies have not separated RIUS in cancer patients from patients with advanced malignancy causing obstruction, so it is difficult to specify the exact benefit of PCN in this cohort. Generally, PCN can be utilized as a temporizing measure when planning for more definitive diversion.

Balloon dilatation

Balloon dilatation with subsequent temporary stent placement can be performed in an anterograde or retrograde fashion with the former avoiding the need for PCN (48). This procedure, which involves inflating a balloon at the site of stenosis, is considered very safe, but treatment associated risks include balloon dilatation failure, ureteral perforation, and stricture recurrence (49). Balloon dilatation has been studied in the setting of benign and malignant ureteral strictures. Numerous studies have found that location in the mid-ureter is associated with higher failure rates than proximal and distal strictures (50). Additionally, RIUS, which tends to be long and ischemic in nature, does not respond well to balloon dilatation therapy as neovascularization during the healing process is compromised (11).

Richter *et al*. reported on a case series of 114 patients with benign ureteral strictures with and without compromised vascular supply who underwent endoscopic management (48). They defined compromised vascular supply according to mechanisms of injury which are prone to devascularization, including abdominal and pelvic surgery, ureteral calculi, and trauma. At 2-year follow up, 89% (33/37) of patients with an intact vascular supply were successfully treated as compared to 40% (2/5) with a compromised vascular supply. These findings were corroborated by two other reports. Tran *et al*. reported on a case series of 25 patients, of which 28% (7/25) patients had a ureteral stricture secondary to radiation therapy. These patients required closer follow up and further open surgical management due to higher rates of endoscopic treatment failure (51). Yam *et al*. demonstrated a recurrence rate of 100% in patients with radiation-induced strictures (5/109) and concluded that balloon dilatation was far more appropriate for short, non-irradiated strictures in patients with normal kidney function (52). Currently, there are no convincing data that any particular set of balloon parameters (small versus large diameter, high versus low pressure, and short versus long duration) produce favorable results over others in any context (5,53).

In general, the highest success rates using balloon dilatation therapy are achieved in short (<2 cm), benign, non-ischemic ureteral strictures (5). In patients with RIUS or a compromised vascular supply, success rates are lower than 40% and these patients most often require retreatment or open surgical management.

Endoureterotomy

Endoureterotomy can be performed using a cold knife (CKI), electrosurgical probe, or laser fiber in an antegrade or retrograde fashion, for both benign and malignant strictures. It is most often performed at the same time as other endoscopic treatments such as balloon dilatation (5). The success rate of endoureterotomy depends on stricture etiology, stricture location, stricture length, and ipsilateral kidney function (5,30). When performing endoureterotomy, the surgeon should make a full-thickness incision, from the ureteral lumen to the periureteral fat and include 2–3 mm of healthy tissue proximally and distally. To avoid injuring nearby vessels, distal ureteral strictures should be incised along the anteromedial wall, whereas upper ureteral strictures are incised posterolaterally (54).

Strictures in the mid-ureter, that are >2 cm length, and in the setting of <25% function of the ipsilateral kidney are associated with higher rates of failure (55). In addition, the effectiveness of endoscopic ureterotomy in post-radiation ureteral strictures is exceptionally low due to ischemic damage and decreased regenerative ability of the ureteral tissue (11). The success rate of endoureterotomy in the treatment of ischemic ureteral stricture ranges from 65–69%, as opposed to 90–100% in non-ischemic strictures (55,56). In summary, endoureterotomy should only be considered in patients with RIUS as a temporizing measure, with discussion of a more definitive surgical reconstruction at the time of initial presentation (51), or in patients who are not fit for open intervention.

Operative management for mid to distal RIUS

Any surgery involving the ureter will present unique challenges due to the complex vascular supply of the tissue. In addition, an anastomosis made between ureter and any other tissue, whether it is urothelial, intestinal, or other graft, must be made under no tension to avoid leakage or re-stricture (4). Prior to any operative management, it is recommended to obtain full imaging to visualize the length and location of the stricture and of the contralateral ureter, if it will be involved in the repair. In addition, it is important to ascertain the function of the renal unit, as function <20% has been associated with a lower success rate of cure (57). In addition, it is critically important to understand the renal function of the contralateral renal unit.

General principles for repair include use of absorbable suture to prevent stone formation, a tension-free spatulated anastomosis over an indwelling ureteral stent, and placement of a closed suction drain in the area of repair (6). The length and location of the stricture will determine the choice of repair. Strictures of the proximal to mid-ureter may be managed with pyeloplasty, primary ureteroureterostomy (UU), transureterostomy, bowel interposition, autotransplantation, or urinary diversion (4). Distal strictures located below the iliac vessels are best managed with ureteral reimplant, with or without the use of a psoas hitch or Boari flap (57). When planning for operative management of post-radiation ureteral stricture, it is important to remember that there is an increased risk of recurrence due to trophic changes in the tissue, which may necessitate repeat and/or more radical surgical interventions in the case of re-stricture (11).

Minimally invasive approaches have been well-adapted to operative management of ureteral strictures and have grown in popularity amongst reconstructive urologists as their utility, safety, and efficacy has been further established. Laparoscopic and robotic-assisted techniques have been shown to have comparable outcomes in terms of complications and stricture recurrence (1), and we will discuss these advances in minimally invasive approaches with select techniques.

UU

A primary repair via UU is commonly used for short strictures, 2–3 cm in length, within the proximal or mid-ureter above the iliac vessels. The distal and proximal ureteral ends are debrided and spatulated, and an interrupted or running anastomosis is performed over a ureteral stent. This approach preserves the natural anti-reflux mechanism of the bladder, but has been associated with higher rates of complications including fistula formation, necrosis, and re-stricture. UU is commonly used to repair ureteral transections and is indicated for strictures less than 3 cm in length. Longer strictures require more extensive excision of fibrotic tissue, which may result in an anastomosis under tension and increase the risk of leak or fistula formation (4,6,54,57). Due to the extensive effects of pelvic radiation on ureteral tissue and the longer length of radiation-induced strictures, UU may not be suitable for most RIUS disease. However, there exists little primary literature on the use of UU in RIUS patient cohorts.

One technique to overcome the poor vascularity of irradiated tissue when utilizing a primary UU is the use of omental wrap to restore blood flow and improve healing of the incised ureteral segment. The omentum is composed of two layers of mesothelium housing adipocytes and phagocytic cells, derived from flaps of peritoneum. When this tissue encounters injury or inflammation, the stromal cells produce substances such as angiogenesis-promoting vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (BFGF), as well as stem cell markers to stimulate healing and regrowth of the damaged basement membrane (58). Omentum has been utilized before in reconstruction of radiation-induced tissue damage in other parts of the body, including pelvic radiation-induced intestinal fistulae (59,60). Neulander *et al.* [2019] reported on a series of 11 patients with RIUSs that underwent reconstruction with use of omental flap. The authors noted that the omentum's angiogenic properties, as well as its length and pliability, make it an ideal material for reconstruction of irradiated tissue and recommended future randomized trials to further corroborate its utility in the repair RIUS (61).

Minimally invasive approaches for UU

The first successful laparoscopic UU was performed by Nezhat *et al*. in 1992 (62), and since then, the procedure has been fully adapted to both laparoscopic and robotic-assisted techniques. Simmons *et al*. [2007] published the first retrospective, comparative study between open and laparoscopic reconstruction for benign stricture disease and found the techniques to be comparable in patency and complication rates, with the minimally invasive approach achieving less estimated blood loss and shorter length of hospital stay (63).

A number of case series on robotic-assisted laparoscopic UU have been published, demonstrating operative success rates above 90% with minimal complications and low recurrence (64,65). discussed the importance of A 2019 study retrospectively comparing laparoscopic and robotic-assisted approaches found that the robotic-assisted approach demonstrated significantly shorter operative and suturing times, decreased length of hospital stay, and a lower degree of postoperative leukocytosis (66). In both laparoscopic and robotic-assisted laparoscopic techniques, it is important to note the resection to healthy ureteral tissue to perform the anastomosis is largely dependent on visual cues, as the tactile feedback is decreased, which may present a technical challenge to the urologic surgeon (67).

Ureteroneocystostomy, psoas hitch, and Boari flap

Ureteroneocystostomy, or ureteral reimplant into the bladder wall, is indicated in patients with distal strictures of the ureter up to 5 cm in length (11). This is an optimal approach if the distal blood supply of the ureter is tenuous, as it allows the surgeon to debride back to viable tissue and spatulate the ureter to prepare for reimplantation (4). The surgeon can choose between a refluxing and non-refluxing operative approach. Generally, non-refluxing is more widely accepted as it reduces vesico-ureteral reflux and subsequent risk of infection (68); however, neither approach has been shown to have better outcomes in terms of renal function or risk of stricture recurrence (69). In the non-refluxing approach, the ureter is pulled through a submucosal tunnel in the bladder wall at the posterior or anterior dome. Reimplantation on the lateral aspects of the bladder is contraindicated as it is prone to kinking as the bladder fills (70). The anastomosis should be closed over a stent, which can be removed in 6 weeks (4). This operation is commonly performed in conjunction with a psoas hitch or Boari flap to cover a longer distance and reduce the risk of tension at the anastomosis (71,72).

When the length of the ureteral defect is long enough (around 5–10 cm) that a primary ureteroneocystostomy would result in an anastomosis under tension, a vesico-psoas hitch can be utilized to bridge the gap (4,11). In this approach, the bladder is mobilized by ligating adjacent attachments in the space of Retzius and releasing the contralateral bladder pedicle. Then the detrusor muscle is hitched to the psoas muscle using nonabsorbable stay stitches, taking care to avoid including the genitofemoral nerve in the stay stitches. Then the ureter is inserted and sewed into the bladder in a similar fashion, through a straight submucosal tunnel to reduce reflux and kinking as the bladder fills. A ureteric stent is placed into the reimplanted ureter for 6 weeks to allow the anastomosis to heal (4). Contraindications include a poorly compliant bladder, bladder outlet obstruction, and neurogenic bladder.

A Boari flap, or tubularized bladder flap, can be used in conjunction with reimplant and/or psoas hitch to repair a mid- or distal ureteral defect with a length of 10–15 cm (73). The Boari flap has the advantage of utilizing only urothelial tissue in the repair without jeopardizing the contralateral ureter or renovascular system and can be performed in patients with decreased renal function and preexisting bowel disease (3). To create the flap, the bladder is incised in a full-thickness manner on the anterior surface, and the bladder flap is reflected cranially. To reduce the risk of flap ischemia, the flap should not exceed a length-to-width ratio of 3:2 (4). Then the bladder flap is tubularized and the ureter re-implanted in a non-refluxing or refluxing manner (72). This technique may be utilized in conjunction with a downward nephropexy, in which the kidney is mobilized and shifted inferiorly without disrupting the renal pelvis, which can account for 3–5 more centimeters of ureteral defects (54,74).

Poor bladder compliance is a limiting factor in the use of both vesico-psoas hitch and Boari flap, and can be seen as a sequela to radiotherapy (75). Similar to the damage seen in ureteric tissue, radiation-induced fibrosis of the bladder is due to chronic alterations in transforming growth factor beta (TGF-β) and connective tissue metabolism (76). It is dose-responsive and often 7 years after radiation (75). A scarred or contracted bladder may not have the mobility or compliance to complete a hitch or flap procedure. In addition, radiation injury can affect the contractility of the bladder and cause incomplete emptying, another contraindication. Therefore, when planning for any ureteral reconstruction, it is important to complete preoperative imaging, such as a cystogram, to evaluate the patient's bladder capacity and compliance, both of which are key factors in the possible reconstruction choices.

Ureteral reimplant has been demonstrated to have good outcomes for RIUS, as long as the surgeon is able to achieve adequate and tension-free mobilization of the proximal ureteral stump after debridement back to viable tissue. Riedmiller *et al.* [1984] published a series of 181 patients who underwent ureteroneocystostomy with psoas hitch with a 97% success rate after a mean follow-up of 4.5 years. The authors reported that the following factors were important to ensure a successful operation: a tension-free anastomosis, a long and straight submucosal tunnel to avoid reflux, and ureteral linking at the vesicoureteral anastomosis (77). Multiple other studies have demonstrated a high rate of success, including low recurrence and improvement of hydronephrosis and renal function, with minimal complications (78,79).

Orchard *et al.* [2016] reported on a case series of 4 patients with RIUS, with 3 of the 4 successfully undergoing reimplant. Notably, all of the patients were treated preoperatively with hyperbaric oxygen to improve the regenerative quality of previously irradiated tissue, and all four reconstructions were performed with the aid of omental flaps to augment blood flow and seal anastomoses (23). In addition, Toia *et al.* [2019] reported on a series of 18 patients who underwent reconstructive surgery for RIUS, many of whom had bilateral disease (14/18, 78%) and concomitant bladder contracture (10/18, 56%). Only two patients were reconstructed with Boari flap alone, due to the irradiated and non-compliant nature of the bladder tissue, with the remaining 16 patients requiring ileal conduits or primary urinary diversion to circumvent fistulae and unhealthy bladder tissue. The authors noted that longer and more proximal ureteral strictures require more complex reconstruction to create successful diversions. They also reported a high rate of anastomotic strictures (about 30%) in patients who underwent reconstruction (80).

In summary, ureteral reimplant with or without adjunctive procedures like psoas hitch or Boari flap is a good option for reconstruction of RIUS, as it allows for the treatment of longer strictures and can be adapted depending on the fibrosis and motility of the surrounding tissues, demonstrating success rates ranging from 88–100%. Importantly, preoperative diagnostic tests like cystogram are critical to planning for the appropriate procedure. In addition, the use of omental flaps at the site of anastomosis can help account for the poor vascularity of irradiated tissue.

Minimally invasive approaches for ureteroneocystostomy

A minimally invasive approach to ureteral reimplant has been the subject of study in recent years. Singh *et al.* [2018] reported on a series of 20 patients underwent laparoscopic ureteroneocystostomy for ureteral stricture of various etiologies. Overall, the patients received less postoperative analgesics and had shorter hospitalization times versus those who underwent reconstruction via a traditional open approach (81). Patil *et al.* [2008] published one of the first series of robotic-assisted ureteral reimplantation for ureteral stricture. All the patients were reconstructed without conversion to open surgery, with no intraoperative or postoperative complications and a success rate of 100% at 15 months (82). The authors noted that, as opposed to the laparoscopic approach (83), the robotic approach offered the surgeon more maneuverability and dexterity in performing the initial ureteral dissection and the creation of the submucosal tunnel within the pelvis (82).

Asghar *et al.* [2020] published a retrospective review of 32 patients who underwent robotic-assisted reconstruction of RIUS, with 83% of patients undergoing ureteral reimplant with omental wrap. At a median follow-up period of 13 months, 88% (30/32) of reconstructed ureteral units were clinically successful, determined by the absence of symptomatic obstruction, and radiologically effective, determined by the absence of obstruction on imaging. The authors noted that while a minimally invasive approach is an appropriate management option for RIUS, surgeons should be prepared to perform adjunctive procedures to account for poor tissue quality and immobility due to contracture and fibrosis, which may increase intraoperative time and postoperative complications (84).

In summary, minimally invasive approaches to ureteral reimplant with or without adjunctive procedures have been shown to be effective, with decreased complication rates and shorter hospital stays, with robotic-assisted approaches offering improved intracorporeal maneuverability and dexterity. However, bladder compliance may be low in patients who have undergone previous radiotherapy and may limit tissue mobility and healing.

Transureteroureterostomy (TUU)

TUU is indicated for ureteral stricture 6–10 cm long (85), when reimplant with or without psoas hitch or Boari flap is not possible due to prior pelvic surgery, radiation therapy, or bowel/vascular injuries that preclude the use of bladder or bowel in reconstruction (57,86). The procedure involves mobilizing the donor ureter and passing it through the posterior mesentery, anterior to the bifurcation of the great vessels, where it is anastomosed to the contralateral recipient ureter (4). Contraindications include inadequate length of the diseased ureter, which would create tension on the anastomosis, and disease of contralateral recipient ureter, including urothelial carcinoma, urolithiasis, or retroperitoneal fibrosis (86).

Iwaszko *et al*. [2010] reported on a series of 63 patients who underwent TUU for a variety of benign and malignant conditions. Sixteen patients had a history of pelvic radiation for treatment of malignancy. This series had a short-term complication rate of 23.8% (n=15), with the most common complications being urine leak at the site of anastomosis (n=6). Patients undergoing reconstruction for malignant etiology, which included those who had received prior radiation, had a significantly higher complication rate versus those with benign indications (47.6% *vs*. 11.9%). Long-term success was attained in 96.4% (n=54) of the patients. The authors noted that, despite the increased risk of short-term complications, the malignant cohort did have a comparable improvement in renal function (86).

This procedure is considered a reserve option, as it involves both ureters, increasing the risk of bilateral urinary tract damage and renal loss (4). In addition, because pelvic radiotherapy often results in bilateral disease, this procedure may not be suitable for patients with RIUS. Preoperative imaging and renal function tests can help the surgeon determine whether there is a suitable recipient ureter with enough healthy tissue on which to anastomose the donor ureter.

Autotransplantation

Renal autotransplantation is a complex procedure that is indicated when the damage to the ureter results in a significant loss of length, the patient has functional renal parenchyma in the ipsilateral kidney, and other reconstructive options are contraindicated. The procedure involves dissecting away the kidney's attachments, including its blood vessels similar to an organ harvest, translating it downwards in the pelvis, and creating an anastomosis with the iliac vessels and a healthy proximal ureteral stump back to into the bladder (87).

Meng *et al*. published a case series of seven patients who underwent laparoscopic nephrectomy and autotransplantation after ureteral trauma resulting in significant loss of length. At a follow-up 17 months post-operatively, imaging demonstrated that all six renal autotransplants had normal function (87). However, this procedure has not been studied specifically in patients with radiation-induced disease, and radiotherapy has reported sequelae that may make it an unsuitable option for this patient population. Pelvic radiotherapy may cause atherosclerosis in the iliac vessels, resulting in a precarious vessel anastomosis, and similar to TUU, may cause bilateral ureteral stricture disease and impaired renal function, which is a contraindication to this procedure. In addition, cancer patients are immunocompromised and may not be fit for such an invasive and morbid procedure.

Graft ureteroplasty

Graft ureteroplasty has been used to address the challenges associated with surgical management of RIUS, allowing the surgeon to supplement the diseased tissue while avoiding the morbidity of bowel substitution or renal autotransplantation (88). This procedure can be performed in an open or robot-assisted laparoscopic fashion and achieve tension-free anastomosis for strictures too long for repair with UU (>2 cm) in the proximal to mid-ureter (89). The ideal graft donor tissue is hairless, easy to access and harvest, resistant to infection, and viable in a wet environment (90). Buccal mucosa, bladder mucosa, preputial skin, and most recently, synthetic grafts have been described in the literature with early but promising results. Importantly, the lumen of the affected ureter cannot be completely obliterated as graft onlay would be impossible and require the creation of an augmented ureteral plate (3).

Buccal mucosal grafts (BMGs) possess a similar histological profile to urethral mucosa, with a thick, non-keratinised epithelial layer and vascular lamina propria (54), presenting an attractive option for ureteral reconstruction that is in early stages of study. A 2018 review identified two major indications for the use of buccal graft ureteroplasty: when the length of stricture is long enough that a tension-free UU is not possible, especially in the proximal ureter when adjunctive procedures like Boari flap or psoas hitch may be technically challenging, and in the setting of reoperation after failed ureteroplasty, as the use of a graft obviates the need for extensive adhesiolysis and tissue mobilization when can threaten the already tenuous blood supply of the ureter (89). While the review did not specifically discuss the use of BMG in RIUS, the clinical characteristics of RIUS, including extensive adhesions, the longer length of radiation-induced strictures, and the high percentage of reoperations in these patients, make BMG an attractive option in this patient cohort.

Badawy *et al.* [2010] published a series of 5 patients who underwent tubularized BMG ureteroplasty for a mean stricture length of 4.4 cm, with a 100% success rate at 24 months follow-up (91). Kroepfl *et al.* [2010] then published a series of 6 patients who underwent BMG ureteroplasty with omental wrap. Three of these patients had undergone previous radiotherapy for pelvic malignancy, with an average stricture length of 9 cm. While the three non-irradiated patients were asymptomatic at a mean follow-up for 44 months, two of the three irradiated patients became symptomatic at 17 and 39 months after surgery, respectively. The authors noted that this technique was especially suitable for patients with long strictures crossing the iliac vessels to avoid long-term stent dependence and that the use of adjunctive omental wrap to restore vascular supply encourages the "take" of the buccal graft (92). Three patients in a case series by Trapeznikova *et al.* [2014] underwent BMG ureteroplasty for RIUS, including one patient with bilateral disease. At a median follow-up of 42 months, all three patients were asymptomatic and had satisfactory renal excretory function (93).

Graft ureteroplasty is an effective surgical management for complex ureteral stricture. However, it can be less effective in patients with long, ischemic strictures secondary to radiation therapy, with success rates ranging from 30–100%, likely due to the compromised vascularity that may increase the risk of graft failure. This risk can be modified with the use of adjunctive omental wrap to restore blood supply to the irradiated tissue. In addition, it has been suggested by multiple authors that BMG ureteroplasty may be a more favorable option for longer strictures than alternative procedures like ileal interposition, as the buccal graft harvest is associated with lower morbidity than a bowel resection, and can offer similar outcomes (89).

Tissue engineering and regeneration

Tissue engineering and regeneration-based ureteroplasty is an emerging field. The goal is to develop an optimized material for ureteral reconstruction. Scaffolds can be used to promote tissue regeneration and can be classified on the basis of whether they are directly implanted, seeded with cells prior to implantation, or pre-implanted before functional implantation (90). Several preclinical studies have shown positive results of tissue engineering-based ureteroplasty in animal models (90). However, there are limited data on synthetic graft ureteroplasty in humans and further studies are needed to assess the long-term success and efficacy of these grafts for complex ureteral reconstruction.

Minimally invasive approaches for graft ureteroplasty

Arora *et al.* [2017] described one of the first case studies of the use of robotic-assisted laparoscopy in the use of BMG for the reconstruction of a complex ureteral stricture. The patient was a 58-year-old male who presented with left flank pain and hydronephrosis and was found to have a 6 cm stricture of the proximal ureter. After a failed robot-assisted ureterolysis, the patient underwent a robotic-assisted buccal graft placement with omental wrap that was fixed to the psoas fascia. The procedure was uncomplicated, and at 6-month follow-up, there was no evidence of recurrence or obstruction on renal scan (94). Lee *et al.* looked at 12 patients who underwent robotic BMG ureteroplasty for complex ureteral strictures. A third of the patients (4/12) had a stricture at the UPJ, another third at the proximal ureter, and the final third had a mid-ureteral stricture. Eight of the 12 patients (66.7%) had failed previous ureteral reconstruction. At 13-month follow-up, 10/12 (83.3%) were clinically and radiologically successful with no symptoms and no evidence of ureteral stricture on imaging (95).

Zhao *et al.* [2018] then described a series of 19 patients who underwent robotic-assisted buccal graft placement for benign proximal or mid-ureteral stricture not amenable to primary anastomosis due to the length of defect or extensive fibrosis. In most cases (15/19, 79%), the stricture was incised and the graft onlaid and sutured to an omental flap to ensure blood supply, with the placement of a ureteral stent prior to final closure. At a median follow-up period of 26 months, the stricture-free rate was 89% (17/19). The authors noted that they were able to reconstruct strictures of up to 8 cm with grafts harvested from a single cheek. The advantages of graft ureteroplasty included its utility in patients with renal insufficiency by avoiding metabolic abnormalities associated with bowel interposition and that this procedure did not preclude further reconstruction as the ureter tissue is largely preserved. Finally, they promoted the advantage of the robotic approach due to its decreased morbidity and increased surgical dexterity (88).

While these results are promising to demonstrate the utility of minimally invasive BMG ureteroplasty in the use of longer, more complex ureteral stricture disease, it should be noted that neither study discussed above specifically identified patients with RIUS within the category of "iatrogenic" etiology. One patient in the RIUS review by Asghar *et al*. [2020] underwent robotic BMG ureteroplasty, and was asymptomatic at 1 year of follow-up (84). As such, the data in this cohort of patients is limited and should be explored in future research.

Urinary diversion

Urinary diversion refers to a group of complex surgical procedures that divert the urinary system away from its normal tract (96). When the use of urothelial tissue for reconstruction is precluded by the length or complexity of the stricture, or fibrosed, noncompliant bladder condition, substitution with non-urothelial tissue can be utilized instead (3). There are various techniques each with unique indications, but they all involve creating an anastomosis between the diseased portion of the urinary tract with a portion of bowel (96). In theory, any segment of bowel can be used. Previous studies have reported on the use of tubularized stomach, portions of small bowel, portions of colon (97). However, the most commonly used bowel segments are the terminal ileum and/or the ascending or sigmoid colon to minimize metabolic derangements (98).

There are two main urinary diversion reconstructive options. First, there are incontinent bowel conduits that require urostomy and external drainage. The gold standard for many years has been an ileal conduit. Secondly, there are continent bowel reservoirs that are drained by catheterization via a cutaneous stoma or by patient-mediated voiding (99). The decision to proceed with a conduit versus a reservoir must be made by using a shared-decision model after considering the extent of the diseased portion of the urinary tract, patient's existing intestinal anatomy and comorbidities, goals of care, and quality of life following surgery. Contraindications to bowel substitution include small bowel disease, compromised renal function, and previous irradiation of the bowel, though this is dependent on the degree of radiation and tissue damage (3,54).

Complications are common after urinary diversion. Patients are at risk for both early and late complications and the risk of experiencing a complication increases over time. Patients who undergo urinary diversion require long-term follow up and surveillance for anatomic, infectious, and metabolic complications that may arise (96).

Urinary diversion offers a more definitive surgical treatment option for RIUS by bypassing the disease ureter or noncompliant bladder. However, due to the complex nature of the surgery and long-term need for either external drainage or catheterization, it is generally not considered a first-line therapy unless there is severe disease or the patient has failed other therapies.

Ileal interposition

Ileal interposition was popularized in the 1950s as a ureteral substitute with acceptable long-term outcomes (100,101). In this technique, the ureter is replaced with a tubularized, pedicled segment of ileum measuring 15–20 cm. In case of bilateral disease, the ileal segment can be utilized to replace both ureters (3). Long-term complications of ileal substitutes are common due to the absorptive and secretory nature of the intestinal mucosa, including metabolic imbalances, mucus-related obstruction, and stone formation. Furthermore, stricture at the anastomotic site due to inflammation and compromised blood supply can be seen (3,90).

The Yang-Monti ileal ureter attempts to address the issues of the ileal ureter by reconfiguring the short ileal segments into long tubes of small caliber and converting the circular fibers to longitudinal (102,103). The modified ileal ureter exhibits antegrade propulsion to aid in urinary drainage, mimicking the function of a native ureter, and the risk of excessive mucus production and metabolic acidosis is largely eliminated because the ileal mucosal surface area is significantly reduced (104).

Armatys *et al*. [2009] reported on a series of 91 patients who underwent ileal ureter replacement. Overall, around 75% of the patients in the series had stable or improved serum creatinine postoperatively. Notably, the postoperative complication rate was significantly higher in irradiated patients, including wound infection, small bowel obstruction requiring adhesiolysis, and fistula formation (101). Then, Monn *et al*. [2018] reported on a series of 104 patients, comparing outcomes of ileal ureter creation in patients with radiation-induced (23/104, 22%) *vs*. non-radiation induced stricture (81/104, 78%). In this study, irradiated patients more commonly developed partial small bowel obstruction and fistula formation (105).

Overall, the long-term outcomes of ileal substitution in irradiated patients was comparable, making it a reasonable choice for this cohort. The selection of a segment of healthy bowel, outside of the field of radiation, is critical to the chance of success. However, the increased risk of small bowel obstruction and fistula formation and the necessity of extensive adhesiolysis intraoperatively should be included in preoperative counseling. In addition, adjunct techniques like ileal detubularization, downward nephropexy, and Boari flap can be used to increase length in the setting of mesenteric tethering (105).

Appendiceal interposition

Ureteral appendiceal interposition (UAI) is a reconstructive procedure that utilizes the appendix to replace the strictured ureteral segment. Although ileal replacement has been more extensively studied, UAI does have several advantages, including increased ease of anastomotic creation, avoidance of the morbidity associated with bowel resection, and reduced risk of tract dilation due to the smaller luminal caliber (90). The reduced risk of electrolyte abnormalities due to the decreased mucosal surface makes it an appropriate choice for patients with decreased renal function (106). In addition, the smaller diameter and intrinsic peristalsis may minimize the risk of urinary stasis and reflux (90). In theory, antiperistaltic interposition should reduce the incidence of mesoappendix torsion, preventing further vascular issues; however, the overall consensus seems to be that orientation (isoperistaltic or antiperistaltic) does not change outcomes (107,108). One drawback to this procedure is the potential lack of appendix due to prior appendectomy or fibrosis and/or stricture from prior appendiceal inflammation (106).

The length of the appendix is finite, replacing approximately 3 cm ureteral defects on average, and right-sided stricture reconstruction has fewer complications than left-sided strictures, which are complicated by a long vascular pedicle (90). Despite this complexity, left ureter reconstruction has also shown promise (106,108-111). Shen *et al*. reconstructed a complete left ureter by combining appendiceal interposition with psoas hitch, with no evidence of obstruction at a follow-up period of 10 months (109).

The success rates of appendiceal interposition ranges from 67–96% (106,112-114). Burns *et al*. tracked UAI outcomes in eleven patients over the past 5 years. None of the patients required repeat intervention due to recurring strictures, and nine of the eleven showed improvement of hydronephrosis on CT scan or no obstructions on Lasix renal scan (112). Duty *et al*. [2015] reported on a series of 6 patients who underwent robotic-assisted appendiceal-onlay ureteroplasty for complex right-sided proximal and mid-ureteral strictures. In this procedure, the detubularized appendix was secured to the posterior wall of the longitudinally opened ureter, preserving ureteral tissue while increasing the diameter of the lumen. Obstruction was resolved radiographically in all 6 patients, while symptoms of obstruction, including flank pain, were resolved in 4 of the 6 patients (106).

Specific to RIUS, four patients in the review by Asghar *et al*. [2020] underwent appendiceal interposition, with a success rate of 75%. One patient developed postoperative obstruction leading to sepsis, and was managed with PCN (84). Six patients in the case series by Burns *et al*. had RIUS (54.5%), with a success rate on appendiceal interposition of 100% at a median follow-up period of 1 year. The authors noted that the use of appendiceal interposition in RIUS may decrease the risk of new lower urinary tract symptoms caused by adjunctive procedures like Boari flap due to the contracted nature of irradiated bladder tissue. However, it should be noted that previous pelvic or abdominal radiation may lead to appendiceal fibrosis that would preclude its use as graft tissue (112). These findings support the use of UAIs as a feasible option in the management of RIUS, especially to avoid the morbidity associated with bowel resection and to address the issue of bladder fibrosis in the setting of radiotherapy.

Minimally invasive techniques for urinary diversion

The first case report of laparoscopic ileal ureter was published in 2000 (115), with further studies demonstrating favorable outcomes when compared to the open approach in regards to postoperative narcotic use and recovery times (116). Brandao *et al*. published the first report of robotic-assisted ileal ureter (117), followed by other case studies and series (118,119). The robotic approach appears to have comparable outcomes to laparoscopic approaches, despite the limitations of small sample sizes and limited follow-up. Baumgarten *et al*. noted that the use of preoperative imaging to estimate the size of ileal substitution allowed them to complete the procedure entirely intracorporeally with only one position change (118).

Conclusions

Management of RIUS is divided into endoscopic, open, and minimally invasive techniques. Stents and PCN are generally used as temporizing measures until definitive repair but may be a long-term option for patients unfit for surgery. Balloon dilatation and endoureterotomy have shown efficacy between 60–80%, but are less effective in RIUS due to the ischemic nature of the insult. UU is best suited for short strictures in the mid to proximal ureter, while ureteroneocystostomy is better suited for longer strictures in the distal ureter and may be paired with psoas hitch or Boari flap to increase coverage length. Importantly, for radiation patients, bladder fibrosis may be a contraindication to these procedures. Buccal graft ureteroplasty is increasingly being used with success rates between 80–90%. Finally, bowel substitutes are suitable for longer strictures and bilateral disease, with ileal interposition having success rates around 75–90%, as well as substantial morbidity due to the bowel resection. Most recently, appendiceal interposition has been studied for both right- and left-sided strictures around 3–5 cm, with success rates around 70%. Generally, minimally invasive approaches, while less studied, have demonstrated similar clinical outcomes and complication rates, with less reported pain and shorter hospital stays.

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