

Pelvic radiation therapy with volumetric modulated arc therapy and intensity-modulated radiotherapy after renal transplant: A report of 3 cases

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ABSTRACT

Aim: Describe characteristics and outcomes of three patients treated with pelvic radiation therapy after kidney transplant.

Background: The incidence of pelvic cancers in kidney transplant (KT) recipients is rising. Currently it is the leading cause of death. Moreover, treatment is challenging because anatomical variants, comorbidities, and associated treatments, which raises the concern of using radiotherapy (RT). RT has been discouraged due to the increased risk of urethral/ureteral stricture and KT dysfunction.

Materials and methods: We reviewed the electronic health records and digital planning system of patients treated with pelvic RT between December 2013 and December 2018 to identify patients with previous KT.

Cases description: We describe three successful cases of KT patients in which modern techniques allowed full standard RT for pelvic malignancies (2 prostate and 1 vaginal cancer) with or without elective pelvic nodal RT, without allograft toxicity at short and long follow-up (up to 60 months).

Conclusion: When needed, RT modern techniques remain a valid option with excellent oncologic results and acceptable toxicity. Physicians should give special considerations to accomplish all OAR dose constraints in the patient's specific setting. Recent publications recommend KT mean dose <4 Gy, but graft proximity to CTV makes this unfeasible. We present 2 cases where dose constraint was not achieved, and to a short follow-up of 20 months renal toxicity has not been documented. We recommend the lowest possible mean dose to the KT, but never compromising the CTV coverage, since morbimortality from recurrent or progressive cancer disease outweighs the risk of graft injury.

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Abbreviations: BF, Biochemical failure; BT, Brachytherapy; C3D-RT, Conformal three-dimensional radiation therapy; CBCT, Cone-beam computed tomography; CCA, Cervix cancer; Dmax, Maximum dose; Dmean, Mean dose; Dmin, Minimum dose; D_x, Dose (in Gy) receiving x% of a volume or more; EBRT, External beam radiation therapy; EQD2, Equivalent dose in 2-Gy fractions; ESKD, End-stage kidney disease; fr, Fractions; FU, Follow-up; HPV, Human papillomavirus; IBT, Intracavitary brachytherapy; IMRT, Intensity-modulated radiation therapy; KT, Kidney transplant; LRDRT, Living related donor renal transplantation; MMF, Mycophenolate mofetil; mo, Months; NED, No evidence of disease; OAR, Organs at risk; OS, Overall survival; PCa, Prostate cancer; PDN, Prednisone; PP, Post-prostatectomy; PSA, Prostate-specific antigen; PTV, Planning target volume; RR, Risk ratio; RT, Radiation therapy; SCCVa, Squamous cell carcinoma of the vagina; SIR, Standardized Incidence Ratio; TBI, Total body irradiation; VCa, Vaginal cancer; VMAT, Volumetric Modulated Arc Therapy; V_x, Volume (in percentage) receiving x dose or more (in Gy).

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1. Background

Kidney transplant (KT) is the recommended treatment for patients with end-stage kidney disease (ESKD); it is associated with improved survival and quality of life.¹ In 2016, the Iberoamerican Donation and Transplant Network/Council recorded 3020 adult KT's in Mexico (932 from deceased donors).² Increased cancer risk has been well established after KT, with the risk 2–3 times higher than in the general population.^{3–4} The reported standardized incidence ratio (SIR), calculated as the ratio of observed to expected number of cases, is 2.0–6.6.⁵ The risk for non-skin cancers is greater in those associated with viral infections and longstanding immunosuppression (cervix cancer [CCa], vulvovaginal cancer and lymphoproliferative diseases) than other solid malignancies.⁶ With a mean 10-year follow-up of 1450 kidney transplants recipients, 194 developed malignancies, and the most frequent pelvic tumors were colon (11%), bladder (10%), and prostate (10%).⁷ Australian SIR after KT was 2.76 (1.51 to 4.64) for anal, 24.54 (14.55 to 38.79) for vulvar, 2.49 (1.33 to 4.27) for cervical, 15.94 (5.85 to 24.69) for penile, and 0.95 (0.68 to 1.29) for prostate.⁸

Post-transplant malignancy is an important cause of mortality in KT patients and is currently the leading cause of death among solid organ transplant recipients.⁷ Survival among transplant recipients with advanced-stage cancer is poor, with a 5-year overall survival (OS) of <10% for all cancers.^{7,9} Cancers that develop in solid organ transplant patients are challenging to treat and have worse prognoses; therefore, being able to offer standard treatment is important.¹⁰ Surgery and chemotherapy are limited by cardiovascular comorbidities often found in ESKD and/or KT hosts. Transplant physicians and recipients often refuse to reduce immunosuppression and initiate immunotherapy due to the associated risks of graft rejection and loss.⁴ Treatment of pelvic malignancies with radiation therapy (RT) is challenging due to anatomical variants secondary to the pelvic location of a KT.⁸ Renal allograft is usually placed near blood vessels often included in standard Clinical Target Volume (CTV) for average pelvic malignancies, such as prostate, cervix, rectum, vaginal and vulvar cancer. Their proximity to treatment volumes often leads to excessive concern of physicians and patients. Furthermore, other clinical management-related issues such as lack of worldwide accessibility of high precision RT, absence of contouring guidelines and recommendations for pelvic transplant patients, immunosuppression protocols and a limited evidence of natural history, management and outcomes often feed this concern.⁸

The pelvic location of a renal transplant limits RT due to doses delivered to the kidney allograft. KT are located heterotopically to reduce concerns related to vascular and ureterovesical anastomosis. The preferred place for KT is the right iliac fossa due to a more superficial placement of external iliac vein, and in the opposite iliac fossa in case of previous surgical procedures. The inferior border of KT located at the iliac fossa usually lies at the bottom of S2 or S3.¹¹ Therefore, radiotherapy with volumes that include pelvic lymph nodes (especially near external iliac vein) will need further evaluation if benefits outweigh the risks. Treatment of locally advanced pelvic tumors with definitive or neoadjuvant radiotherapy usually includes iliac lymph nodes in the nodal target volume. This nodal target is also included in some cases of adjuvant radiotherapy. The location of the KT in relation to radiation therapy fields increases the risk of irreversible damage of the renal allograft when high doses are delivered to the pelvic lymph nodes.¹²

We describe three successful cases of LRDRT in which modern techniques allowed full standard RT treatment for pelvic malignancies with or without elective pelvic nodal irradiation, without allograft toxicity at short and long follow-up (up to 60 months).

1.1. Aim

Describe characteristics and outcomes of three patients treated with pelvic radiation therapy after kidney transplant.

2. Materials and methods

We reviewed the electronic health records and digital planning system of patients treated with pelvic RT between 1 December 2013 and 31 December 2018 to identify patients with previous renal allograft.

2.1. Cases presentations

We first describe one case of prostate bed irradiation in which modern techniques reduce doses mainly to the ureter and urethra. The two last cases also confirm a better conformation and accomplishment of constraints to KT and better conformity.

2.1.1. Case 1

An elevated prostate-specific antigen (PSA) was detected (4.8 ng/mL) during routine evaluation of a 65-year-old male with a medical history of living related donor renal transplantation (LRDRT) in the right iliac fossa (40 years ago) and long-term immunosuppressive therapy with prednisone (PDN) and azathioprine. After confirming prostate adenocarcinoma by biopsy, retropubic prostatectomy was performed. Histopathologic review revealed a moderately differentiated prostate acinar adenocarcinoma, Gleason score 4 + 4, with positive apical margin, and neither extraprostatic extension, seminal invasion, nor lymphovascular / perineural extension. Postoperative PSA was <0.02 ng/mL. Due to his medical history he underwent close surveillance. Two years later, his PSA levels increased to 0.32 ng/mL, denoting a postoperative biochemical recurrence. He was referred to our radiation oncology department for salvage RT. The patient underwent no-contrast CT simulation with full bladder, empty rectum and 2.5 mm slices. Case was contoured following RTOG 0534¹³ treatment planning / target volumes for postoperative prostate cancer. Primary CTV included all surgical clips and prostate bed from the top of the penile bulb and above the genitourinary diaphragm inferiorly; 2 cm above the pubic symphysis superiorly; to the medial edge of internal obturator muscle laterally; anteriorly including the entire neck bladder and above the pubic symphysis gradually reducing the expansion to include only 3 mm of the posterior bladder wall. PTV was generated with a 3-mm isotropic margin. For all three cases organs at risk (OAR) included: (1) rectum, bladder, femoral heads, bowel; (2) renal allograft with a Planning organ at Risk Volume (PRV, created by adding a 3 mm margin to KT), PRV was mainly used for planning purposes; (3) penile bulb in males and vulva in female. Allograft was 3.5 cm in its closest point to the PTV and 6 mm separate the upper limit of the PTV from the KT.

The prescribed dose was 66 Gy in 33 sessions (2 Gy per day, 5 days per week). Initial planning with Conformal 3-Dimensional Radiation Therapy (C3D-RT) using 3 fields (anteroposterior and two posterior obliques) and 4-field box technique. Although with C3D-RT constraints were accomplished, the maximum doses were significantly higher (Table 1). Therefore, volumetric modulated arc therapy (VMAT) planning was performed with a single counter-clockwise complete arc limited to the prostate bed, with the upper limit lying 6 mm under the bottom of the renal allograft. One arc instead of 2 or 3 non-coplanar arcs were preferred to reduce the probability of increasing low dose to KT with non-coplanar arcs. Patient-Specific QA was done using Octavius Phantom, and the treatment was delivered on Varian TrueBeam™ linear accelerator with 6 MV X-rays. The patient's VMAT treatment plan (Fig. 1 and 2) and dose constraints recommended per protocol are shown in

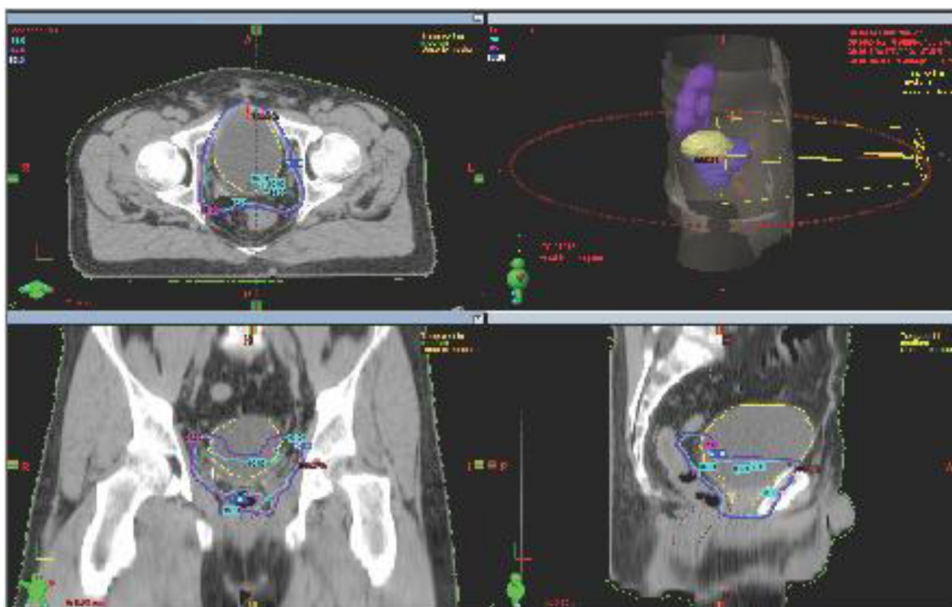


Fig. 1. Plan for Case 1. Salvage radiation therapy was limited to surgical bed and was administered using Volumetric Modulated Arc Therapy. Simulation and daily treatment were performed ensuring full bladder and empty rectum with daily cone-beam computed tomography verification. Upper left and lower right and left images: 98% isodose curve in cyan, 95% isodose curve in magenta, and 90% isodose curve in blue. Upper right image: in purple kidney transplant, in yellow bladder, in brown rectum and in blue PTV.



Fig. 2. Plan for Case 1. Showing the distance of 6 mm from the upper limit of the planning target volume to the bottom of the kidney transplant.

Table 1
Constraints of organs at risk (OAR) for case 1 with C3D-RT: 3-fields, 4-field box and VMAT.

Volumes and OAR	As per protocol	3 fields	4-field box	VMAT
Graft				
D_{max} (Gy)		27.39	30.92	8.97
$D_{0.3cc}$		25.59	29.41	6.56
D_{mean} (Gy)	<4 Gy	1.50	1.77	0.89
Urethra				
D_{max} (Gy)		70.9	71.2	67.5
D_{mean} (Gy)		64.3	65.2	47.7
V_{80} (%)	<5%	0	0	0
V_{70} (%)	<10%	5	7.1	0
Ureter				
D_{max} (Gy)		38.9	30.46	11.03
D_{mean} (Gy)		4.15	3.83	1.42
V_{80} (%)	<5%	0	0	0
V_{70} (%)	<10%	0	0	0

Table 2. Cone-Beam Computed Tomography (CBCT) was used prior to every treatment for daily position and bladder size verification. During treatment and follow-up renal function (basal creatinine level of 1.25 mg/dL) and blood counts remained normal. No acute or chronic renal failure or hematologic toxicity was documented. Forty-eight months after RT, he reported concerns of obstructive urinary symptoms. A cystoscopy revealed bladder neck stenosis (<40% of neck circumference). Bladder neck dilatation was performed which led to complete remission of the stenosis and symptoms. With a follow-up of 60 months, he remains free from biochemical and clinical recurrence. The results of his last PSA and creatinine tests were within reference range (<0.01 ng/mL and 1.25 mg/dL, respectively), and the size of the kidney allograft remains stable.

2.1.2. Case 2

A 55-year-old man was referred to our department with acinar adenocarcinoma of the prostate, intermediate-risk (clinical stage T2a, Gleason 3 + 3, initial PSA 14.4 ng/mL) and World Health

Table 2
Treatment planning doses to volume and organs at risk (OAR).

Volumes and OAR	As per protocol	VMAT Case 1	VMAT Case 2	IMRT Case 3
PTV				
D _{min} (Gy)		57.74	70.82	38.68
D _{max} (Gy)		70.06	83.87	53.76
D _{mean} (Gy)		66.00	80.16	51.77
Rectum				
D ₁₅ (Gy)	<75 Gy	55.86	71.82	50.5
D ₂₅ (Gy)	<70Gy	48.11	65.20	49.19
D ₃₅ (Gy)	<65 Gy	41.83	59.28	47.11
D ₅₀ (Gy)	<60Gy	36.26	52.01	44.33
Bladder				
D ₁₅ (Gy)	<80Gy	65.57	75.23	49. ^a 1
D ₂₅ (Gy)	<75 Gy	64.01	62.48	46.22
D ₃₅ (Gy)	<70Gy	52.02	51.32	43.08
D ₅₀ (Gy)	<65 Gy	35.35	43.93	36.82
Graft				
D _{max} (Gy)		8.97	29.12	32.27
D _{0.3cc}		6.56		
D _{mean} (Gy)	<4 Gy	0.89	4.88	8.67
Right femoral head				
D _{max} (Gy)		40.83	52.64	49.30
D _{mean} (Gy)	<40 Gy	18.04	16.10	30.88
V ₅₀ (%)	<10%	0	0.10	0
Left femoral head				
D _{max} (Gy)		38.35	48.29	48.47
D _{mean} (Gy)	<40 Gy	14.94	17.66	30.68
V ₅₀ (%)	<10%	0	0	0
Penile bulb				
D _{mean} (Gy)	<52.5 Gy	18.27	33.27	–
Bowel				
V ₄₅ (%)	<195 cc	0	54.12	0.10
Urethra				
D _{max} (Gy)		67.5	67.5	–
D _{mean} (Gy)		37.7	66.1	–
V ₈₀ (%)	<5%	0	0	–
V ₇₀ (%)	<10%	0	0	–
Ureter				
D _{max} (Gy)		11.03	11.0	46.99
D _{mean} (Gy)		1.42	1.92	26.93
V ₈₀ (%)	<5%	0	0	–
V ₇₀ (%)	<10%	0	0	–

Abbreviations: D_{max}: maximum dose; D_{mean}: mean dose; D_{min}: minimum dose; D_x: dose (in Gy) receiving x% of a volume or more; OAR: organs at risk; PTV: planning target volume; VMAT: Volumetric Modulated Arc Therapy; V_x: volume (in percentage) receiving x dose or more (in Gy).

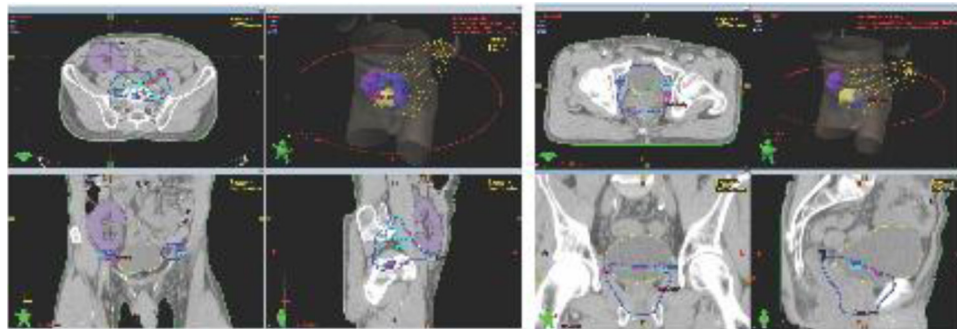


Fig. 3. Plan for Case 2. Definitive radiation therapy was administered using Volumetric Modulated Arc Therapy (3 arcs). Phase 1 (4 images on the left): primary and elective pelvic lymph nodes to a total dose of 46 Gy. Phase 2 (4 images on the right): primary boost to achieve a total dose of 78 Gy. For each phase: Upper left and lower right and left images: 98% isodose curve in cyan, 95% isodose curve in magenta, and 90% isodose curve in blue. Upper right images: in purple kidney transplant, in yellow bladder, in brown rectum and in blue PTV.

Organization Risk-Group 1. He had a medical history of LRDRT in the right iliac fossa due to secondary ESKD 6 years before, and his maintenance immunosuppressive therapy consisted of tacrolimus, mycophenolate mofetil (MMF), and PDN. Since he declined surgery, he received radical external beam RT (EBRT) with concurrent hormone therapy, beginning 2 months prior to RT with a gonadotropin-releasing hormone analog (leuprolide) until he completed 6 months of therapy. The patient underwent no contrast CT simulation with full bladder. Case was contoured following the

treatment planning / target volume recommendations of RTOG 0815¹⁴ prostate cancer protocol. Nodal CTV included obturators, external, internal and common iliac lymph nodes below the L5-S1 interspace, it was generated by adding a 7-mm margin around these vascular structures and excluding bowel, bladder, bone and KT. The primary CTV included the prostate and seminal vesicles. PTV was generated with an isotropic margin of 5 mm (3 mm posteriorly for primary PTV). PTV overlaying the KT was cropped to remove the part extending inside KT and an additional margin of

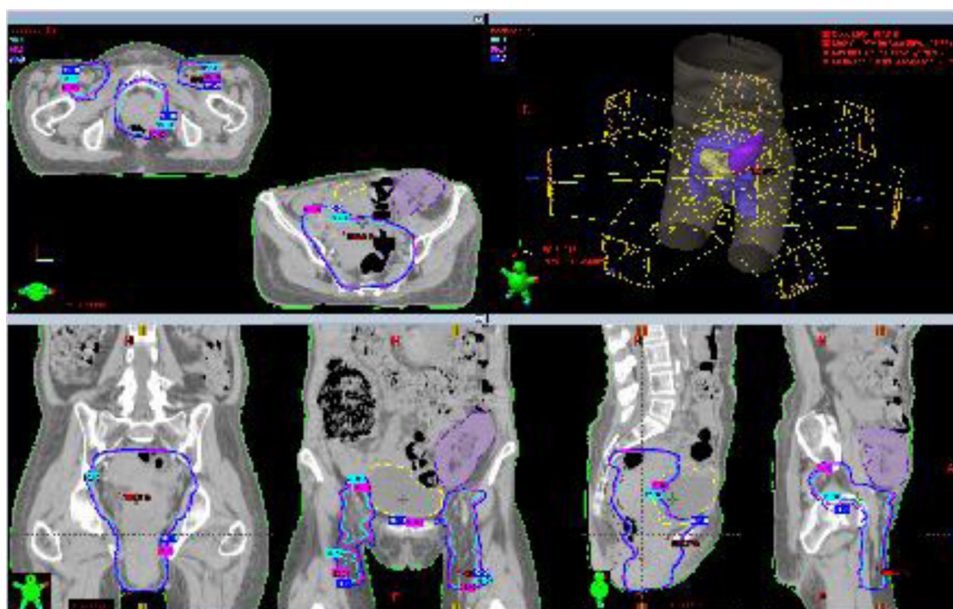


Fig. 4. Plan for Case 3. Definitive radiation therapy to primary, pelvic, and inguinal lymph nodes using Intensity Modulated Arc Therapy. Upper left and lower right and left images: 98% isodose curve in cyan, 95% isodose curve in magenta, and 90% isodose curve in blue. Upper right image: in purple kidney transplant, in yellow bladder, in brown rectum and in blue PTV.

Table 3
Patient, treatment, and outcome characteristics.

Case	Gender; Age at EBRT	KT; Immunosuppression; Baseline Creatinine	Cancer (mo after KT)	EBRT	Mean Dose to Kidney	Follow-up
1	Male; 67 years	LRDRT in right iliac fossa; PDN + azathioprine; Creat: 1.2 mg/dL	PCa PP BF: 482 mo	66 Gy in 33 fr to the surgical bed with VMAT	0.9Gy	Alive NED at 60 mo FU; Last PSA: 0.01 ng/mL; Creat 1.08 mg/dL
2	Male; 55 years	LRDRT in right iliac fossa; Tacrolimus + MMF + PDN; Creat: 1.2–1.6 mg/dL	Intermediate-risk PCa: 68 mo	46 Gy in 23 fr to pelvis and 78 Gy in 39 fr with VMAT; 6-mo leuprolide	4.88 Gy	Alive NED at 20 mo FU; Last PSA: 0.01 ng/mL; Creat: 1.08 mg/dL
3	Female; 52 years	LRDRT in left iliac fossa; MMF + PDN; Creat: 1.04 mg/dL	VCa stage IVa: 194 mo	50.4 Gy in 28 fx with IMRT + BT for a total EQD2 of 85 Gy	8.66 Gy	Alive NED at 24 mo FU; Creat: 1.09 mg/dL

Abbreviations: BF: biochemical failure; BT: brachytherapy; Creat: creatinine; EBRT: external beam radiation therapy; EQD2: equivalent dose in 2-Gy fractions; fr: fractions; FU: follow-up; IMRT: intensity modulated radiation therapy; KT: kidney transplantation; LRDRT: living related donor renal transplantation; MMF: mycophenolate mofetil; mo: months; NED: no evidence of disease; PCa: prostate cancer; PDN: prednisone; PP: post-prostatectomy; VCa: vaginal cancer; VMAT: Volumetric Modulated Arc Therapy.

2 mm, since at some areas KT was next to the external iliac vessels. The treatment planning technique was performed with VMAT with triple, non-coplanar 10MV-energy arcs. The upper limit for the pelvic node arc was 1 cm above the top of L5, which corresponds to the upper limit of KT. VMAT plan required further optimization to reduce dose to KT. Dose constraints achieved in the current case are shown in Table 2. He received EBRT with conventional 2-Gy daily fractions, 5 days per week for a total dose of 78 Gy in 39 fractions (elective pelvic lymph nodes received 46 Gy and primary target volume including prostate received 78 Gy). During his initial evaluation, his renal function was well compensated with a creatinine level between 1.2 and 1.6 mg/dL and no acute renal injury was documented during treatment and early follow up. The treatment was delivered with a TrueBeam linear accelerator and verification was conducted using daily CBCT prior to every fraction. Details of the treatment planning are shown in Fig. 3. With a short follow-up of 20 months, he has achieved PSA reduction (his recent PSA was 0.48 ng/mL), creatinine levels (1.43 mg/dL), glomerular filtration rate (58 mL/h) and hematologic counts remain stable. No further complications have been documented.

2.1.3. Case 3

A 52-year-old woman with medical history of LRDRT in the left iliac fossa 16 years ago, was diagnosed with irresectable clinical-stage IV-A squamous cell and verrucous carcinoma of the vagina (SCCVa) due to invasion of the urethra, rectum, and anal canal. At the time of diagnosis of SCCVa, her renal function was within reference ranges with a basal creatinine level of 1.09 mg/dL, and she remained under long-term immunosuppressive therapy with PDN and MMF. The patient underwent non contrast CT simulation with full bladder and in a “frog-leg” position for upper inner thigh skin sparing. Since currently there are no consensus guidelines for delineation of volumes and OAR, it was done following Consensus Recommendations for Radiation Therapy Contouring and Treatment of Vulvar Carcinoma¹⁵ with adaptations to avoid vulva irradiation. GTV was based on magnetic resonance imaging that showed primary vaginal tumor with circumferential involvement, with anterior infiltration of the urethra and posterolateral involvement of the puborectal muscle and rectum. The entire vagina was included in CTV and proximal involved rectum and urethra. Nodal CTV included internal and external lymph, and inguinal lymph nodes. KT was in contact with the left external iliac vessels, and

Table 4
Summary of the literature: Radiation therapy for prostate and cervical cancer in patients with previous kidney transplant.

Study	N	RT dose and technique	KT location and received dose	Mean F/U	Cancer outcome at last F/U	Allograft outcome	RT late toxicity
Konety (1998) ⁴⁸	3 post-RP PCa	2D RT 65 Gy	Location n/a Allograft shield	46 mo	2 alive NED 1 death NED	Functional	n/a
Deti (2011) ¹²	1 post-RP PCa	IMRT 70 Gy with 5 CoBeams	Location n/a D _{mean} 0.36 Gy D _{max} 1.88 Gy	n/a	NED	Functional	No toxicity
Mohiuddin (2012) ³⁸	1 CC IB1 post-RH	IMRT 45 Gy (P1), boost 59.4 Gy (P2)	Location at RIF V ₁₀ 28% P1 V ₁₀ 18% P2	36 mo	Recurrence out of field resected, at last F/U NED	Functional	No toxicity
Dahlke (2012) ²⁶	4 PCa 2 rectal 1 anal 1 pelvic metastases 1 HL	C3D-RT D _{mean} PTV 60.2 Gy (30–73.8 Gy)	Location n/a D _{max} 10 Gy (0–32 Gy) D _{mean} 2.1 Gy (0.1–6.4 Gy)	23 mo (3–63)	5 NED 1 new CIS 1 new bladder Ca 2 systemic progression	Functional	n/a
Mouzin (2014) ²⁹	8 PCa	C3D-RT 70Gy	Location n/a D ₁₀ * <5 Gy (5 pt) D ₁₀ * 2 Gy (1 pt) D ₁₀ * 11 Gy (1 pt) D ₁₀ * 13 Gy (1 pt)	28 mo	2 death NED 2 alive BF 4 alive NED BF: 14.3%	1 RF at 3 mo	2 obstruction of terminal ureter
Rosenfelder (2014) ⁴⁹	1 PCa T3b N1	IMRT 74 Gy prostate 65 Gy + PLN 60Gy EPLN	Location at RIF D _{max} 31.5 Gy D _{mean} 2.7Gy D _{1cc} 10.8 Gy	8 mo	1 alive NED	Functional	No toxicity
Iizuka (2016) ⁵⁰	2 PCa T1 N0	2 IMRT 74 Gy in 37 fr to prostate 6 coplanar fields	Location at RIF Constraints n/a	43 mo	2 alive NED	Functional	No toxicity
Gojdic (2018) ³²	4 PCa T1–2c N0	3 BT ¹²⁵ I 145 Gy + 12 mo AD 1 C3D-RT 74 Gy to prostate + AD	Location n/a D _{max} 14.79 Gy Location n/a	49 mo (30–73)	Undetectable PSA	Functional	1 urinary incontinence 1 urethral stricture at 30mo

AD: androgen deprivation; BF: biochemical failure; BT: brachytherapy; C3D: Conformal 3-Dimensional RT; CC: Cervical cancer; CoBeam: Coplanar beams; D_{max}: maximum dose; D_{mean}: mean dose; DMFS: distant metastasis-free survival; EBRT: External Beam Radiotherapy; EPLN: elective pelvic lymph nodes; F/U: follow-up; HL: Hodgkin lymphoma; ¹²⁵I: iodine-125; IMRT: Intensity Modulated RT; IR: intermediate risk; LR: low risk; mo: months; n/a: no information available; NED: no evidence of disease; +PLN: positive pelvic lymph nodes; P1 and P2: phase 1 and 2, respectively; PCa: Prostate cancer; OS: overall survival; RF: renal failure; RH: Radical Hysterectomy; RIF: right iliac fossa; RP: Radical Prostatectomy; RT: Radiation Therapy, with conventional fractionation (1.8–2 Gy per fraction) if not otherwise specified.

so were CTV and PTV. Therefore, editing to exclude overlap, with an additional safe margin of 3 mm (separating KT from CTV and PTV) was required. EBRT planning was performed with intensity-modulated radiation therapy (IMRT) using 7 coplanar fields with 6 MV energy (Fig. 4). Dose to OAR are shown in Table 2. She initially received EBRT to a total dose of 50.4 Gy in 28 fractions to the primary, pelvic, and inguinal lymph nodes with conventional 1.8 Gy daily, 5 days per week. She received weekly concurrent cisplatin (60 mg/day). Concurrent chemoradiotherapy was followed by intracavitary brachytherapy (IBT) to a total dose of 85 Gy. There was no acute or late reported renal or hematologic toxicity. With a 24-month follow-up, her last physical examination and positron emission tomography-computed tomography imaging revealed no evidence of disease. Her renal function remained stable (her creatinine level was 1.09 mg/dL and glomerular filtration rate of 44 mL/min).

Table 3 presents a summary of the 3 case examples of KT and pelvic cancer patients treated with pelvic RT.

3. Discussion

In patients with KT, preserving the allograft function is important given its impairment is associated with a reduction in 5-year OS up to 60%.¹⁶ Despite anatomical difficulties secondary to prior KT and peritoneal dialysis, the current safe and effective recommendation for PCa management is prostatectomy.^{12,16} Moreover, although the 5-year OS of patients with PCa with previous KT treated with surgery and/or radiotherapy is similar to the general PCa population (77% versus 72%, respectively),¹⁰ primary EBRT is usually discouraged due to the potential risk of ureteral and urethral stricture and kidney transplant dysfunction.¹⁷ Brachytherapy

is another treatment option that confers a lower risk of allograft and ureteroneocystostomy injury. However, access to brachytherapy is limited in our setting.^{18,19} For SCCVa, 5-year OS is equal to that seen in the general population when stratifying according to stage and when standard treatment is offered. Currently, there are no standard recommendations for patients with SCCVa with previous KT.^{19,20} The management options for gynecologic cancers include surgery, RT, and chemotherapy. Chemotherapy can affect the allograft function and interact with immunosuppression, while surgery and RT may represent a direct risk of allograft or ureteral damage, and in surgical cases, an indirect risk through injury to blood vessels. However, whenever it is resectable, surgery is preferred. In locally advanced SCCVa, decision must be taken on a case-by-case basis.²⁰

When radiotherapy is needed, the dose to renal allograft should be limited to the lowest possible dose. The standard QUANTEC constraints correlated with <5% of clinical dysfunction are mean bilateral kidney <15–18 Gy, and, volume receiving 12, 20, 23 and 28 Gy less than 55%, 32%, 30% and 20%, respectively.²¹ For native kidneys, Dawson reported an estimated probability of <5% for RT-induced renal dysfunction with a mean bilateral kidney dose < 10 Gy and < 18 Gy²¹ in patients receiving total body irradiation (TBI)²² and non-TBI.²³ In the same setting, minor glomerular nephritis was documented in 3 of 32 patients receiving a total dose of 12 Gy with TBI,²⁴ and more recently, renal toxicity was documented in 25% of patients treated with TBI with a total dose of 4–12 Gy.²⁵ In patients with KT, RT-dose tolerance may be lower due to long-term immunosuppression, graft condition, vascular anastomosis, past history of rejections and clinical evolution of kidney graft among others. Based on previous information and whenever possible, the mean dose should be <4 Gy. This was not

achieved in two of our three cases. At the time we determined local control of the tumor surpassed the risks of graft injury, mainly based on the weak evidence supporting KT dose constraints and information inconsistent in the literature. Table 4 shows reviewed literature of similar case reports where received doses to the KT were sometimes even higher with good oncologic and renal function outcomes. We do make emphasis dose tolerances must be considered in a case-by-case basis and that received doses (especially mean dose) should always be as low as possible.

While contouring PRV is especially useful for serial-like structure as a subrogate of motion maximum dose, using it for renal allograft could help sparing KT during planning optimization.²⁶ Additionally, contouring of the urethra, ureter and ureterovesical junction is important to maintain the dose as low as possible to reduce the risk of induced radiation therapy stricture or stenosis. Mean dose constraint for the proximal prostatic urethra should be ≤ 65 Gy and for distal prostatic urethra ≤ 74 Gy,²⁷ and the volume of the urethra receiving 80Gy²⁸ and 70Gy²⁹ should be $<5\%$ and $<10\%$, respectively. Urethra and ureteral constraints were met in 3 cases; however, this could not have been achieved with C3D-RT (as showed in case 1).

Previous reports showed that C3D-RT with doses from 20 Gy to 40 Gy had been associated with ureteral stricture and ureteroneocystostomy injury, which, in turn, could increase the risk of allograft dysfunction.³⁰ Therefore, some contraindicate EBRT in patients with previous KT, and reserve it as adjuvant or salvage therapy.³¹ However, doses to the kidney allograft, ureter, and urethra could be dramatically reduced with modern RT planning techniques and by assuring a full bladder during each treatment and daily CBCT.^{30,32} Our first PCa patient was treated with RT two years after prostatectomy due to postoperative biochemical failure. Initial C3D-RT planning was elected because the RT field was limited to the surgical bed and it has also been previously demonstrated to be feasible with low mean KT doses of 0.36 Gy.¹² However, the dose to the urethra and ureter implant was not low enough to be considered a safe treatment technique (urethra and ureter received three times the maximum doses with C3D-RT compared to VMAT planning). Hence, to comply with dose constraints, his treatment was planned and delivered with only one arc of VMAT with no additional non-coplanar arcs to limit the possible dose as non-coplanar arcs could contribute to the KT. The second PCa patient received RT to primary and pelvic lymph nodes with VMAT to reduce the dose delivered to his kidney allograft and ureteral implant. And, even though nodal CTV and PTV was in contact with KT, achieved dose was low enough (mean 4.88 Gy) to approve the treatment plan, considering that reducing the volume could compromise the outcome and that no other treatment option was available. In both cases, at last follow-up (60 and 20 months, respectively), there was no evidence of allograft or ureteral junction dysfunction, confirming the evidence reported in the literature.^{26,33,34}

The third case in our series developed SCCVa 194 months after LRDRT. To the best of our knowledge, this is the first case of SCCVa treated with definitive pelvic EBRT and IBT in a patient with previous LRDRT. Because RT compromises irradiation to primary and pelvic and inguinal lymph nodes, newer planning techniques involving IMRT or VMAT should be considered to reduce the dose to OAR and allow adequate coverage to treatment volumes as shown in our third case. In a retrospective review, regional nodal recurrence in patients with SCCVa that did not undergo elective irradiation was 38% for stage I and 40–50% in stage III-IV.³⁵ Our third case's outcome is consistent with other case reports that confirm the safety and effectiveness of definitive and adjuvant RT for gynecologic cancers.^{36–39} Due to irresectability, the tumor board selected chemoradiotherapy as definitive treatment. Dose exceeding the limit constraint was accepted since pelvic lymph node recurrence outweighs the risk of allograft injury (5-year OS for

stage-IV SCCVa is 0–35% versus 60–90% after graft failure),^{40,41} with 12% of mortality in the first year after renal allograft failure.⁴²

Other OAR that must be considered for planning RT treatment are the bladder, rectum, and bowel with their standard dose constraints. Beside these OARs, special consideration for femoral heads should be considered because long-term immunosuppression and steroid therapy is associated with a higher risk of avascular necrosis. Evidence in the literature limits the maximum dose to <40 Gy for femoral heads to reduce the risk of complications.^{12,20,26}

We have reported three successful cases of patients with KT with a mean follow up of 24 months (20–60), with no acute or late effects associated to RT. We believe this short series of cases reflect the importance of high precision treatment techniques even when the graft is outside conventional fields or PTV. Techniques such as VMAT as stated on case number 1, were able to reduce D_{max} , $D_{0.3cc}$ and D_{mean} of KT up to 70.9%, 77.7% and 49.7%, respectively. In Table 4 we summarize previous case reports of post-KT patients with prostate or cervical cancer treated with RT either adjuvant or definitive. We exclude articles with no information available of the dose constraint to the KT or allograft outcome.^{34,43–47} It clearly shows how previous studies did not use the same constraints, as there are neither standard recommendations nor clearly stated constraints, and even some recent studies do not report them. Major limitations of the study are the retrospective nature of the article and limited sample size of the study. We also acknowledge a longer follow-up is needed for case 2 and 3.

4. Conclusions

An increased incidence of primary pelvic cancer in KT recipients needing RT is expected due to a rise in long-term survival and the use of immunosuppressive therapy. Treatment options are limited due to anatomical changes, comorbidities and management-related issues. The graft itself is often near or inside average CTV contouring for pelvic malignances. Furthermore, excessive concern exists over the kidney allograft function, ureteral junction, and urethral injury associated with radiotherapy which ultimately leads to radiotherapy underusage. Nevertheless, when needed, RT modern techniques remain a valid option with excellent oncologic results and acceptable toxicity. Physicians should give special considerations to accomplish all dose constraints of OAR in the patient's specific setting and keep the doses as low as possible. Several publications recommend graft mean dose <4 Gy, but graft proximity to CTV makes it unfeasible. We present 2 cases where dose constraint was not achieved, and to a short follow up of 20 months renal toxicity has not been documented. We recommend the lowest mean dose to the KT as possible, but never by compromising the CTV coverage, since morbimortality from recurrent or progressive cancer disease outweighs the risk of graft injury. Further clinical trials are warranted on specific dose tolerance for KT.

Conflict of interest

None.

Financial disclosure

None.

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