INTERSTITIAL BRACHYTHERAPY USING TEMPLATE FOR LOCALLY ADVANCED GYNAECOLOGICAL MALIGNANCIES- REVISITING THE FORGOTTEN CLASSICAL ART- A SINGLE INSTITUTE EXPERIENCE

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ABSTRACT

BACKGROUND
Brachytherapy is an important therapeutic strategy for the treatment of locally advanced gynaecologic (GYN) cancers despite evolution of different newer radiotherapy techniques like high-dose-rate and image-guided BT. Despite being used in the management of advanced gynaecological cancer, currently there is a scarcity of studies and data on interstitial BT in Indian context. This is a retrospective analysis on 71 patients with locally advanced gynaecological malignancies treated in the period of 2010 to 2016 to assess the local tumour control, survival, and complications with the template (Syed-Neblett) guided interstitial technique.

MATERIALS AND METHODS
The patients with a median age of 51 years treated from July 2010 to May 2016 were retrospectively reviewed. This study included previously unirradiated 71 patients with advance stage of gynaecological malignancies, not suitable for intracavitary brachytherapy due to distorted anatomy or extensive disease stage. Histologically all patients had squamous cell carcinoma (cervix= 56, vault= 9, vagina= 6) and treated by whole pelvis external beam radiation therapy (EBRT) up to a total dose of 50 Gy in 25 fractions. These patients were further treated by high-dose-rate interstitial brachytherapy using Syed-Neblett dedicated vaginal plastic template. During treatment all these patients were re-optimised and a dose of 15-21 Gy was delivered in 3 fractions with a minimum gap of 6 hours between fractions using Varisource IX HDR unit.

RESULTS
Out of 71 patients 5 were lost to followup during study period and they were excluded from the final analysis. The average followup duration ranged between 6-71 months and median followup was 20 months. This study included parameters like local disease control, acute/late complications and distant metastasis. Out of 66 patients, local disease control was seen in 54 (81.81%) patients, whereas local recurrence was observed in 12 patients (18.18%). Distant metastasis developed in 10 patients, 8 were locally controlled and 2 had local recurrence. Late complications seen were cystitis and proctitis in 23/66 (34%- RTOG Gr II) and vaginal stenosis in 61/66 (92%).

CONCLUSION
By using Syed-Neblett template in locally advanced gynaecologic malignancies, a high dose of radiation-sparing adjacent vital organs with homogenous dose distribution could be achieved. The observed improved local control, survival and decreased operative and radiation associated morbidity without compromising the therapeutic efficacy was better than EBRT alone.

KEYWORDS
Interstitial Brachytherapy, Template, Carcinoma Cervix, Intracavitary Brachytherapy, Syed-Neblett Template.

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BACKGROUND
Locally advanced gynaecological cancer is a major health burden worldwide and especially in developing countries like India,1 and is a major cause of death despite advancement and paradigm shift in management, treatment approaches and technology. Cervical cancer is the second most common female cancer in women aged between 15-44 years in India and 67,477 cervical cancer deaths occur annually. Majority of patients (80%) have locally advanced disease at the time of presentation (stage IIB- IVA; FIGO).2,3 Radiation therapy is an essential component in treating cancers of the uterine corpus, uterine cervix, vulva, and vagina4 and provides an opportunity for cure for women with unresectable locally advanced disease. Radiotherapy is also suitable for patients with resectable disease in whom the risk of surgical morbidity is high and medical contraindications for primary surgical therapy.
EBRT helps in sterilisation of the nodal metastasis and also in shrinking of the primary tumour for an optimal brachytherapy treatment in later stage.5,6 Cervix and vagina can be treated with high radiation dose, but it is not possible to deliver EBRT as it will damage the neighbouring vital structures like urinary bladder and rectum which are having limitation for dose tolerance.3,4,5,7,8

In such cases, brachytherapy helps in escalating the radiation dose to primary tumour area sparing the surrounding normal tissues resulting in improved tumour control and minimum morbidity.9,10,11 Intracavitary radiotherapy (ICRT) and vaginal cylinder (CVC) conventionally deliver a very high dose to cervix and vagina with minimal dose to rectum and bladder resulting in good cure rate and acceptable morbidity.12 Interstitial brachytherapy is recommended for those cases in which either ICRT is expected to result in a suboptimal dosing or not possible to deliver homogenous dose distribution.5,8,9

Interstitial brachytherapy is generally for patients either with extensive pelvic and/or vaginal disease to improve local control or with anatomy not allowing intracavitary brachytherapy with standard applicators.13,14 The Syed-Neblett template originally described as the “transperineal parametrial butterfly”, were designed in order to get a better target volume coverage. Combination of intracavitary and interstitial brachytherapy is possible to improve optimal dose distribution even for deeply infiltrated tumours.

Aims and Objectives

The aim of this retrospective study was to assess the treatment outcomes in patients with locally advanced gynaecological malignancies treated with interstitial brachytherapy using Syed-Neblett template to study local control, acute and late sequelae of the treatment.

MATERIALS AND METHODS

This retrospective study included 71 patients treated with Syed-Neblett template, during the period July 2010 to May 2016, and traced till December 2016. Out of these, 56 patients were of carcinoma cervix, 9 were of carcinoma of vault and 6 were of carcinoma of vagina. All these patients were treated with combination of EBRT followed by interstitial brachytherapy using Syed-Neblett applicator. As 5 patients were lost to followup, only 66 patients were finally analysed. All patients had routine workup and examined under anaesthesia and biopsy was done. All patients were given external beam radiotherapy (EBRT) up to a dose of 50 Gy in 25 fraction with 2Gy /#, five days a week schedule to whole pelvis using either anterior and posterior parallel opposed portals or four field technique on linear accelerator. After 15 fractions of EBRT every patient was assessed for intracavitary radiation. Those patients who responded well were delivered ICR weekly for 3 weeks along with EBRT, those patients with gross residual disease were continued with EBRT only and were assessed every week for suitability for ICR. But even after completing 50 Gy of EBRT some patients were not suitable for ICR due to gross residual disease or distorted anatomy. These patients were taken for interstitial brachytherapy after examining them under anaesthesia. Other inclusion criteria for the patients were Hb minimum 10 g%, performance status 0-2 (ECOG), histopathological confirmation and clinical stages IIB-IIIB (FIGO).

Implant Procedure

Under aseptic precautions and thorough bowel wash, using epidural anaesthesia, per vaginal examination was performed to assess the tumour dimension, parametrial and paravaginal tissue involvement, tumour spread to the uterus and other pelvic organs. The inferior extent of tumour was marked with silver markers. Foley’s catheterisation was completed with 7 mL of Urografin pushed into its bulb. A stay suture was taken over anterior lip of cervix or anterior fornix, while inserting needles a guide needle was inserted mostly through the posterior vaginal wall. The tip of this needle was taken 1-2 cm beyond the clinically palpable disease. Vaginal length was determined and vaginal cylinders were fixed to the template at that length. The cylinder was then inserted in the vagina with the guide needle in one of its groove. The template was then secured to the perineum by means of stitches through peripheral holes. The remaining needles were placed around the vaginal cylinders up to the preset depth. The number and position of needles were according to the extent of the disease. Needles were bilaterally symmetrical in most of the cases. Check cystoscopy was done to confirm there was no needle in the bladder. Per rectal was done to confirm that no needle has pierced the rectal mucosa. The rectal plate was attached with the rest of the template to complete the assembly; modified Malecot catheter was inserted through the lowermost central hole. The cover plate was fixed over the template assembly (Figure 1). Packing was done with gauze pieces soaked in Betadine solution to prevent any possible infections.

Treatment Planning- Planning CT scan was taken. The needles, target volume and organs at risk were contoured and planning was done according to stepping source dosimetry for the treatment to be delivered on HDR micro Selectron. The computer program used was Brachy Vision TPS. Needles were loaded with dummies up to the treatment length the isodose covering the treatment volume uniformly was selected to prescribe the dose (Figure 2). Geometric and dose point optimisation was used to achieve the uniform dose distribution. Doses to bladder and rectum were...
calculated by selecting points according to ICRU criteria. A total dose of 1500-2100 cGy in 3# (500-700 cGy per #) was delivered on microSelectron HDR. Two fractions were delivered a day with a minimum of 6 hours gap in between two fractions. Implant was removed after completion of treatment. Throughout the treatment period, adequate antibiotic coverage was given and hydration of patient was maintained.

Post-implant followup- For the first three months, all patients were kept on monthly followup, quarterly up to two years, six monthly in the third to fifth year and thereafter annually. During followup, patients were evaluated for parameters like local response, complications post treatment and distant metastasis.

RESULTS
Out of 71 patients included in this retrospective study of locally advanced gynaecological malignancies, 5 patients were lost to followup and they were excluded from the study. The age of patients ranged from 32 to 80 years with a median age of 51 years. (Table- 1). All patients were having histologically proved squamous cell carcinoma and clinical staging was done as per FIGO (Table- 2). External beam radiotherapy was given to all patients using 50 Gy in 25# over five weeks schedule and assessed for response after 15 fractions and every week thereafter. The patients who were not suitable for intracavitary brachytherapy even after completion of EBRT were treated with ISBT after a gap of 2 weeks to 1 month. The dose schedule followed was of 15-21 Gy in 3#, 2 # per day with minimum of six hours of gap between two fractions.

The duration of followup period ranged between 12 to 70 months. Local control of the disease was seen in 54 (81.81%) patients at three months followup period. Patients who achieved local control at 3 months were locally disease free in subsequent followups also. The patients who did not respond to ISBT were never disease free locally and some of them developed distant metastasis in subsequent followups. Local control of disease as observed in relation with stage is shown in Table 3. Metastatic spread was seen in 10 patients and 4 of them had liver, 3 in lung and 1 each in brain, bone and supraclavicular nodes. Palliative treatment was offered to 10 patients who developed metastasis and 8 of them were locally disease free and remaining 2 had local recurrence. All of them died during followup.

<table>
<thead>
<tr>
<th>Age (Years)</th>
<th>Number of Cases</th>
<th>Percentage</th>
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<tbody>
<tr>
<td>31-40</td>
<td>11</td>
<td>16</td>
</tr>
<tr>
<td>41-50</td>
<td>21</td>
<td>31.8</td>
</tr>
<tr>
<td>51-60</td>
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<td>13.6</td>
</tr>
<tr>
<td>71-80</td>
<td>3</td>
<td>4.5</td>
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Table 1. Age-wise Distribution of Cases

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<th>Stage</th>
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</thead>
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<td>24.2</td>
</tr>
<tr>
<td>Ca Cx IIIB</td>
<td>35</td>
<td>53</td>
</tr>
<tr>
<td>Ca vault</td>
<td>9</td>
<td>13.6</td>
</tr>
<tr>
<td>Ca vagina</td>
<td>6</td>
<td>9</td>
</tr>
</tbody>
</table>

Table 2. Stage-wise Distribution of Cases

<table>
<thead>
<tr>
<th>Stage</th>
<th>Local Control</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ca Cx IIIB (16)</td>
<td>12</td>
<td>75</td>
</tr>
<tr>
<td>Ca Cx IIIB (35)</td>
<td>30</td>
<td>85</td>
</tr>
<tr>
<td>Ca vault (9)</td>
<td>8</td>
<td>88</td>
</tr>
<tr>
<td>Ca vagina (6)</td>
<td>4</td>
<td>66</td>
</tr>
</tbody>
</table>

Table 3. Local Control in Relation to Stage

The time gap between EBRT and implant also had an impact on the disease outcomes. Patients who completed the whole treatment within 8 weeks fared better than those who were treated 8 weeks after EBRT and ISBT.

Complications
There were no acute complications noted, but late complications like cystitis and proctitis (RTOG Gr II) in 23/66 (34%) and vaginal stenosis in 61/66 (92%) were observed.

DISCUSSION
Standard therapy for advanced gynaecological malignancies includes combination of both external beam radiotherapy and brachytherapy. Conventionally fractionated EBRT was...
delivered with 1.8 to 2 Gy per fraction to reduce the tumour size, to enable further irradiation with brachytherapy. However, even with higher doses using 50 Gy by EBRT, tumour response was not achieved as expected, leaving the tumour and patient not suitable for conventional intracavitary brachytherapy. Conventional intracavitary applicators (tandem and ovoid) deliver a large central dose with rapid dose fall off. It offers the advantage of homogenous dose distribution to the tumour volume and spares the surrounding normal organs.\textsuperscript{15,16,17}

A number of retrospective analysis in the past showed that most of tumour recurrence especially in locally advanced cases occurred in pelvis after conventional tandem and ovoid treatment. Templates were therefore invented which are not only easy for application but also achieves uniform dose distribution while sparing normal tissues.\textsuperscript{18}

When perineal interstitial implant was used after EBRT, a dose of 20 or 30Gy is delivered in 4-6 fractions. Thus, the procedure may last for a period of three to six days and the whole applicator system may cause pain and discomfort to the patient. In this study, brachytherapy was delivered using high activity (10 Ci) Ir -192 stepping source using microSelectron HDR.

Martinez et al\textsuperscript{19} published a clinical experience accumulated in two institutions with a total of 104 patients. Among them, 37 patients had bulky Stage IIB and III cervical malignancies. The majority of the local failures occurred during the first 10 months of followup. Ten patients developed distant metastasis without local failure. In the initial experience reported by Martinez et al\textsuperscript{2}, two out of 35 patients developed major complications: one necrotic rectal ulcer which required colostomy and one contracted painful bladder which necessitated urinary diversion. A tendency for complications to increase was observed when the dose of external irradiation exceeded 50 Gy. In the experience reported by Gupta et al\textsuperscript{19}, disease volume was the sole significant prognostic factor of local recurrence in the multivariate analysis (p=0.011) with a 3-year local control rate of 89% if the disease volume was less than or equal to 100 cc versus 0% when the disease volume exceeded 100 cc. The majority of the patients (12 out of 18) with tumoural volume greater than 100 cc had cervical cancer. A dose-rate of less than 70 Cgy/hour appeared to significantly increase the risk of grade 4 complications in the limit of a univariate analysis. In the series reported by Monk et al\textsuperscript{16} in an attempt to compare interstitial and intracavitary brachytherapy, the same serious complication rates were observed in the two groups, and reached 21% in each group. The most frequent complications were from digestive origin: intestinal obstruction was encountered in 4% in the interstitial group and 10% in the intracavitary group respectively. Digestive fistula occurred in 9% in the interstitial group and 3% in the intracavitary group respectively. Seven percent of the patients in the interstitial group and 2% in the intracavitary group respectively experienced severe proctitis. Urinary complications were observed in 3% of the patients in the interstitial group and 2% in the intracavitary group respectively. One of the largest experience reported in the literature using the Syed-Neblett template in cervical carcinoma was published by Aristizabal et al\textsuperscript{2,3} with 106 patients. All the patients had primary cervical tumours and were treated with a combination of external irradiation and interstitial brachytherapy. With a mean followup of 23 months (12 - 60), local control was achieved in 75% of the cases: 85% in stage IIB, 75% in stage IIIB and 40% in stage IVA. Sixty percent of the recurrences occurred within six months and 97% within 12 months after the beginning of irradiation. They reported their complications using a specific classification in three grades. Eighteen percent of the patients presented with grade II and III, with 6 of the 19 patients developing vesico- or recto-vaginal fistulae while 6 other patients developed rectal stenosis, three requiring colostomies. The frequency of the complications was correlated with the geometric distribution of the radioactive sources. Hughes-Davies et al\textsuperscript{20} also reported a large number of patients treated in two institutions, Harvard Medical School and Stanford University Medical Center with a total of 139 patients. The conclusion of the authors was a modest chance of patient cure with the template parametrial implant. In this series, late complications requiring surgical intervention were observed in 17% of locally controlled patients, with a 4% rate of fistula, 11% bladder complications and 17% bowel complications. The vast majority of published data were reported with low-dose rate. Demanes et al\textsuperscript{21} however, analysed the outcome of 62 previously untreated patients with either advanced cervical cancer or early stage with unsatisfactory tandem and ovoid placement treated with a combination of external irradiation and interstitial high-dose-rate brachytherapy. The scheme of brachytherapy consisted of six fractions of 5.5 to 6 Gy after a dose of 36 Gy of external irradiation followed by a central shielding with a total dose of 50 Gy to the pelvic sidewalls. In this Grade 3 - 4 complications were observed in 6.5% of the patients. These complications consisted of one vesicovaginal fistula, one vaginal necrosis leading to a fatal haemorrhage, and two small bowel obstructions. Recent retrospective study from India by Nandwani et al\textsuperscript{22} showed local control rates using MUPIT system were 64.7% in 85 patients analysed with complication rates of 17.8%. Comparing to the above studies in our series also we have achieved the local control rates of 81% with acceptable complications using Syed-Neblett implant in advanced gynaecological malignancies.

**CONCLUSION**

Syed-Neblett template in locally advanced gynaecologic malignancies is a good alternative to successfully deliver high radiation dose and avoid excessive dose and injury to adjacent vital pelvic organs by delivering homogeneous radiation dose distribution. Improved local control, survival and high tumour control with decreased operative and radiation associated morbidity was achieved and was found better than EBRT alone and with acceptable complications and can be used in Indian patients who are at the highest risk of relapse in advanced stage disease without compromising the therapeutic efficacy.
In Indian scenario, simplicity and applicability of the method makes it a good option in daily clinical practice for managing cases where parametrial boost is necessary or in poorly maintained cases or those not feasible to treat with intracavitary application. Interstitial brachytherapy is also a natural choice in such cases for effective therapeutic tool for local control and managing toxicities.

REFERENCES