Section: Radiation Oncology

Original Research Article

ROLE OF INTRACAVITARY BRACHYTHERAPY COMBINED WITH INTERSTITIAL BRACHYTHERAPY IN LOCALLY ADVANCED CARCINOMA OF UTERINE CERVIX

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ABSTRACT

Background: Intracavitary radiotherapy is standard technique of brachytherapy used for uterine cervix carcinoma. However in cases with large tumor and lateral parametrium involvement, dose distribution is suboptimal beyond point A without compromising dose constraints for rectum and bladder. To overcome this issue many came up with modification in intracavitary applicator. Two interstitial brachytherapy applicator has been developed, but lacks central uterine tandem. **Materials and Methods:** Here in this study we have combined one of interstitial template; Martinez Universal Perineal Interstitial Template with central uterine tandem from Fletcher-Suit intracavitary brachytherapy applicator. With that we could be able to do CT based planning for target delineation, less chances of target missing, better positioning, reproducibility, and dose distribution of prescribed radiation isodose beyond point A concomitantly decreases dose to rectum and bladder to reduce late toxicity. **Results:** With the combined application we can increase the target volume coverage with prescription dose in addition to decrease the dose to urinary bladder and rectum. **Conclusion:** Interstitial template combined with intracavitary uterine tandem is better and more suitable treatment option for brachytherapy in locally advanced uterine cervix carcinoma involving lateral parametrium.

INTRODUCTION

High Dose Rate (HDR) Intracavitary Radiotherapy (ICRT) is the standard technique of brachytherapy used for cervical carcinoma. In most cases, a typical pear-shaped isodose results from intravaginal and intrauterine source loading patterns is optimal, but in case of large tumors and especially with parametrial involvement, dose distribution is sub-optimal. The height, width, and thickness of the resulting dose distribution are always limited by anteriorly bladder, posteriorly rectum, and sigmoid. Dose adaptation or optimization is limited to an increase or decrease in isodose radius with only intracavitary applications. Local control rates of cervical cancer have been reported at 80-90 %for early cases.[1] However, those for advanced stages show a range of 50-60% and further improvement is needed.[2] One of the reasons for local failure is inadequate dose coverage to bulky and/or irregular-shape tumors. Intracavitary plus interstitial brachytherapy is recommended for these type of cases in which either ICRT is expected to result in a suboptimal dose distribution or it is technically not possible. Interstitial plus intracavitary brachytherapy techniques for cervical carcinoma is carried out through transvaginal and transperineal approach. A number of templates and devices have been invented and validated in clinical practice by different institutions with the aim to establish an accurate and reproducible system with fixed geometry for needle placement and direct treatment planning.

Aim of study

To achieve high dose at central disease combined with better tumor coverage in lateral parametrium up-to pelvic wall with prescribed isodose in brachytherapy of locally advanced carcinoma cervix, we have combined two brachytherapy technique and applied central tandem from Fletcher-Suit intracavitary brachytherapy applicator and MUPIT (Martinez Universal Perineal Interstitial Template).

MATERIALS AND METHODS

In a two years period of 2015 to 2017 we had enrolled 50 patients of biopsy proven FIGO stage IIIB cervical squamous cell carcinoma. Post op patients, recurrent disease and metastatic tumors were not included in

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this study. Examination under anaesthesia and biopsy from cervix were done for confirmation of disease and for proper clinical staging as per the FIGO (International Federation of Gynaecology and Obstetrics) staging system. All the patients received external beam radiotherapy (EBRT) with concurrent weekly chemotherapy followed by brachytherapy.

EBRT: The patients had been treated with external beam radiotherapy (EBRT) in supine position with proper immobilization either with conventional or conformal technique. In conventional, parallel opposed AP-PA field or four field box beam arrangement was used. While in conformal 3DCRT was planned. Pelvic RT was given using photon beam on either Linear accelerator or Co-60 machines with mid-plane dose 50 Gy in 25 fractions, 5 fractions per week in 5 weeks.

Brachytherapy assessment: After one week of completion of EBRT, patients were clinically examined in OPD and / or posted for examination under anesthesia with proper pre anesthetic clearance for an assessment of tumor size, amount and pattern of tumor regression after EBRT with chemotherapy and tumor topography.

Examination under anaesthesia (EUA): A gynecologic examination under anesthesia was performed in the lithotomy position after proper painting and draping in a dedicated brachytherapy operation theatre. The primary disease status, regression of primary disease, parametrial involvement, anatomy of uterus in the pelvis, location of external os, distensibility of vaginal wall and fornices were assessed during EUA by both inspection and palpation.

Brachytherapy Procedure: Brachytherapy procedure was done under epidural and spinal anaesthesia. An epidural catheter was maintained for intraoperative and postoperative pain management. Patients were examined under anesthesia in the dorsal lithotomy position. The examination was performed to assess the dimension of tumor, parametrial and paravaginal tissue involvement and relationship of the tumor to the uterus and other pelvic organs. Urinary catheterization was done and Foley's bulb was filled with 7 cc radio-opaque iodine dye. The uterine sound also used to assess the length of uterine cavity to guide choice of IU applicator, so that central Fletcher-Suit applicator tandem can be placed in uterine cavity. Interstitial applicator used for all these patients in the study was the MUPIT (Martinez Universal Perineal Interstitial Template) (Figure 1-2). The applicator consists of two acrylic cylinders, one acrylic template, one cover plate, screws and stainless-steel needles. Flat acrylic template and cover plate are 11 cm × 8 cm × 1 cm size. Three large holes are located along the midline in template. The top hole is for the passage of Foley's catheter from the urethra, and the central and bottom holes are for the vaginal cylinder and rectal catheter, respectively. There is an array of holes that for the most part determine the geometry of source placement with respect to anatomic structures. The template has 7 rows 1 cm apart to introduce straight and oblique steeled needles for cervix. Type I holes are perpendicular to the template and only volumes extending 4 cm to either side can be covered through these holes. Type II holes are oblique or in diverging fashion to the template, angled approximately 13° laterally outward. Divergent rows allow coverage of larger volume of parametrium without hitting the ischium. Through these type II holes, volumes extending outward to 7 cm can be covered up to a depth of 14 cm. In the central hole in vaginal cylinder, there is a space for uterine tandem or hole for drainage of secretions. Each cylinder has got eight holes for placement of trocars near vaginal or rectal walls. The 18 gauge needles are stainless steel with a blinded end.[3]

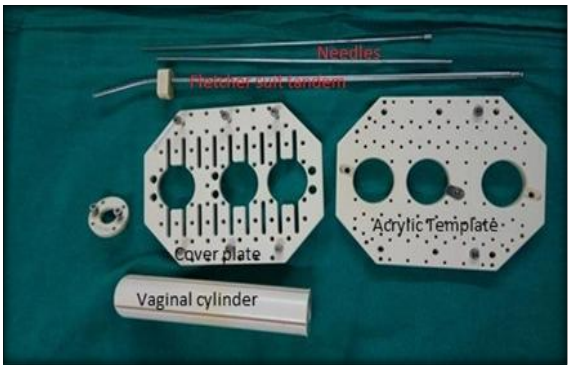

Figure 1: MUPIT instrument with its different parts- acrylic template, the cover plate, the vaginal cylinder, the needles, the Fletcher suit tandem.

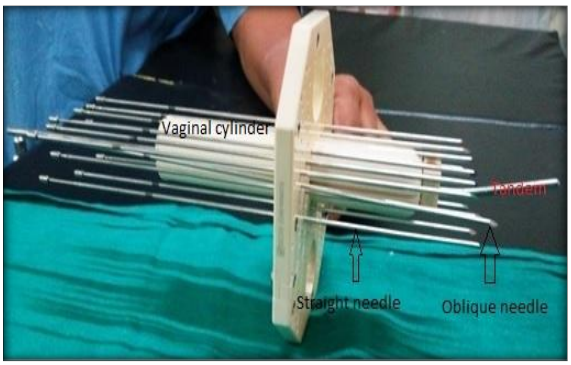

Figure 2: MUPIT with straight needle, oblique needle and Fletcher suit Tandem.

The uterine tandem of length suitable for patients as assessed by uterine sound was inserted into uterine cavity and fixed to cervix. Vaginal length was measured for the determining the length of obturator to be inserted. The obturator was moved over the tandem in to vagina till its ring touched to flange and locked with screw at the outer end of obturator in the inner plate. The inner plate of MUPIT was secured to the perineum by the means of five-six stitches taken through its peripheral holes with perineal skin so that the inner plate is positioned against the perineum and the obturator is in the vagina. A guide needle (18-20cm) was inserted through the hole of template into posterior vaginal wall and through the perineum into

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1-2 cm beyond the clinically palpable disease. Per rectal examination carried out to ensure that no needle had pierced the rectal mucosa. The remaining needles were placed around the vaginal cylinder up to a preset depth. The number and position of needles were decided as per the extent of disease. The needles were inserted straight, and their number varied according to target volume. To increase lateral coverage, needles were inserted obliquely as and when required. After the implant, outer plate was placed covering the one fixed to the perineum to prevent longitudinal displacement of the needles. A sterile gauze soaked in betadine was placed between the template and the skin to ensure that the template does not hurt the patient. The rectal tube was inserted through the lowermost rectal hole to relieve flatus. (Figure 3)

Target delineation

After placement of applicators, patient was taken for Computed tomography (CT) simulation. Bladder volume was maintained at 50cm3 during the image acquisition for planning and during the brachytherapy treatment. Contiguous CT images of 2.5 or 3 mm slice thickness from L4-5 level to 5.0 cm below the outer plate were obtained. The scanned images were transferred to the treatment planning system through a DICOM network. The position of external cervical Os on the CT image was defined by the cervical marker ring placed on the tandem. Countouring was done as per the GEC-ESTRO guidelines and ICRU 89 by radiation oncologist according to EUA finding and CT finding. Due to artifects from needles it was difficult to identify gross tumor. To overcome this issue, we have used clinical findings of EUA and noted down the needles covering the edge of tumor. The following targets were contoured. [4, 5]

GTV: Gross residual tumor at the time of brachytherapy.

HRCTV (High Risk CTV): GTV, the whole cervix, and adjacent residual pathologic tissue, if present.

IRCTV (Intermediate Risk CTV): This represents the initial GTV with a margin surrounding the anatomical cervix.

LRCTV (Low Risk CTV): the whole parametria, the whole uterus, the upper part of the vagina, and the anterior/ posterior spaces toward the bladder and rectum.

OARs (Organs at Risk): Outer contours of bladder, rectum and sigmoid colon were delineated.

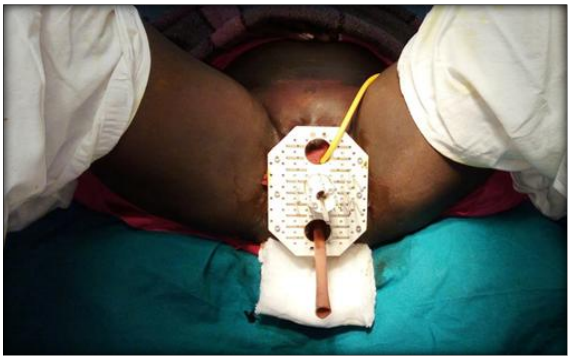

Figure 3: MUPIT with intrauterine tandem in-situ.

Treatment planning

Treatment planning was carried out using the ONCENTRA Brachytherapy Planning System (software version 14.2.6 or 14.3.6, Nucletron) with computer optimization and manual modification. The planning process always starts with standard loading pattern for the tandem based on typical Fletcher loadings. A dwell position and time adaptation is performed first to optimize the initial standard dose distribution. The needles are then loaded starting from medial to lateral and cranio-caudally to encompass the target volume. The planned depth of needle placement in the parametrium was determined by the cranial extent of HRCTV with an appropriate margin (an extra 5 mm was added to account for the inactive end of the needle tip). Dwell positions and dwell weights were manually modified according to dose-volume constraints. Manual optimizing method based on Manchester system is appropriate in combining brachytherapy for target coverage. The resulting isodose covered anterior, posterior, cranial and caudal extent according to target and OARs. Final treatment plan was analyzed by using dose-volume histogram (DVH) parameters for HRCTV and all the OARs. Cumulative dose-volume histograms were used to estimate V100, D90, D100, and minimum doses to 0.1 cc, 1 cc, 2cc most irradiated volumes of bladder, rectum, and sigmoid colon. TRAK values were recorded.

The dose volume parameters data were recorded as per guidelines recommended by gynecological GEC-ESTRO working group.[6]

Forward treatment planning is based on desired dose, which are D90 for HRCTV is equal to or greater than the prescribed dose. For tumor, α/β 10 and for normal tissue α/β 3 was used. D2cc value should below 90Gy for bladder, and 75Gy for rectum and sigmoid. The planning aim was to deliver at least 70-80Gy to HRCTV D90 considering both EBRT and brachytherapy. Point A was not used as a reference point for dose specification with this method, because of its restricting impact on the coverage of the lateral parametria. Point A was irradiated at more than 4Gy per fraction in this method. Four 4Gy fractions prescribed to HRCTV and given in 2 days, six hours apart, two fractions were administered daily through Iridium 192 source loaded MicroSelectron-HDR.

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Figure 4 & 5 shows treatment plan prescription isodose covering HRCTV in axial and sagittal view.

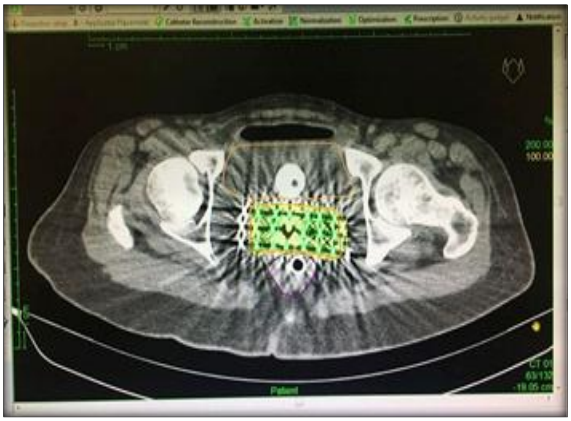

Figure 4: Isodose of 100% dose (green colourwash) covering to HRCTV (yellow line) in axial view

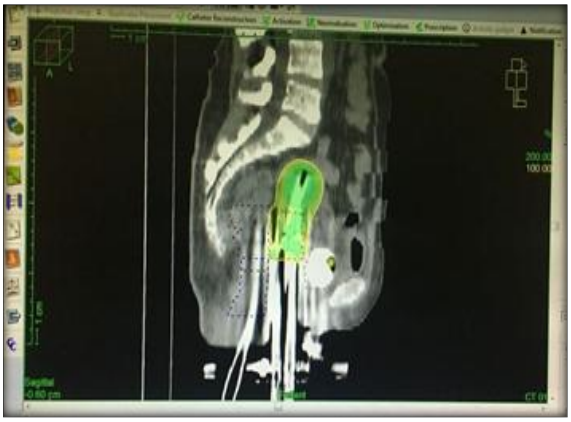

Figure 5: isodose of 100% dose (green colourwash) covering HRCTV (yellow line) in sagittal view

RESULTS

We analyzed tumor characteristics and dose volume histogram of brachytherapy plan to assess the dose received by tumor and OARs and to assess tumor response, loco-regional control and survival analysis.

Tumor Characteristics

Following table 1 shows different tumor characteristics and number of patients

Table 1: Tumor characteristis

Tumor characteristics	No of patients (%)
Growth type	
Exophytic	13(26)
Ulceroproliferative	27(54)
Infiltrative	10(20)
Size of tumor	
<5 cm	22 (44)
≥5 cm	28(56)
Parametrium extension	
Bilateral	20(40)
Unilateral	30(60)
Vaginal involvement	
Upper two third	32(64)
lower one third	14(28)
No vaginal involvement	4(8)
Grade of tumor	
well differentiated	0
moderately differentiated	38(76)
poorly differentiated	6(12)
not specified	6(12)
HRCTV volume (cc)	
Max	248
Min	62.4
Mean	123.5

Dose to target: Mean ± SD dose to D90 HRCTV in Gy (EQD2 α/β10) is 71.18 Gy±1.35. Maximum, Minimum, Mean and SD value of D100 dose in Gy is 66.95, 58.66, 62.20Gy±2.00 respectively. 48 patients had a value of V100> 93% while 2 patients had V100 <92%. Mean ± SD V100 % is 96.16± 1.86%. Dose to point A (average of point A1 and A2) in Gy per fraction; max 13.69, min 2.28, Mean ± SD 6.17 ± 2.14.

Dose to OAR: Mean dose of D2cc, D1cc, D0.1cc in EQD2 α/β3 in Gy; mean±SD for bladder65.90±3.51, 67.92±4.15, 73.27±7.41, for rectum 66.27±2.27, 68.55±3.36, 72.91±5, for sigmoid colon 58.69±5.68, 61. 99 ±5.78, 66.61±8.76, for anal canal D2cc mean is 58.93±4.08.

Total treatment duration: EBRT with brachytherapy max 65 days, min 40 days, mean±SD 52.07±5.43 days. Gap between EBRT and

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brachytherapy in days max 20, min 7, mean±SD 13.10±3.77.

Acute complication: Intraoperative bleeding occurred in five patients (10%) during needle insertion. None of the patients needed any active intervention to attain hemostasis. Thirteen patients (26%) suffered from bleeding during template removal. Eight of the above mentioned patients were implanted with oblique needles. All of the patients were managed conservatively with manual pressure and injection Tranexemic acid. None of the patients required blood transfusion. None of the 13 patients reported any delayed bleeding during subsequent follow up. Three patients (6%) developed stitch-line infection that was managed with oral antibiotics.

Late complication: At seven year median follow up ten patients (20%) developed vaginal stenosis and 16 patients (32%) developed pseudo- vault on subsequent follow up. Five patients (10%) had Grade I per rectal bleeding but all were managed conservatively. One patient developed Grade III hematuria for which she required blood transfusion and was subjected to further investigations and managed accordingly.

Response assessment: At 3month after completion of brachytherapy 41 (82%) had complete response, 9(18%) had partial response with residual disease. Three year disease free survival (DFS) was 54%, and overall survival (OS) 64%. At median seven year follow up 10 patients were lost to follow up and couldn't be contacted telephonically. Total 20 patients were expired in nine year period of total follow up, two developed distant metastasis, six had loco-regional recurrence, one had second primary in lung, nine had progressive disease and two patients died due to causes other than malignancy. At seven year DFS is 30%.

Table 2: Dosimetric comparison between different studies and our study

	Datta et al	Kirisits et al	Berger et al	Nomde n et al	Saitoh et al	Baillex et al	Villalba et al	Present study
Total needles Range	-	8-Jan	Vienna + Oblique needle	6-Jan	18-Sep	6-Feb		14-26
Dose	8Gy/ #	7Gy* 4#	-	-	6Gy*5 #	7Gy*3 #	4Gy*6#	4Gy*4#
Volume cc Mean/ median	266	44	50cc	66cc	103cc	31.9	-	123.499cc
D90 (Gy)	8.6	96	86	83.9	67.6	84.8	79.8	71.18
D100 (Gy)	-	70	-	66.9	3.3Gy/ #	-	-	62.2
V100 %/cc	88%	93%	92%	109cc	87%	99%	-	96.16%
Point A (Gy)	5.9	-	-	-	-	-	-	6.17
Bladder D2cc (Gy)	12	83	79	83	76.7	74.5	77.6	65.9
Rectum 2cc(Gy)	5.2	66	61	69	68.6	64.3	71.9	66.73
Sigmoid 2cc(Gy)	-	67	67	62		60.7	-	58.69

DISCUSSION

In intracavitary brachytherapy, a very high dose of radiation is achieved over the cervix and up to the reference point 'A'. However, beyond point A, there is be rapid dose fall off as per the inverse square law, with the dose delivered to the parametrium and pelvic wall decreasing significantly. Dose delivered to the lateral parametrium and the pelvic sidewalls are often found to be insufficient with intracavitary brachytherapy alone. Standard ICR application is not only appered to be inadequate for lateral expansion of isodose but it was also hampered by narrow vagina with enlargement of distant between the ovoids.

In the study by Dutta et al,[7] when 6 Gy was prescribed point A, coverage of the 6 Gy isodose line was 88%. The coverage depends significantly on the volume of target, implying decreased coverage with the increase in tumour volume when dose is prescribed with reference to a specific point. This might result in cold spots within the target peripherally. The authors also commented that maximum reference dose to bladder on orthogonal plan is underestimated from bladder max dose of CECT planning. Residual bulky disease in the lateral parametrium might also be inadequately irradiated by intracavitary application even with CT/MRI based plan. All these factors might result in failure of response to intracavitary brachytherapy. Hence, these are the ideal candidates for interstitial brachytherapy where multiple needles can be implanted to attain a desirable dose distribution according to disease burden in the area. Interstitial brachytherapy in gynecologic cancer was originally performed with free-hand placement of needles. For better and more reproducible needle positioning, transperineal and transvaginal templates were developed.

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Interstitial brachytherapy utilizes a transperineal template through which several hollow tubes are inserted directly into tissues. A tandem and central vaginal cylinder are incorporated into the template.
Primarily, these templates consist of a central large hole for placement of tandem and an array of small holes around this large hole for insertion of needles. Syed-Neblett parametrial butterfly template,[8] and Martinez Universal Parametrial Interstitial Template,[9] have been the two major innovations in this direction. In our study we used the Martinez Universal Perineal Interstitial Template (MUPIT).
Different applicators used as combined intracavitary and interstitial brachytherapy were proposed to improve parametrial coverage and decrease dose to OAR. An interstitial component has been added to the basic Intracavitary (IC) applicators using metallic or plastic needles compatible with CT/MRI. When extension to parametrium is moderate, Vienna applicator (tandem, ring and straight needles), Utrecht applicator (tandem, ovoid +needle), Deventer modification of the Rotterdam applicator are available.
Nomden et al,[10] investigated the benefit of the Utrecht interstitial CT/MR applicator using MRI image guided brachytherapy in 20 patient of locally advanced carcinoma cervix. Needle could be inserted into 5 drilled holes at 15° angle in each ovoid so that needles are more or less parrellel to the tandem. The dosimetric gain with this applicator was 4.4 Gy compared to standard intracavitary applicator.
Kuipers et al,[11] presented the Deventer modification of the Rotterdam applicatorwith one afterloading needle inserted through each ovoid in order to achieve lateral expansion of reference isodose exceeding 25mm from the axis of cervical canal in 41 patient with 76 combined application of HDR endocavitary and HDR interstitial brachytherapy in same session. The Maximum Transverse Diameter of Reference isodose (MTDR) of the combination of IC+IS HDR brachytherapy increase 2mm from 59mm to 61mm compared to HDR endocavitary standard application (HESA). The site of MTDR coincide with the central part of cervix compare to HESA in which it was the upper part of vagina. At this level, the volume enclosed by reference isodose had been widened by 6.5mm in both side. When compared to HESA, the volume covered by the reference isodose in the Deventer method was decreased by 17% despite more dose being delivered to the parametrium. Also, there was increase in dose delivered to the mid cervical level, 8.5 Gy, with the Deventer method when compared to 6 Gy delivered with HESA.
Kirisits et al,[12] also show tandem ring applicator with addition of needles increased the width of prescription isodose and target volume covered by it. The Vienna Applicator and similar applicators is, however, inadequate when bulky lateral parametrial extension (more than 15 mm to point A), bulky primary disease, extensive paravaginal extension to middle and lower vagina mandates usage of more source positions to attain adequate tumor coverage, which can be achieved only by implantation of interstitial needles.
In interstitial template application as in MUPIT and Syed-Neblett lateral expansion of prescription isodose beyond point A to lateral parametrium is achieved. However they lack in central intracavitary component which is most beneficial for central high dose in cervix. Hence, in an attempt to combine the advantages of superior coverage of MUPIT and Utrecht applicators with the advantages of MRI based planning, a new MRI compatible applicator was developed.
Villalba et al,[13] demonstrated the use of new MRI based Benidorm applicator for IC+IS brachytherapy. This template allows coverage of distal parametrium up to 4.5cm from middle of intrauterine tube. Median EQD2 dose to target, D2cc bladder, D2cc rectum were found to be 79.8Gy, 77.6Gy, 71.9Gy. They concluded that use of this MRI compatible template is efficient, allowing improved contouring and CTV conformation.
Bailleux et al,[14] studied MRI compatible Nice Gynecologic applicator and concluded that concomitant cervical and transperineal parametrial HDRBT boost appears safe and feasible with no specific acute toxicity and no increase the risk of bleeding. Berger et al,[15] also shown same results. Comparison of different study DVH data shown in table 2.
Saitoh et al,[16] carried out study of Dose volume analysis of high dose interstitial brachytherapy with CT based treatment planning and investigated the treatment outcomes in 15 patients of locally advanced, bulky and /or irregularly shaped cervical carcinoma treated with EBRT followed by HDR interstitial brachytherapy with MUPIT with or without tandem with a dose of 30Gy in 5 fractions. They compared dose distribution of image based ISBT with or without tandem with that of conventional ICRT. The dose to the target was found to be improved and exposure to bladder and rectum was markedly decreased.
In our study CT-based HDR IC+ISRT combined with EBRT was analyzed in 51 patients of locally advanced cervical cancer of FIGO stage IIIB. All the patients were within 35-65 years
of age. All the patients received EBRT followed by IC+IS brachytherapy. MUPIT was used with the Fletcher-Suit applicator tandem. As mentioned in results and compared with other studies Interstitial brachytherapy combined with intracavitary tendam application has better advantage in covering target volume with prescription isodose and concomitant decrease in bladder and rectum dose in comparison to intracavitory or interstitial application alone.

CONCLUSION

Combined intracavitary plus interstitial brachytherapy procedure appears to be feasible, safe,

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accurate, reproducible and no specific acute toxicity and offers an efficient promising option and superior than only intracavitary brachytherapy in selected subgroup of patients with unfavourable characteristics.

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Author's contribution: All authors have contributed equally in the process starting from literature search, proposal & formulation of study design, clinical procedure of brachytherapy, data collection, data analysis and manuscript editing.

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