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Dosimetric and clinical outcomes of CT based HR-CTV delineation for HDR intracavitary brachytherapy in carcinoma cervix — a retrospective study

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ABSTRACT

Background: Brachytherapy for carcinoma cervix has moved from Point A based planning to optimization of dose based on HR-CTV. Guidelines have been published by GEC ESTRO on HR-CTV delineation based on clinical gynecological examination and MR sequences. These have given significant clinical results in terms of local control. However, many centers around the country and worldwide still use CT based planning, which restricts HR-CTV delineation, as disease and cervix can rarely be differentiated on a planning CT. Various studies have been done to develop CT based contouring guidelines from the available data, but enough evidence is not available on the clinical outcome when treatment is optimized to HR-CTV contoured on CT images. The purpose of this study is to find out the relation between local control and dosimetry of HR-CTV as delineated on CT images.

Materials and methods: Patients of locally advanced carcinoma cervix treated radically with EBRT of 50 Gy in 25# and at least 4 cycles of concurrent weekly Cisplatin having a complete or partial response to EBRT were taken for study. All patients had completed CT based Intracavitary brachytherapy to 21 Gy in 3# of 7 Gy per # with dose prescription at point A and optimizing dose to reduce bladder and rectal toxicity. Follow up data on locoregional recurrence was obtained. HR-CTV delineation was done retrospectively on the treatment plan following guidelines by Viswanathan et al. EQD2 doses for EBRT+BT were calculated for point A and HR-CTV D90. The dosimetric data to HR-CTV and to Point A were then compared with patients with locoregional control and with local recurrence.

Results: 48 patients were taken, all had squamous cell carcinoma. The median age was 48 years. 33.33% were stage IIA, the rest were stage IIB. Median follow-up was 30 months with 25% developing recurrence of the disease. HR-CTV D90 EQD2 dose was significantly higher in patients with locoregionally controlled disease than in patients with local recurrence (83.97 Gy_{10} *vs.* 77.96 Gy_{10}, p = 0.002). Patients with HR-CTV D90 EQD2 dose greater than or equal to 79.75 Gy 10 had better locoregional control than patients receiving dose less than 79.75 Gy_{10} (p = 0.015). Kaplan Meier plot for PFS showed significantly improved PFS for patients receiving HR-CTV D90 dose of at least 79.75 Gy_{10} (log-rank p-value = 0.007). Three year progression free survival was 87.1% in patients receiving HR-CTV D90 dose of at least 79.75 Gy_{10}.

Conclusion: CT based HR -CTV volume delineation with the help of pre brachytherapy clinical diagrams and MRI imaging may be feasible in a select subgroup of patients with complete or near-complete response to external beam radiation.

Key words: carcinoma cervix; brachytherapy; HR-CTV; CT scan

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Introduction

Carcinoma cervix is one of the major contributors to the cancer burden in developing countries like India. The widespread risk factors favor the high incidence of the disease in the rural parts of the nation. The government had taken utmost measures to implement screening programs like Lugol's iodine screening, Pap smear examination, and health education programs with a prime idea to aid early diagnosis and prompt treatment [1]. Although screening programs are available, they remain highly unutilized leading to a large number of patients presenting at a locally advanced stage at the first point of contact with healthcare. With the majority presenting at a locally advanced stage of the disease, radiation therapy becomes the primary treatment modality in our country.

The basic treatment of locally advanced carcinoma of the cervix is external beam radiotherapy with concurrent chemotherapy followed by brachytherapy, radical surgery being preserved for selected cases only [2, 3]. Brachytherapy forms the most integral part of carcinoma cervix radiotherapy aiding to deliver a very high local dose to the region. For many years, the dose was prescribed to Point A as described by Todd and Meredith and dose reporting was done based on the International Commission of Radiation Units and Measurements (ICRU) 38 protocol [4], with orthogonal radiographs as imaging. However, high dose rate (HDR) brachytherapy requiring multiple applications, slight variations in the application geometry led to a change in positions of point A and dose reporting points resulting in reporting variations [5, 6]. Another drawback was that the original definition being based solely on anatomical landmarks was not identified on a radiograph. Point-based prescription also did not correlate well with local control [7].

With the introduction of modern imaging devices like Computed Tomography (CT) scan and Magnetic Resonance Imaging (MRI), dose prescription to the actual Clinical Target Volume (CTV) and dose reporting to target and Organ at Risk (OAR) made more sense than arbitrary points [8]. Most recent guidelines recommend MRI based Image Guided Adaptive Brachytherapy for Carcinoma [9–14]. Evidence from RetroEMBRACE and EMBRACE I studies have shown improvement in survival which also paved the way for dose prescription to High Risk Clinical Target Volume (HR-CTV) from conventional point A [15, 16]. However, recommendations for HR-CTV and intermediate risk clinical target volume (IR-CTV) delineation are provided by guidelines I–IV by Gynaecology Groupe Européen de Curiethérapie and the European SocieTy for Radiotherapy & Oncology (Gyn GEC ESTRO) which is applicable only for MRI based applications [10, 11, 13, 14]. Although considered the gold standard, limitations to the use of MRI based brachytherapy is the availability of advanced MRI simulator, MRI compatible applicators, and some degree of institutional experience.

Such standards cannot be maintained in resource-constrained high volume institutions in our country which only have CT simulators. Certain drawbacks of CT based target delineation are the inability to identify the Gross Tumour Volume (GTV) from normal cervical tissue, and difficulty to identify the upper border of the cervix [17]. Various attempts at HR-CTV delineation based on CT scan have been made, with the study by Viswanathan et al. [17–19] being the most standardized of them. This study has provided contouring guidelines and atlas for standardized CT based HR-CTV delineation based on Gyn GEC ESTRO MRI recommendations, although, data on clinical outcome of such recommendations are inadequate. A part of the sample of the RetroEMBRACE study had patients who had been treated following Viswanathan et al. guidelines, however, the clinical outcome from that subgroup was not separately reported in the [15].

Our objective is to determine whether dose to HR-CTV delineated on a CT scan based on available guidelines correlate with adequate local control in locally advanced carcinoma cervix treated with intracavitary brachytherapy.

Materials and methods

Computer tomography based intracavitary brachytherapy was started in Medical College Hospital, Kolkata, around 2006; however, for over a decade target delineation was not routinely done. Only around and after 2013, CT based HR-CTV contouring was started in selected cases, however, dose prescription and planning was still point-based. We have retrospectively selected a cohort of patients receiving intracavitary HDR brachytherapy during the period from January 2015 till December 2015 for this study.

Patient selection

The inclusion criteria were biopsy proven cases of locally advanced carcinoma cervix who had completed external beam radiotherapy with a total dose of 50 Gy in 25 fractions in 5 weeks with at least 4 cycles of concurrent Cisplatin chemotherapy, had a complete or partial response to external beam radiotherapy (EBRT) as validated by post-EBRT clinical examination and/or by MRI, and received CT based intracavitary brachytherapy with 3 fractions of 7 Gy per fraction with dose prescription to point A as per our institutional protocol. Other inclusion criteria were Performance Status of 0 or 1 before starting brachytherapy, normal blood and biochemistry profile, and treatment completion within 9 weeks. Presence of any degree of uterine prolapse, past pelvic surgery apart from biopsy, intracavitary applications other than standard tandem ovoid or tandem ring, and EBRT dose other than 50 Gy, altered fractionation were excluded from the study. The presence of a retroverted uterus or an imperfect application also led to the exclusion from the study.

During the study period selected, a total of 245 patients of cervical cancers were treated at our department, among whom 72 cases received postoperative radiotherapy and the remaining 173 were treated radically with radiotherapy. Among these, 51 needed interstitial application or combination of intracavitary and interstitial application due to residual parametrial disease or less than near complete response to EBRT, which could not be covered with a standard intracavitary technique. The remaining 122 patients were screened and only 48 deemed suitable for the study as per the inclusion and exclusion criteria.

External beam radiotherapy

All patients in the study had completed EBRT to the whole pelvis to a total dose of 50 Gy in 25 fractions over 5 weeks with concurrent weekly Cisplatin 40 mg/m^2 body surface area (BSA). The EBRT machine was a Theratron 780C (Best Theratronics, Canada) Cobalt 60 unit. The treatment was done using a conventional 4 field box technique. The stringent EBRT inclusion criteria were to ensure that the limitations of the EBRT technique and reporting had less control on the outcome in terms of local control and the local control thus assessed can be attributed more to the dosimetry of brachytherapy.

Brachytherapy

Brachytherapy was delivered using an Iridium 192 remote after loader (GammaMed plus, Varian Medical Systems, Palo Alto, California) based on our Institutional Protocol of 3 fractions of 7 Gy per fraction weekly. Two types of CT compatible applicators, namely Fletcher and Ring applicators, were used for Intracavitary brachytherapy (ICBT) application. The applicators consisted of uterine tandem with various angles (15°, 30°, 45°). Before each application, a urinary catheter was inserted and the catheter balloon was inflated with contrast media (7 mL) to localize the bladder neck. Patients followed specific instructions for rectal preparation before the ICBT procedure which included the taking of bisacodyl tablets (20 mg) the previous night and use of sodium phosphates enema early in the morning on the day of the procedure. Appropriate anterior and posterior vaginal packing was used to fix the applicator position and to displace the bladder and rectum away from the vaginal applicators. After the intracavitary application, the applicator was fixed with the help of roller gauze bandages.

All patients underwent a CT scan followed by treatment planning during the first and third fraction of brachytherapy application, the treatment for the second fraction was done based on the approved plan of the first fraction. Before the scan, 10 mL of diluted Contrast in NS (Normal Saline) is instilled in the bladder as a routine protocol. No intravenous contrast is given as a routine procedure. To minimize patient movement during CT scans, every attempt was made to keep the applicator in position and to complete the entire procedure within the shortest possible time. The scan was taken with 3 mm slice thickness through the pelvis, from the highest point of the iliac crest to the upper thigh using a 16 slice CT simulator (Brilliance Big Bore, Philips, Amsterdam, Netherlands); all CT slices were transferred to the treatment planning computer. Contouring of the organs at risk, OARS (bladder, rectum, and sigmoid colon) was done on axial sections as solid organs. The treatment planning was done using Varian Treatment Planning System (Eclipse version 13.5, Varian Medical Systems, Palo Alto, California). The planning was done using a uniform loading pattern with dose prescriptions to point A only. The plan was further optimized by dose point optimization to keep the bladder, rectum and sigmoid D2cc doses limited

to 85 Gy_3 equivalent dose in 2 Gy fraction (EQD2) 70 Gy_3 EQD2 and 70 Gy_3 EQD2, respectively. Dose prescription to HR-CTV was not done.

Study technique and data collection

Brachytherapy plans were accessed in the Treatment Planning Computer; HR-CTV contouring was done following Viswanathan et al. guidelines with the help of available pre-brachytherapy MR images [17]. The presence of any post-EBRT viable disease in the parametrium led to exclusion of cases. Contouring was rechecked by another senior radiation oncologist, and with any discordance by more than 10%, the volume was redrawn. The volume of HR-CTV, bladder, and rectum was collected from dose statistics. HR-CTV D90, D98, rectal dose (2cc, 1cc, 0.1cc), bladder dose (2cc, 1cc, 0.1cc), sigmoid dose (2cc) was collected from DVH (Dose Volume Histogram). Dimensions of HR-CTV were recorded from appropriate sagittal, coronal, and axial sections. Follow up information was evaluated from records, data on disease recurrence was noted. The recurrence was detected clinically and confirmed either by MRI/PET — positron emission tomography computed tomography (PET-CT) or wherever possible, by biopsy. Local recurrence was defined as any clinical and/or radiological evidence of disease in the pelvis in patients achieving complete response clinically after completion of brachytherapy.

Definitions

HR-CTV — high-risk clinical target volume. It is the volume bearing the highest risk for recurrence and is selected by clinical examination and imaging at the time of brachytherapy (ICRU 89);
HR-CTV D90 — it is the minimum dose received by 90% of the volume of the HR-CTV;
HR-CTV D98 — it is the minimum dose received by 98% of the volume of the HR-CTV (near minimum target dose);
D2cc — minimum dose received by maximally irradiated 2cc volume (OAR).

Analysis of data

The statistical analysis was done using IBM SPSS (Statistical Package for the Social Sciences) 20 software. Descriptive statistics were used to report patient characteristics and dose-volume characteristics of HR-CTV and OARs. Comparison of mean Point A and HR-CTV D90 and D98 dose in patients with disease recurrence and locoregionally controlled disease was done using Independent Samples T-test with a significance level of 0.05. Fisher's exact test was used to compare local recurrence in terms of HR-CTV D90 dose. Kaplan Meier time to event analysis was used to assess progression-free survival (PFS). The time to progression was taken from completion of brachytherapy to any evidence of local progression/recurrence.

Results

48 patients were taken for the study; all had histologically proven Squamous Cell Carcinoma. The median age was 48 years. 13 patients (27.1%) were in the pre-menopausal age group, the rest were post-menopausal. 32 patients (66.67%) were International Federation of Gynecology and Obstetrics (FIGO) Stage IIB, the rest were at FIGO Stage IIA [19]. 45.83% of patients had received at least 4 cycles of concurrent cisplatin 40 mg/m^2 BSA (Tab. 1).

The dose-volume parameters are reported in Table 2. Mean point A EQD2 dose was 77.62 ± 2.10 Gy_{10}. Mean HR-CTV volume was 28 ± 5.03 cc and mean HR-CTV D90 and D98 EQD2 dose was 82.46 ± 6.58 Gy_{10} and 69.29 ± 3.96, respectively. The rectal volume, bladder volume, and their respective D2cc, D1cc, and D0.1cc EQD2 doses are mentioned in Table 2. Age, bladder volume, rectal volume, and HR-CTV volume were not significantly different between patients with recurrent and locoregionally

Table 1. Patient characteristics

Patient characteristics	
Median age	48 years (minimum — 35 years, maximum — 62 years)
Menopausal status	
Premenopausal	13 (27.1%)
Postmenopausal	35 (72.9%)
Histopathology	
Squamous cell carcinoma	48 (100%)
FIGO stage	
IIA	16 (33.33%)
IIB	32 (66.67%)
Concurrent CT cycles received	
4	26(54.17%)
5	22 (45.83%)

FIGO — International Federation of Gynecology and Obstetrics; CT — cisplatin

Table 2. Dose volume characteristics

	Mean ± SD
HR-CTV volume	28 ± 5.03 cc
HR-CTV dimensions	
Height	3.27 ± 0.27 cm
Width	3.15 ± 0.52 cm
Thickness	2.9 ± 1.8 cm
Rectal volume	48.12 ± 19.73 cc
Bladder volume	70.31 ± 16.83 cc
Point A EQD2	77.62 ± 2.10 Gy_{10}
HR-CTV D90 EQD2	
D90 EQD2	82.46 ± 6.58 Gy_{10}
D98 EQD2	69.29 ± 3.96 Gy_{10}
Rectum dose	
D2cc EQD2	68.31 ± 5.75 Gy_3
D1cc EQD2	72.78 ± 7.01 Gy_3
D0.1cc EQD2	82.53 ± 10.79 Gy_3
Bladder dose	
D2cc EQD2	81.30 ± 10.34 Gy_3
D1cc EQD2	87.15 ± 10.32 Gy_3
D0.1cc EQD2	100.22 ± 12.39 Gy_3
Sigmoid D2cc EQD2	64.28 ± 2.68 Gy_3

controlled disease (p-value = 0.272, 0.767, 0.556 and 0.575, respectively, all non-significant, from independent samples T-test).

A median follow up was 30 months with 36 (75%) patients having locoregionally controlled disease and 12 (25%) developing local recurrence. The comparison of mean doses to Point A and HR-CTV in patients with local recurrence and locoregionally controlled disease are reported in Table 3. The mean point A EQD2 dose in patients with local recurrence of disease and loco-regionally controlled disease was 77.94 ± 2.49 Gy_{10} and 77.52 ± 1.99 Gy_{10} respectively (non-significant, p-value 0.59 from unpaired T-test). The mean HR-CTV D90 EQD2 dose in patients with local recurrence and patients with loco-regionally controlled disease was 77.96 ± 4.81 Gy_{10} and 83.97 ± 6.46 Gy_{10}, respectively. Mean HR-CTV D90 EQD2 dose was significantly greater in patients with locoregionally controlled disease (p-value = 0.002, significant). Similarly, HR-CTV D98 EQD2 dose was significantly higher in patients with locoregionally controlled disease (p-value = 0.013).

Table 4. Locoregional control in patients based on HR-CTV D90 EQD2 dose (less than 79.75 Gy_{10} or more than equals to 79.75 Gy_{10})

	Local recurrence	Loco regionally controlled disease
HR-CTV D90 EQD2 dose		
Less than 79.75 Gy_{10}	47.1%, (8)	52.9%, (9)
More than equal to 79.75 Gy_{10}	12.9%, (4)	87.1%, (27)

The total prescription dose to point A was 79.75 Gy_{10} (from 50 Gy EBRT and 3# of 7 Gy to point A ICBT). Thus, for comparison of clinical outcome, we divided the patients into two groups based on whether the HR-CTV receives the prescription dose (79.75 Gy_{10} EQD2) or not (Tab. 4). During the follow up period, the patients who received an HR-CTV D90 EQD2 dose of more than or equal to 79.75 Gy_{10} EQD2 had significantly higher locoregional control than patients receiving less than 79.75 Gy_{10} EQD2 (87.1% *vs.* 52.9%,p = 0.015, Fisher's exact test).

Figure 2 represents Kaplan Meier plot for progression free survival based on HR-CTV D90 EQD2 dose.

Progression free survival was significantly better for patients receiving HR-CTV D90 EQD2 dose of 79.75 GY_{10} or more (p-value = 0.007, log-rank test). The median PFS was not reached. Three-year progression free survival was 87.1% in patients receiving HR-CTV D90 EQD2 dose of 79.75Gy_{10} or more, while it was 52.9% in patients receiving HR-CTV D90 dose of less than 79.75 Gy_{10}.

Table 3. Comparison of mean point A and HR-CTV doses in patients with disease recurrence and locoregionally controlled disease

	Mean ± standard deviation [Gy_{10}]		p-value (independent samples t-test)
	Local Recurrence	Loco regionally controlled	
Point A EQD2	77.94 ± 2.49	77. 52 ± 1.99	0.59
HR-CTV D90 EQD2	77.96 ± 4.81	83.97 ± 6.46	0.002
HR-CTV D98 EQD2	67.36 ± 3.82	69.94 ± 3.76	0.013

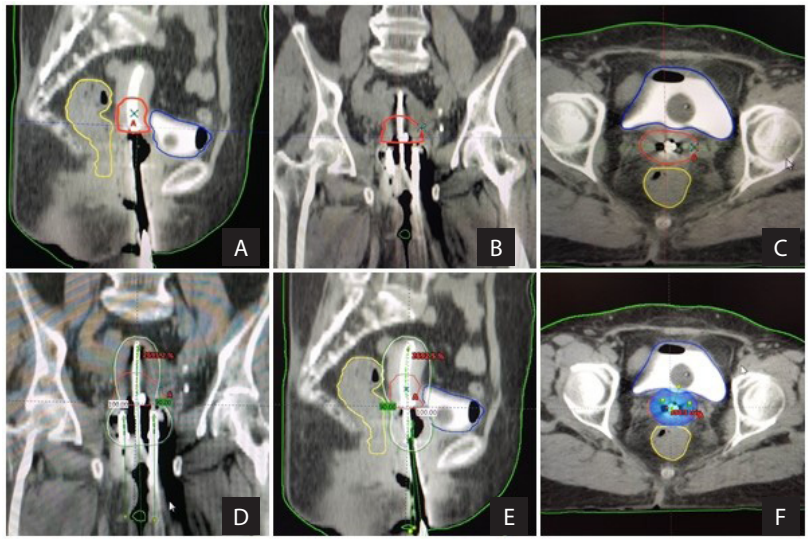

Figure 1. Brachytherapy planning CT in various sections showing HR-CTV (red), bladder (blue), and rectum (yellow) contouring and isodose curves covering HR-CTV in various sections. **A–C.** HR-CTV contoured on CT scan in sagittal, coronal, and axial sections, respectively. **C, D.** 90% (green) and 100% (white) isodose curves covering the HR-CTV in coronal and sagittal sections. **E.** Dose color wash showing covering of HR-CTV with 90% isodose in the axial section

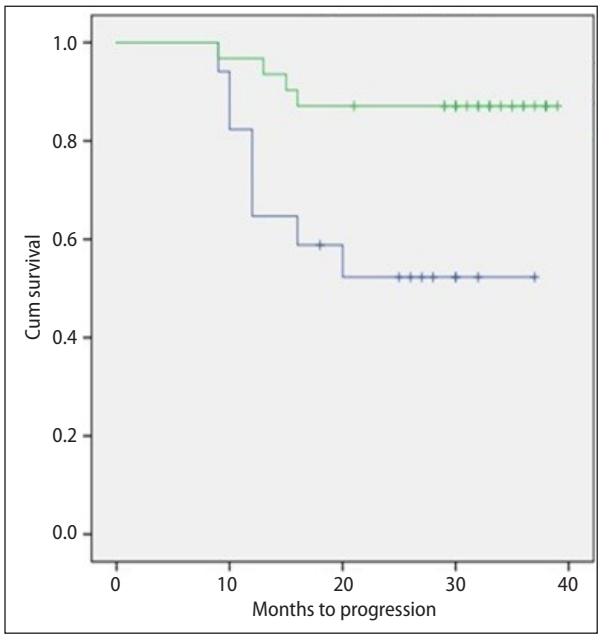

Figure 2. Kaplan-Meier plot for progression-free survival based on HR-CTV D90 EQD2 dose. Green curve represents patients receiving HR-CTV D90 dose ≥ 79.75 Gy_{10}, blue curve represents patients receiving HR-CTV D90 dose of < 79.75 Gy_{10}

Discussion

MRI based adaptive brachytherapy is the gold standard for intracavitary brachytherapy of carcinoma cervix and recent recommendations are provided by Gyn GEC ESTRO [10, 11] working group and ICRU 89(9). The standard was set based on the results of various studies [21–23]. With the publication of results of RetroEMBRACE & other studies, improvement in target coverage and overall survival was shown with [15, 24, 25].

However, implementation of such recommendations is not just limited to knowledge, training, and experience, it requires state of the art equipment and applicators, much of which is not available at state-funded high volume centers. A practice pattern survey by the same author among young radiation oncologists in India found that only about 9% of centers use routine MRI based planning versus 50% using CT based planning [25]. This is perhaps because most centers have a CT simulator which is essential for EBRT planning, and hence the availability of CT based recommendation is very essential for brachytherapy planning in such centers. However, the use of CT as cervical brachytherapy imaging is limited by the poor anatomical delineation [17]. The GTV cannot be delineated on a CT scan, there is a limited visualization of parametrial disease, the upper end of the cervix cannot be differentiated from the uterus, and the disease extension on the uterine cavity cannot be visualized. In this study we have selectively included the subgroups of patients without any residual parametrial dis-

ease post EBRT or concurrent chemoradiotherapy, thus eliminating the contouring uncertainties of the parametrial disease.

A study by Rahul Krishnatry et al. suggested that no significant dosimetric difference in terms of V100, D90, and D100 exists between CT and MR contouring, standardized guidelines were not dictated [21]. The requirement of CT guidelines has been addressed in various trials that have tried to establish a CT based guidelines for CTV contouring in the cervix [17–19, 27]. The recommendations provided by JRSOG [26] used MRI scans at diagnosis and at brachytherapy to delineate cervical CTV. Those recommendations could not be taken in our study as the contouring was done retrospectively and MRI plates were not always available for reference. The CT standardized guidelines provided by Viswanathan et al. [18] did not require the use of MRI scans or contrast enhancement. The updated guidelines from the same author were adopted for our study [17].

The CT based HR-CTV contouring recommendations lacked adequate clinical data on local control and survival. However, in the RetroEMBRACE, 139/731 (19.1%) of patients were treated with CT based HR-CTV contouring, separate data on the clinical outcome of that particular subgroup was not available [15].

Although our study showed good locoregional control in the group where HR-CTV D90 received at least 79.75 Gy_{10} EQD2 (from table 4), there was more local failure in our study population, which is more than historical image-guided brachytherapy cohorts [15, 27–30]. A study by Mahanshetty et al. reported local control in 22/24 patients after a median follow up of 10 months [31]. A study by D Simpson et al. reported a 1-year locoregional failure of 2.2% [30]. Kusada et al. reported a 2-year local control of 83% [32]. Rijkmans et al. reported a 3-year overall survival and local control of 93% and 86% with the use of image-guided brachytherapy [29].

Our inferior local control could be due to several limitations in our study. Firstly, the study protocol was designed after completion of patients' treatment, so there was no protocol for quality control of EBRT and brachytherapy technique and our study relied on treatment decisions, dose prescription and optimization partially from institutional protocols and partially from treating physician's experience. Secondly, the HR-CTV contouring was done post-treatment, so dose prescription and optimization was not based on HR-CTV so the recommended D90 dose of ≥ 85 GY_{10} could not be achieved in several patients. However, our aim was not to achieve good local control in the population which was not under the control of the study protocol, we wanted to show whether dose to the HR-CTV contoured on CT scan had any impact on local control. We managed to show a significantly good local control in patients who received the prescription dose to HR-CTV compared to those who did not. A comparative study from TMH, Mumbai, inferred that HR-CTV volumes can be contoured on CT as compared with MRI, provided there is documentation of disease at diagnosis by clinical drawings and MRI, and real-time acquisition of TRUS images at various levels in relation to the cervical canal during the procedure [19]. However, since there is an overestimation of HR-CTV volumes on CT based contouring as compared to MRI based contouring, this could result in a lower HR-CTV D90 that correlates to local control.

Though more validation is required with a prospective protocol with quality control of EBRT and ICBT, dose prescription and optimization to HR-CTV and a longer follow up, this study merits in providing an indirect validation of using CT based HR-CTV contouring backed by providing clinical results of recurrence correlation with the mean D90 of the HR-CTV thus contoured. Incorporation of real-time ultrasonography may add to the validity and reliability of such CT based delineation. However, since original dose prescription and optimization were not done to HR-CTV, there was no control on the toxicity profile of OAR based on HR-CTV dosimetry, hence no comment could be made on the same.

Conclusion

CT based HR-CTV volume delineation with the help of pre-brachytherapy clinical diagrams and MRI imaging may be feasible in a select subgroup of patients with complete or near-complete response to External Beam radiation. Prospective studies need to be undertaken to rationalize dose prescription CT based HR-CTV as this would popularise image-based adaptive brachytherapy, especially in the resource constraint settings.

Conflict of interest

None declared.

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