

High-dose-rate interstitial brachytherapy for female peri-urethral cancer

Daya Nand Sharma, MD¹, Ajeet Kumar Gandhi, MD¹, Neeraja Bhatla, MD², Sunesh Kumar, MD², Goura Kisor Rath, MD¹

¹Department of Radiation Oncology, ²Gynecology and Obstetrics, All India Institute of Medical Sciences, New Delhi, India

Abstract

Purpose: Peri-urethral cancer (PUC) in females is a rare malignancy. Surgery is not usually contemplated due to associated morbidity. Radiation therapy (RT) can be employed in the form of interstitial brachytherapy (IBT) alone for early lesions, and external beam radiation therapy (EBRT) with or without IBT for advanced lesions. We report our first experience in the literature to evaluate the role of high-dose-rate (HDR) IBT in female PUC.

Material and methods: Between 2008 and 2013, 10 female patients with PUC (5 primary and 5 recurrent) were treated with HDR-IBT with or without EBRT at our center. Size of the lesion ranged from 1.5 cm to 5.0 cm. A 2-3 plane free-hand implant was performed using plastic catheters. The prescribed dose of HDR-IBT was 42 Gy in 14 fractions for brachytherapy alone (5 patients), and 18-21 Gy for the boost along with EBRT (5 patients). Patients were followed up regularly for assessment of disease control and toxicity.

Results: At a median follow up of 25 months, six patients were disease free at their last follow up. Four patients developed recurrence: 2 at inguinal nodes, 1 at local site, and 1 at both local as well as inguinal nodes. Moist desquamation was the commonest acute toxicity observed in all 5 patients treated with IBT alone, which healed within 4 weeks' time. Overall, grade II delayed complication rate was 30%.

Conclusions: Though small sample size, the results of our study have shown that HDR-IBT provides good loco-regional control with acceptable toxicity for female PUC.

J Contemp Brachytherapy 2016; 8, 1: 41-47

DOI: 10.5114/jcb.2016.57461

Key words: brachytherapy, high-dose-rate, peri-urethral cancer.

Purpose

Peri-urethral tumors in females are masses that grow around the urethra and do not communicate with the urethra, bladder, or vagina (Figure 1) [1]. These include lesions located in para-urethral and sub-urethral space [2,3]. They can be both benign as well as malignant [1,4]. The benign lesions include leiomyomas, hamartoma, urethral caruncles, Skene's gland abscess/cysts, urethral diverticulum, Gartner's duct cyst, etc. [4]. Malignant lesions are rare and can be primary or recurrent/secondary from other primary malignancies like cervical [5], endometrial [5], or rectal carcinoma [6]. Primary malignancies include adenocarcinoma, squamous cell carcinoma, histiocytoma, melanoma, and sarcoma [1]. The distinction between urethral, peri-urethral, and anterior vaginal wall lesions may be difficult because of their anatomic proximity and overlapping clinical features. Imaging techniques such as computed tomography/magnetic resonance (CT/MR) (preferably MR) are helpful in diagnosis [7,8]. Cysto-urethrogram helps in excluding the urethral origin and invasion.

The literature on female peri-urethral cancer (PUC) is extremely limited, and it is very challenging to predict

the clinical course and decide management. Treatment options include surgery and radiation therapy (RT), and the decision is usually individualized. Surgery is often tried in the form of 1) local excision for small tumors and requires plastic repair (urethroplasty), and 2) pelvic exenteration for larger lesions, which is associated with significant morbidity. Hence surgical treatments are not usually contemplated. Radiation therapy can be employed in the form of brachytherapy alone for early lesions and external beam radiation therapy (EBRT) with or without brachytherapy for advanced lesions. Target volume usually consists of primary tumor with or without inguinofemoral nodes. Treatment with EBRT is quite challenging due to anatomic location and poor tolerance of the adjoining organs like vulva, urethra, and rectum. Interstitial brachytherapy (IBT) can precisely deliver the radiation to the tumor with sparing of the adjacent organs. Role of IBT has been reported in a small series [5], though in patient populations having recurrent PUC. No data is available on primary female PUC treated with HDR-IBT. We report our first ever experience in the literature to evaluate the role of HDR-IBT in female PUC, primary as well as recurrent.

Address for correspondence: Daya Nand Sharma, MD, Department of Radiation Oncology, All India Institute of Medical Sciences, New Delhi 110029, India, phone: +91 11 29575241, fax: +91 11 26588663, e-mail: sharmadn@hotmail.com

Received: 05.10.2015

Accepted: 02.01.2016

Published: 26.02.2016

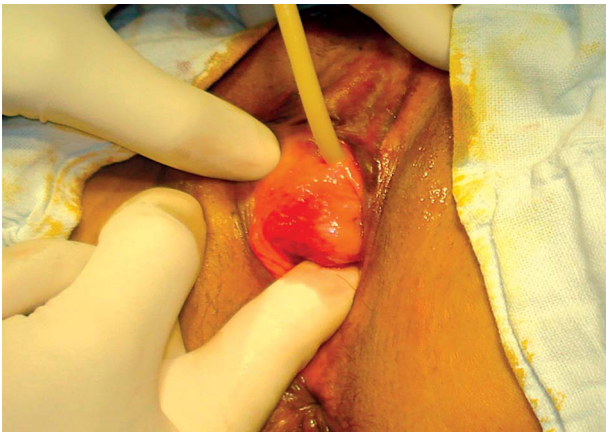


Fig. 1. Clinical photograph showing a tumor in the peri-urethral region protruding in the vagina

Material and methods

Between 2008 and 2013, 10 female patients with PUC were treated with HDR-IBT with or without EBRT at our center. The decision of treatment was taken in combined gynecologic oncology clinic by a team comprising of gynecologists and radiation oncologists. Written consent was

Table 1. Patient characteristics

Attribute	
Age (years)	
Median	49
Range	37-65
Anatomical site (no. of patients)	
Primary	5
Recurrent*	5
From cervix	4
From endometrium	1
Histopathological type	
Squamous cell carcinoma	9
Adenocarcinoma	1
Size of tumor (cm)	
Median	3.0
Range	1.5-5.0
Nodal status (no. of patients)	
Node negative	10
Node positive	0
Follow up period (months)	
Range	4-74
Median	25

*Median disease free interval was 21 months (range 7-48 months)

obtained from all patients. The various clinical characteristics of the patients are presented in Table 1. Median age was 49 years (range 37-65). Pretreatment evaluation consisted of detailed clinical examination, routine blood investigations, plain X-ray chest, CT/MR imaging of the abdominopelvic region, and histopathological examination of the primary lesion. The urethral/bladder involvement was ruled out by cystourethroscopy examination. No patient had inguinal lymph node metastases on clinical examination or imaging. Five patients had primary lesions and the remaining 5 had recurrent tumors. Alone HDR-IBT was usually the preferred treatment for patients having small lesions (< 3.0 cm). For lesions larger than 3.0 cm, EBRT was added to IBT for regional nodal treatment. Thus, 5 patients were treated with IBT alone and rest 5 patients were treated with combination of EBRT and IBT. Chemotherapy was not given to any of the patients. Various details of treatment are shown in Table 2. For combined treatment, we preferred to perform IBT implant ahead of EBRT as the tumor is well demarcated and the subsequent EBRT course might cause acute inflammation of the local area.

Brachytherapy implant procedure

After pre-anesthetic evaluation, all patients were hospitalized one day prior to the procedure. The implant procedure was done under spinal anesthesia. After inserting the Foley catheter into the bladder, thorough assessment of the tumor dimensions was made. The area to be implanted included gross tumor plus a margin of at least 5 mm. A 2-3 plane free-hand implant was performed depending on the implant area. 16-G stainless steel needles along with trocars were inserted manually without using any template (Figure 2A). Trans-vaginal ultrasonography was used in some patients to guide the needle insertion. In order to avoid close proximity of the needles to urethra and urethral injury, the intra-planar and inter-planar distance was usually kept between 0.8-1.2 cm. Then the trocars of the needles were removed and the tails of the plastic catheters having button at one end were negotiated through the hollow needles. Subsequently, the needles were removed and replaced by plastic catheters which were fixed with buttons (Figures 2B, 2C, and 2D). In patients with lesions near proximal urethra, implant was performed with stainless steel needles having blind ends as it was difficult to negotiate the plastic catheters. Antibiotics and analgesics were prescribed till the implant removal.

Brachytherapy planning and dosimetry

A planning CT scan of the implant area was done with slice thickness of 2.5 mm. Brachytherapy planning was performed on PLATO planning system, version 14.1 (Nucletron, an Elekta company, Elekta AB, Stockholm, Sweden). The clinical target volume (CTV) and various organs at risk (OAR) were contoured. Urethra was contoured from bladder neck to meatus around the Foley catheter. No planning target volume (PTV) margin was given around the CTV. The implant catheters were also marked on each slice in order to reconstruct the catheter length. Using step size of 2.5 mm, a plan was generated for prescription dose to the CTV. If needed, both graphic and geometric optimi-

Table 2. Summary of treatment and clinical outcome

S.N.	Diagnosis	Previous malignancy (treatment)	Previous RT dose	Treatment	Dose of brachytherapy (Gy)	Dose of EBRT (Gy)	Follow up (months)	Disease status	Site of rec.
1	Rec. SCC	SCC cervix (RT)	EBRT = 50.4 Gy ICRT = 7 Gy × 3	IBT	42	–	26	NED	–
2	SCC	–	–	IBT	42	–	36	Rec.	Nodal
3	SCC	–	–	EBRT + IBT	21	45	5	NED	–
4	SCC	–	–	EBRT + IBT	21	45	26	NED	–
5	Rec. adeno.	Endo. adeno. (surgery + RT)	EBRT = 50.4 Gy	EBRT + IBT	18	36	15	Rec.	Local
6	Rec. SCC	SCC cervix (surgery + RT)	EBRT = 50.4 Gy ICRT = 7 Gy × 3	EBRT + IBT	18	40	4	NED	–
7	SCC	–	–	IBT	42	–	25	Rec.	Local Nodal
8	Rec. SCC	SCC cervix (RT)	EBRT = 50.4 Gy	IBT	37	–	74	NED	–
9	SCC	–	–	EBRT + IBT	21	50	5	NED	–
10	Rec. SCC	SCC cervix (surgery + RT)	EBRT = 50.4 Gy	IBT	42	–	24	Rec.	Nodal

rec. – recurrence, Gy – Gray, SCC – squamous cell carcinoma, adeno. – adenocarcinoma, endo. – endometrial, RT – radiation therapy, EBRT – external beam radiation therapy, IBT – interstitial brachytherapy, ICRT – intracavitary radiation therapy, NED – no evidence of disease

zation was done to achieve the best plan. The volumes receiving 100% (V_{100}) and 150% (V_{150}) of the prescribed dose were calculated. Urethral dose was kept as low as possible without compromising CTV dose. After the study period, plans were retrieved to calculate the urethral $D_{0.1cc}$ (dose received by 0.1 cm³ of the urethra). Cumulative dose received by 2.0 cm³ (D_{2cc}) of bladder and rectum was also calculated and expressed as 2 Gy-equivalent dose (EQD₂) using α/β ratio of 3. The previous irradiation dose was accounted while calculating the cumulative EQD₂.

Dose homogeneity index (DHI) was calculated using the following formula:

$$DHI = \frac{V_{100} - V_{150}}{V_{100}}$$

Usually, an HDR dose of 42 Gy in 14 fractions, using 3 Gy per fraction, over 7 days was prescribed for definitive treatment employing twice daily fractionation schedule. In one patient, dose was modified to 37 Gy in 10 fractions over 5 days due to three consecutive holidays towards the end of treatment since our institute does not permit radiation treatment on Sundays and National Holidays. For IBT boost, the usual dose was 18-21 Gy in 6-7 fractions using 3 Gy per fraction (twice daily fractionation schedule).

Brachytherapy treatment delivery

Treatment was delivered on HDR remote after loading brachytherapy unit (Nucletron, an Elekta company,

Stockholm, Sweden) using ¹⁹²Ir radioactive source with initial activity of 10 Ci for treatment delivery. A minimum of 6 hours interval was kept between two fractions. Brachytherapy catheters were removed immediately after the end of treatment. Foley catheter was removed 5-7 days after the implant removal to prevent the contamination of the local area by urine.

External beam radiation therapy

It was planned 2-3 weeks after the IBT boost to encompass the primary disease, inguinal nodes, and external/internal iliac nodes. The treatment was delivered on ⁶⁰Co or Linear accelerator. Two anteroposterior-posteroanterior (AP-PA) fields were used with wide AP field and narrow PA field. The superior border was kept at L5-S1 level and inferior border at 2.0 cm below the lower extent of the disease. Lateral borders anteriorly were placed to cover the inguinal regions and posteriorly placed 2 cm lateral to pelvic inlet. Electron fields were used to supplement the dose to inguinal nodes. Usually, a dose of 45-50 Gy in 1.8 Gy daily fractions was prescribed but a lower dose (36 Gy) was preferred for post-irradiation recurrent cases.

Follow up and clinical assessment

Patients were followed up at regular intervals for assessment of disease status and toxicity. Initially, monthly follow up was done for the first 6 months and then every 3 months till 2 years. Clinical examination was performed at every visit and appropriate imaging was advised when-

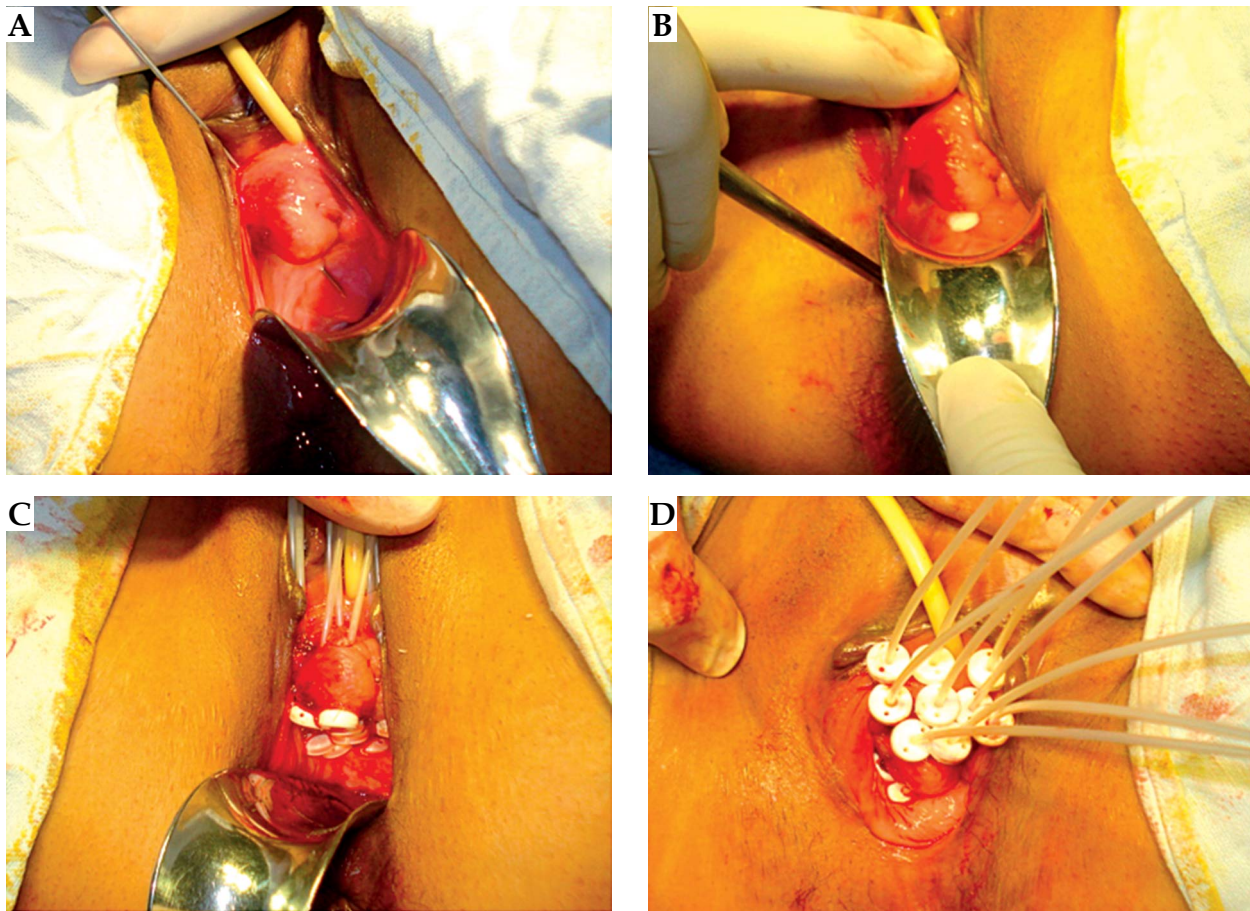


Fig. 2. Clinical photographs demonstrating the implant procedure. A) shows free hand insertion of the implant needle; B, C, and D show the negotiation of the plastic catheters through the needle and fixing with buttons

ever there was a suspicion of recurrence in the inguinal or pelvic region. All the recurrences were histopathologically proven by either biopsy or aspiration cytology examination. Local recurrence (LR) was defined as any recurrent lesion observed in the primary site. Rest of the recurrences were labeled as regional (inguinal or pelvic region) or distant. Early and late toxicities were assessed and recorded as per Radiation Therapy Oncology Group (RTOG) morbidity criteria [9]. Toxicities observed between the date of implant and the 3rd month after the completion of the treatment was defined as early, and beyond 3 months it was classified as late.

Results

All patients completed the scheduled IBT treatment without any interruption. Two of the 5 patients in the combined therapy group had interruption of 3-5 days during EBRT due to moist desquamation of the skin in the perineal area. Both of these patients had previous EBRT to pelvis. Table 3 shows various brachytherapy implant and dosimetric characteristics. For all patients, DHI ranged from 0.64-0.88 with a median of 0.67. Median D_{2cc} for bladder and rectum was 88 Gy and 72.5 Gy, respectively. Figure 3 demonstrates the CT based brachytherapy planning of a patient showing isodose distribution.

Disease control

Median follow up was 25 months (4-74 months). As shown in Table 2, six patients were disease free at their last follow up. Thus, the locoregional control rate was 60%. Four patients developed recurrence: 2 at inguinal nodes, 1 at local site, and 1 at both local as well as inguinal nodes. Therefore, local recurrence rate and nodal recurrence rate was 20% and 30%, respectively. No patient had distant metastases. All 3 patients with nodal recurrence had been treated with IBT alone. One patient with local recurrence only was effectively salvaged by surgery while remaining 3 patients with nodal failure eventually died of their disease. No patient had developed distant metastases. The 2-year actuarial overall survival was 54%.

Toxicity

Table 4 shows the details of acute toxicity profile. Moist desquamation was the commonest acute toxicity observed around 2 weeks in all 5 patients treated by IBT alone, which healed within 4 weeks' time. This was confined to the area of implant. Two of the 5 patients treated by combined therapy developed acute grade III skin reactions in the inguinal region. This was managed by interrupting the treatment for 5-7 days and by giving them narcotic analgesics and antibiotics. Seven out of 10 patients

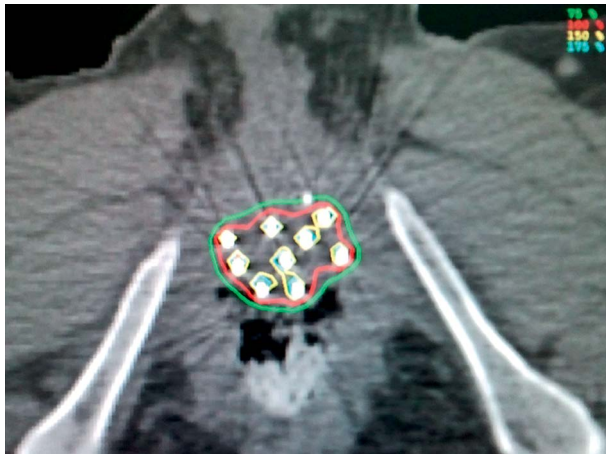


Fig. 3. Computed tomography scan based brachytherapy planning showing isodose distribution in a tumor implanted with 9 catheters in three planes. The red line represents the prescription isodose line. Anteriorly Foley’s catheter can also be seen for urethral demarcation

had either acute skin or mucosal grade III toxicity. No patient developed late grade III-IV toxicity. Two of the IBT alone patients had fibrosis of the anterior vaginal wall adjacent to the implanted area but it was asymptomatic. Additionally, these two patients had chronic dysuria but none of them required urethral dilatation or any other active intervention. One patient had delayed grade II proctitis, which was managed by often use of laxatives, hematinic, and steroid enemas.

Discussion

Female PUC is an extremely rare malignancy. Although some reports are available in the literature, most of them elaborate either on pathological [2,3] or radiological [7,8] aspects. Therefore, treatment of such patients remains a challenge. Our present study was aimed to explore the role of HDR-IBT in female PUC. To the best of our knowledge, ours is the first report, which deals with the role of HDR-IBT in female PUC. The report by Kathryn Greven [5] comprises patients with recurrent PUC and none with primary PUC. Our series had 50% patients with primary PUC.

The results of our study have shown that HDR-IBT is a very effective treatment for female PUC. We observed a local control rate of 80% and locoregional control rate of 60% in our series. Our delayed grade I-II complication

Table 3. Details of brachytherapy

Attribute	
Duration of implant procedure (minutes)	
Average	55
Range	40-75
No. of catheters	
Median	5
Range	4-9
Brachytherapy dose (Gy)	
For definitive	37-42
For boost	18-21
Dose per fraction (Gy)	
For definitive	3-3.7
For boost	3
V ₁₀₀	
Median	12
Range	7-30
V ₁₅₀ (c.c.)	
Median	4
Range	2-10
DHI	
Median	0.67
Range	0.64-0.88
D _{0.1cc} urethra* (Gy)	
Median	86
Range	80-112
D _{2cc} bladder* (Gy)	
Median	88
Range	36-118
D _{2cc} rectum* (Gy)	
Median	72.5
Range	30-92

*Represents EQD₂, which includes dose from previous RT
 DHI – dose homogeneity index, Gy – Gray, V₉₀ – volume receiving 90% of prescribed dose, V₁₀₀ – volume receiving 100% of prescribed dose, V₁₁₅ – volume receiving 115% of prescribed dose, V₁₅₀ – volume receiving 150% of prescribed dose, D_{0.1cc} urethra – dose received by 0.1 cm³ of urethra, D_{2cc} bladder – dose received by 2 cm³ of bladder, D_{2cc} rectum – dose received by 2 cm³ of rectum, EQD₂ – equivalent dose in 2 Gy fractions

Table 4. Acute and late toxicity assessed as per RTOG morbidity criteria

Toxicity*	Acute		Late	
	Grade I-II	Grade III-IV	Grade I-II	Grade III-IV
Skin	1	2	0	0
Bladder/genito-urinary	0	5	2	0
Bowel/rectum	2	0	1	0
Vagina	3	5	2	0

*Toxicities were overlapping. RTOG – Radiation Therapy Oncology Group

rate of 30% is within acceptable limits, keeping in mind that 5 out of 10 patients received re-irradiation.

Greven [5] reported a series of 10 consecutive women with recurrent lesions from cancer of cervix (3 patients) and endometrium (7 patients). Five of them had been previously treated with pelvic RT. The size of tumor ranged from 1-6 cm. Of them, 4 patients were treated with template based low dose rate (LDR) IBT with dose ranging from 40-50 Gy. Remaining 6 patients were treated with combination of EBRT (39-50 Gy) and LDR-IBT (20-38 Gy). The total doses to the tumor for patients who had received previous RT ranged from 40-65 Gy and 65-75 Gy for those who received upfront RT. With a median follow up of 34 months (range 1-64 months), all patients had achieved local control of the sub-urethral disease at the time of last follow-up. Four of the 10 women remained alive without evidence of disease. Four women died of metastatic disease. One patient developed a late radiation related complication (recto-vaginal fistula), which required colostomy. The author concluded that recurrent endometrial and cervical cancer in the sub-urethral area show excellent local control with treatment that incorporates IBT. Since Greven's study [5] is the only published study evaluating the role of IBT in female PUC, it is worth comparing with our study. Apparently, Greven's study [5] has shown superior local control rate than ours (100% vs. 80%) but this difference may be due to small sample size in both studies. Clearly, both studies have shown excellent local control rates. Distant metastatic rate was higher in her series than ours (40% vs. 0%). This may be due to relatively shorter follow up in our study (25 vs. 34 months), and hence we intend to carefully examine our patients to detect distant metastases during the subsequent follow up visits. Regarding treatment related complications, we did not encounter any serious toxicity unlike Greven [5] who noticed recto-vaginal fistula in one patient (10%), possibly due to higher prescription dose (75 Gy). However, overall grade II delayed complication rate was 30% in our series.

Since urethra is in close vicinity to these tumors, it is likely to receive considerable dose during IBT. The length and circumference of the urethra irradiated will possibly correlate with the toxicity. As there was no dose constraint mentioned for urethra in the literature during our study period, we tried to keep the urethral dose as low as possible without compromising CTV dose. The study by Rajagopalan *et al.* [10] was published after our study period and hence we could not follow the suggestions mentioned in their study. Since the authors [10] observed a correlation between urethral $D_{0.1cc}$ and urethral toxicity, we retrieved the plans of all ten patients from the brachytherapy treatment planning system and determined the urethral $D_{0.1cc}$. Median $D_{0.1cc}$ urethra (EQD₂) in our series was 86 Gy but no patient developed urethral stricture. Rajagopalan *et al.* [10] have reported a higher risk of urethral toxicity in patients with urethral EQD₂ of more than 85 Gy.

The common acute toxicities related to brachytherapy are moist desquamation, local pain, and difficulty during urination because of urethritis. It should be managed with hygienic care, oral antibiotics, and analgesics (including narcotic analgesics) and non-steroidal anti-inflammatory drugs. Treatment should be interrupted if necessary. All

5 patients in our series treated with IBT alone developed moist desquamation but it completely resolved within 4 weeks' time.

Ours is the first ever study using HDR for female PUC. Greven [5] had used LDR in her series. We decided the dose of HDR-IBT (42 Gy using 3 Gy per fraction) based on our experience with HDR-IBT in other sites particularly penile cancer [11]. We were skeptical in choosing a higher dose due to fear of toxicity. Keeping in mind the acceptable toxicity rate in our study, we are considering of escalating the HDR-IBT dose beyond 42 Gy to further improve local control rate.

Due to limited literature, the incidence of regional metastases in female PUC is not known. We decided to treat the regional lymph nodes in patients having tumor size of 3 cm or more. The nodal failure rate of 30% in our study seems to be unexpectedly high. This could be due to lack of regional nodal treatment as all the nodal failures were noticed in patients treated with IBT alone. We, therefore, suggest treatment of regional nodes in patients having tumor size more than 2 cm.

Most perineal IBT implants are template based. We preferred free-hand technique as, with template, the position and direction of the needle is fixed. In contrast, free-hand technique permits to change both position and direction of the needle; hence giving better opportunity to avoid needle injury to urethra and also to improve the dosimetry. The DHI, urethral doses, and avoidance of urethral trauma achieved in our study justifies our free-hand approach.

Although boost brachytherapy generally follows EBRT for vast majority of cancers, we preferred to perform boost ahead of EBRT for multiple reasons. Firstly, the tumor is clearly visible and palpable upfront and easier to implant. The sizable tumor itself displaces the normal organs like urethra and vaginal mucosa. On the contrary, after EBRT tumor might show complete or near complete disappearance and therefore difficult to implant. It becomes difficult to demarcate the area to be implanted. The urethra and vaginal mucosa approximate after tumor regression. Secondly, EBRT if delivered first, might delay the brachytherapy implant due to acute toxicity since perineum is a sensitive area. Thirdly, with brachytherapy, a reasonably large dose is delivered in smaller period. Recently, large doses delivered in quick time (for example in stereotactic body radiation therapy) have shown favorable biological effects by inciting immunogenic responses [12]. On the other hand, upfront brachytherapy boost might delay the EBRT and increase the risk of disease progression at regional site. Such risk is not robust in female PUC since its regional behavior is not well known.

The role of chemotherapy is not clear in female PUC. Greven [5] had suggested exploring the role of systemic therapy in view of high metastatic rate observed in his series. This aspect is worth exploring in future trials especially in patients with larger and recurrent lesions.

Even though urethral cancer might have different biological behavior as compared to female PUC, experience of brachytherapy for treatment of urethral cancer might be helpful [13,14]. One of the largest series was reported by Milosevic *et al.* [14]. Of the 34 patients, 5 received

brachytherapy, 14 EBRT only, and 15 a combination of EBRT and brachytherapy. The median dose to the primary tumor delivered by EBRT was 50 Gy versus 65 Gy for EBRT and brachytherapy. One of the main findings of this study was a significant improvement in local control attributable to the use of brachytherapy. For patients treated with brachytherapy alone or combined with EBRT, the local relapse free rate was 77% compared with 32% for patients treated with EBRT alone. The beneficial effect of brachytherapy was most prominently seen in patients with bulky primary disease. The authors [14] hypothesized that brachytherapy confers an independent improvement in local tumor control, probably as a result of the higher radiation dose that can safely be delivered.

Conclusions

Female PUC is a rare malignancy and the literature is extremely sparse. Ours is the first study exploring the role of HDR-IBT in female PUC. We realize the limitations of our study: 1) small sample size, 2) mixed population of patients (primary and recurrent), and 3) diverse treatment in the form of primary vs. re-irradiation. Yet, our study is an important addition to the literature highlighting the technical feasibility, clinical safety, and efficacy of HDR-IBT in female PUC.

Disclosure

Authors report no conflict of interest.

References

1. Blaivas JG, Flisser AJ, Bleustein CB et al. Periurethral masses: etiology and diagnosis in a large series of women. *Obstet Gynecol* 2004; 103: 842-847.
2. Kato H, Kobayashi S, Islam AM et al. Female para-urethral adenocarcinoma: histological and immunohistochemical study. *Int J Urol* 2005; 12: 117-119.
3. Cocco AE, MacLennan GT. Unusual female suburethral mass lesions. *J Urol* 2005; 174: 1106.
4. Fletcher SG, Lemack GE. Benign masses of the female peri-urethral tissues and anterior vaginal wall. *Curr Urol Rep* 2008; 9: 389-396.
5. Greven KM. Interstitial radiation for recurrent cervix or endometrial cancer in the suburethral region. *Int J Radiat Oncol Biol Phys* 1998; 41: 831-834.
6. Bernstine JB. Metastatic carcinoma to the female suburethral region from the rectum. *Dis Colon Rectum* 1963; 6: 206-208.
7. Chaudhari VV, Patel MK, Douek M et al. MR imaging and US of female urethral and periurethral disease. *Radiographics* 2010; 30: 1857-1874.
8. Del Gaizo A, Silva AC, Lam-Himlin DM et al. Magnetic resonance imaging of solid urethral and peri-urethral lesions. *Insights Imaging* 2013; 4: 461-469.
9. Cox JD, Stetz J, Pajak TF. Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC). *Int J Radiat Oncol Biol Phys* 1995; 31: 1341-1346.
10. Rajagopalan MS, Kannan N, Kim H et al. Urethral dosimetry and toxicity with high-dose-rate interstitial brachytherapy for vaginal cancer. *Brachytherapy* 2013; 12: 248-253.
11. Sharma DN, Joshi NP, Gandhi AK et al. High-dose-rate interstitial brachytherapy for T1-T2-stage penile carcinoma: short-term results. *Brachytherapy* 2014; 13: 481-487.
12. Brown JM, Carlson DJ, Brenner DJ. The tumor radiobiology of SRS and SBRT: are more than the 5 Rs involved? *Int J Radiat Oncol Biol Phys* 2014; 88: 254-262.
13. Micaily B, Dzeda MF, Miyamoto CT et al. Brachytherapy for cancer of the female urethra. *Semin Surg Oncol* 1997; 13: 208-214.
14. Milosevic MF, Warde PR, Banerjee D et al. Urethral carcinoma in women: results of treatment with primary radiotherapy. *Radiother Oncol* 2000; 56: 29-35.