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ORIGINAL ARTICLE

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Challenges in intracavitary brachytherapy application in anatomically variable uterus

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ABSTRACT

Introduction: Cancer cervix is the 2nd most common malignancy among Indian females with 1,23,907 new cases every year. Treatment options include radical radiotherapy wherein internal radiation plays an imperative role. Intracavitary applications in anatomically distorted uteri present a challenge and often result in sub-optimal applications. The purpose of this study is to determine the incidence of anatomically variable uterus in cancer cervix patients and the rate of intra-operative complications with Intracavitary brachytherapy (ICBT).

Materials and methods: An audit of 276 biopsy-proven cancer cervix patients treated with ICBT between Jan 2019 to June 2022 was undertaken. FIGO stage I-IVA were included while metastatic and post-operative cases were excluded. All applications were done using the Modified Fletcher-Suit applicator, and planned on CT using Brachy vision 13.6.5, based on Point A.

Results: 41/276 (14.9%) patients presented with anatomically variable uteri. 20/41 (48.78%) were retroverted uteri, 11/41 (26.82%) were anteflexed and 5 each (12.19%) had cervical stenosis and atrophied uteri respectively. The total number of applications performed was 120, and complications were recorded in 42 applications. There was a statistically significant correlation between the patient's age and the incidence of procedural complications, with an increased incidence of complications in the advanced age group (p-value — 0.001). Similarly, a significant correlation was found between distorted anatomy and the incidence of complications (p-value — 0.045). The higher rectal dose was observed in anteflexed uteri (p-value — 0.001) while retroverted uteri was associated with a higher bladder dose (p-value — 0.001).

Conclusions: In anatomically difficult uteri, brachytherapy application is a challenge with significantly high rates of complications including perforation. Careful selection of tandem length and orientation of the uterine anatomy after the first fraction may enable better application in subsequent fractions.

Keywords: intracavitary brachytherapy, cancer cervix, perforation

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Introduction

Brachytherapy is an integral part of the treatment of locally advanced cancer cervix, which is the second most common gynaecological malignancy in India [1]. The addition of brachytherapy to external beam radiotherapy helps boost the dose to the gross tumour as well as improve disease control and survival along with reducing the dose to the organ at risk. Optimal placement of a brachytherapy applicator is imperative for achieving an acceptable brachytherapy plan [2]. Optimal placement of the tandem and ovoid is essential for an acceptable brachytherapy plan. An ideal intracavitary insertion results in improved treatment outcomes as is seen in a study by Corn et al., [3] demonstrating a strong trend towards improved 5-year survival in ideal versus inaccurate insertions (60% vs. 40%) in patients with locally advanced cervical cancer. Anatomical variations and positional abnormalities of the uterus can be associated with treatment complications, including a higher incidence of bowel and bladder injury. A major concern with inappropriate positioning is injury to

pelvic viscera and intestines, be it either immediate and direct in onset, or delayed, secondary to subsequent radiation injury as a result of inadequate separation between the radiation source and the damaged viscus [4]. Applicator placement and instrumentation with standard tandem carry a substantial risk of uterine perforation and mispositioning of the intrauterine tandem. Perforation of the uterus can result in the spread of the tumour to the abdominal cavity. Moreover, if perforation goes undetected and treatment is initiated, it can increase the risk of delayed radiation injury to nearby pelvic structures. Therefore, precise placement of the application is crucial to prevent unfavourable treatment outcomes [5]. The purpose of this study was to determine the incidence of anatomically variable uteri and the resulting rate of intra-operative complications with Intracavitary brachytherapy (ICBT) using a standard 'Modified Fletcher Suit' Applicator.

Materials and methods

An audit of 276 biopsy-proven cancer cervix patients treated with IC between Jan 2019 to June 2022 was conducted at the institute. Patients were staged with FIGO 2018 classification update and stage IVB were excluded from the present study. Post-operative patients were also excluded from the present audit.

External beam radiotherapy (EBRT)

Patients received a dose of 45–50.4 Gy at 1.8–2 Gy per fraction over 5–6 weeks with weekly concurrent chemotherapy using cisplatin 40mg/m^2 or carboplatin 150 mg. The study also incorporated patients who underwent External Beam Radiotherapy (EBRT) at external medical facilities and were subsequently referred for Intracavitary Brachytherapy (ICBT) at the hospital. Therefore, the study also encompassed both 2D-CRT treatment modalities utilizing Cobalt-60 and 3D-CRT utilizing linear accelerator with the dose of 50.0Gy at 2 Gy per fraction. Internal candidates, indicating those who received EBRT at the study hospital, were treated with Intensity Modulated Radiotherapy (IMRT) using the Varian Vital Beam system with the above-mentioned dose schedule.

Pre-ICBT investigations

A minimum of a 1-week gap was maintained between EBRT and ICBT during which a pre-anaesthetic checkup was done and all routine investigations were performed. Patients with a haemoglobin level of < 10gm% received a blood transfusion. All patients underwent a clinical examination and were re-staged accordingly. Patients with a residual disease of more than FIGO stage IIIA were not planned for ICBT.

Intracavitary brachytherapy (ICBT)

All patients uniformly received 21 Gy in 3 fractions at 7 Gy per fraction with a minimum of 1-week gap interval with EBRT. All applications were done under short General Anaesthesia using a Modified Fletcher-Suit applicator and received High Dose Rate (HDR) brachytherapy planned on CT using Brachy vision 13.6.5, Version Gamma Med Plus ix (24 Channels with Ir-192 Radioactive Source) based on Point A. All intra-operative complications were recorded after each fraction. 2cc dose to the bladder and rectum and their equivalent dose in 2 Gy per fraction (EQD2) were also recorded.

Statistical analysis

Data was described in terms of range; mean ± standard deviation (± SD), median, frequencies (number of cases) and relative frequencies (percentages) as appropriate. To determine whether the data is normally distributed, a Kolmogorov-Smirnov test was used. A comparison of quantitative variables between the study groups was done using ANOVA. For comparing categorical data, the Chi-square (χ^2) test was performed and the Fisher exact test was used when the expected frequency was less than 5. A probability value (p-value) less than 0.05 was considered statistically significant. All statistical calculations were done using (Statistical Package for the Social Science) SPSS 21version (SPSS Inc., Chicago, IL, USA) statistical program for Microsoft Windows.

Observation

Patient characteristics have been summarized in Table 1. The median age of the patient was 52. 41/276 (14.9%) patients presented with anatomically variable Uteri. 39 patients underwent all 3 applications, 1 patient received 2 fractions and defaulted while the remaining 1 patient received only 1 fraction. A total of 120 applications were performed.

Retroverted uterus

20/41 (48.78%) patients had retroverted uteri. All 20 patients received 3 fractions of ICBT making it a total 60 fractions. Amongst them, 12/60 (20%)

applications had perforation, all of them being anterior. During subsequent fractions, an attempt was made to improve application by inverting the central tandem followed by its subsequent upward rotation. All perforations were limited to the first fraction only. Mean 2cc EQD2 bladder and rectal doses were 26.85 Gy and 19.75 Gy respectively.

Anteflexed uteri

11/41 (26.82%) patients had anteflexed uteri.10 patients received all 3 fractions while 1 received only 1 fraction, hence total applications were 31. Amongst those 5/31 (16.13%) applications resulted in posterior perforation, 1/31 (3.2%) had anterior perforation and 8/31 (25.8%) applications were found to be subserosal. For correction, an attempt was made to fill the bladder with 50cc Ringer's Lactate (RL) followed by clamping of Foley's pre-procedure. All perforations were limited to the first fraction only. The subserosal application was limited to the first fraction in 4 patients, and the second fraction in 2 patients. Mean 2cc EQD2 bladder and rectal doses were 22.64 Gy and 24.45 Gy respectively for anteflexed uteri.

Cervical stenosis

5/41 (12.19%) patients presented with stenosis of the internal cervical OS. 4 patients received all 3 application fractions while the remaining 1 received only 2, hence total number of applications was therefore 14. None of the patients had perforation while 12/14 (85.7%) applications were inadequate. Dilatation of the cervical Os with artery forceps before tandem insertion improved 4/14 (28.57%) applications. Mean 2cc EQD2 bladder and rectal doses were 21.4 Gy and 16.6 Gy respectively.

Atrophic uterus

5/41 (12.19%) patients presented with atrophied uteri in which a total of 15 fraction applications were done. 1/15 application resulted in fundal perforation. Mean 2cc bladder and rectal doses were 20Gy and 23.8Gy respectively.

Results

The correlation of procedural complications with Age, Stage and Anatomy is represented in Table 1. A total of 19 perforations were recorded. The brachytherapy dose was delivered in all 19 cases with proper optimization. During planning, the dwell position of the tip of the source was shifted to exclude the length of the tandem beyond the uterine musculature, as confirmed by the transverse and sagittal section of the planning CT scan. After completion of ICBT, 10 patients had vaginal bleeding and 3 required hospitalization with 1 unit Packed Red Blood Cells (PRBC) transfusion to each patient while the remaining 7 were managed conservatively over 6 hour observation period with vaginal packing supplemented with a single dose of intravenous tranexamic acid 500 mg and prophylactic antibiotics. The subsequent fraction in all 10 patients was delayed by 15 days instead of 7 days. None of them had bleeding during or after 2nd fraction.

There was a statistically significant correlation between the patient's age and the incidence of procedural complications with an increased incidence of complications in the advanced age group (p-value — 0.001). Similarly, a significant correlation was found between distorted anatomy and the incidence of complications (p-value — 0.045). Also, a statistically significant correlation was found between anatomy and bladder and rectal doses (Table 2 and Table 3). The higher rectal dose was observed in anteflexed uteri (p-value — 0.001) while retroverted uteri was associated with a higher bladder dose (p-value — 0.001).

Table 1. Patient characteristics

Age	Age range	Number of subjects (n)	Percentage
	< 51	17	41.5%
	51–60	16	39.0%
	> 60	8	19.5%
	Total	41	100.0%
Histology	**Subtype**	**n**	**Percentage**
	Adeno-carcinoma	2	4.9%
	Squamous	39	95.1%
Stage	**Disease stage**	**n**	**Percentage**
	I	1	2.4%
	II	18	43.9%
	III	21	51.3%
	IV	1	2.4%
Anatomy	**Types**	**n**	**Percentage**
	Retroverted	20	48.8%
	Anteflexed	11	26.8%
	Stenosis	5	12.2%
	Atrophy	5	12.2%

Table 2. Intra-operative complications

Complications	N	Bleeding	Requiring blood transfusion	Damage to bowel/ bladder/peritonitis/ /death
Anterior Perforation	13	6	2	0
Central Perforation	1	1	0	0
Posterior Perforation	5	3	1	0
Subserosal Insertion	8	0	0	0
Inadequate Insertion	15	0	0	0
Total	42/120	10	3	0

Table 3. Correlation of procedural complications with age, stage and anatomy

		Procedural complications				Total	Chi-square value	p-value (< 0.05)
		Absent		Present				
Age group	< 51	13	68.4%	4	18.2%	17	13.618	0.001
	51–60	6	31.6%	10	45.5%	16		
	> 60	0	0.0%	8	36.4%	8		
Histology	Adenocarcinoma	0	0.0%	2	9.1%	2	1.816	0.178
	Squamous	19	100.0%	20	90.9%	39		
Stage	IB3	0	0.0%	1	4.5%	1	3.968	0.681
	IIA	5	26.3%	3	13.6%	8		
	IIB	6	31.6%	4	18.2%	10		
	IIIA	2	10.5%	3	13.6%	5		
	IIIB	4	21.1%	6	27.3%	10		
	IIIC	2	10.5%	4	18.2%	6		
	IVA	0	0.0%	1	4.5%	1		
Anatomy	Anteflexed	4	21.1%	7	31.8%	11	7.64	**0.045**
	Atrophy	4	21.1%	1	4.5%	5		
	Retroverted	11	57.9%	9	40.9%	20		
	Stenosis	0	0.0%	5	22.7%	5		
Total		19	100.0%	22	100.0%	41		

Discussion

There is a paucity of literature on the intra-operative or acute complications resulting from an imperfect application in an anatomically distorted uterus. A study by Powell et al., [6] has reported a 14% incidence rate of retroverted uteri among cancer cervix patients while another study by Mayr et al., [7] has reported a 22% incidence of the same. In a study by Bikramjit Chakrabarti et al., [8] demonstrating the Clinical and Dosimetric consequences of imperfect applicator insertion in cervical cancer, 18 plans had improper/inadequate insertions including perforations, out of which, 4 had retroverted uteri, 4 had acutely anteflexed uteri and 5 had small/atrophied uteri. In the same study, anterior perforations were more common in retroverted uteri, posterior perforations were more commonly found in acutely anteflexed uteri, and the incidence of central perforations was higher among small uteri. Brachytherapy dose was delivered in all but one patient, and patients with bleeding were managed conservatively. Similar findings have been reported in the current study.

In the present study, the rate of retroverted uteri is 7.2% (20/276) while it constitutes 48.78% of clinically variable uteri, while the rate of acutely anteflexed uteri, atrophy and stenosis is 26.82%, 12.19% and 12.19%.

Studies by Prabhakar et al., [9] and Mayr et al., [7] have reported an above-normal incidence of perforations in markedly anteverted and retroverted uteri. They found that 60% of the perforations occurred in the posterior uterine wall, 25% in the fundus, and 15% in the anterior wall, while Segedin et al*.,* reported 70% in the posterior uterine wall, 15% in the fundus, and 15% in the anterior wall [10]. Several studies have demonstrated the benefit of using Ultrasound guidance for applicator insertion [5, 11]. Granai *et al*., in their study [11] employed post-operative B-mode ultrasound to evaluate the final tandem position in 50 consecutive insertions in 28 patients and reported a 34% incidence of sub-optimal application, with a 24% rate of subserosal insertion, 10% rate of perforated uterus.

In the present study, the rate of perforation (15.82%) was high among the variable uteri since it was a blind procedure. However, the rate of subserosal insertion is low (6.66%). Also, like most studies, the incidence of anterior perforations was high among retroverted uterus, while anteflexed uteri had a higher rate of posterior perforation (Fig.1 and Fig. 2). Only 1 application in atrophied uteri resulted in fundal perforation. In this study, a higher rectal dose expressed in EQD2 was observed in anteflexed uteri and this variation was statistically significant (p-value — 0.001). Similarly, retroverted uteri had a higher bladder dose (p-value — 0.001) (Table 4).

Regarding death following the perforation, no single death was reported in the present study while in Gupta *et al*. 11 cervical and 3 endometrial cancer patients were detected with complete uterine perforation after 3rd insertion, of whom 5 cervical and 1 endometrial cancer patient died, rest recovered. Similarly, partial uterine perforation was detected in 29 cervical and 3 endometrial cancer patients after 3rd insertion and all recovered [12].

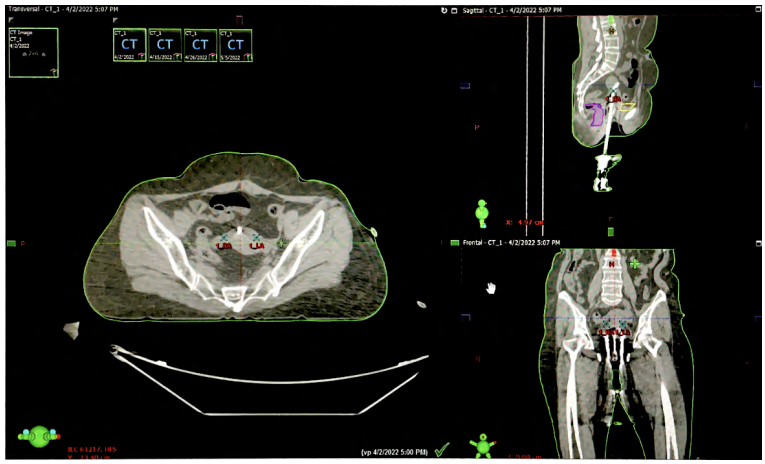

Figure 1A. Retroverted uterus with perforation in 1st fraction

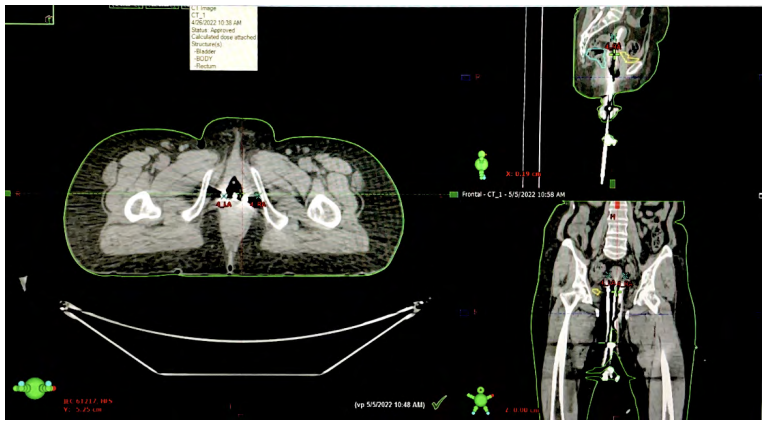

Figure 1B. Correction of application in the same patient with retroverted uterus in 2nd fraction

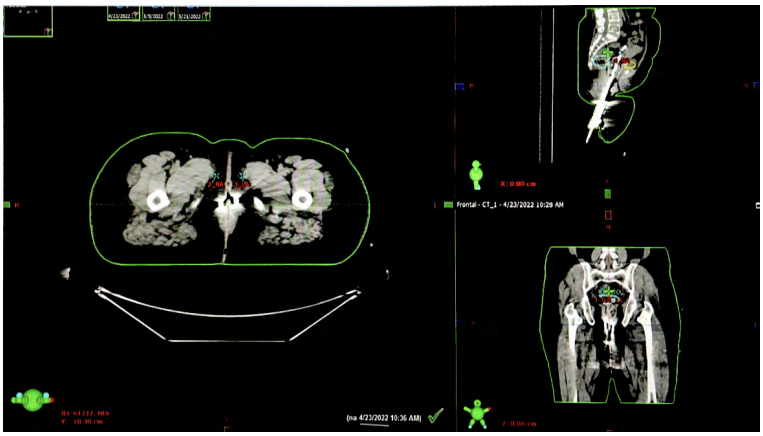

Figure 2A. Anteflexed uterus with perforation and subserosal insertion in 1st fraction

Figure 2B. Correction of application in the same patient with anteflexed uterus in 2nd fraction

Table 4. Correlation of distorted anatomy with age, rectal and bladder dose respectively

	Anatomy	N	Mean	F	p-value (< 0.05)
Age	Retroverted	20	51.25	1.07	0.374
	Anteflexed	11	53.64		
	Stenosis	5	58.80		
	Atrophy	5	52.60		
	Total	41	52.98		
Rectal dose (Gy)	Retroverted	20	19.75	18.893	**0.001**
	Anteflexed	11	24.45		
	Stenosis	5	16.60		
	Atrophy	5	23.80		
	Total	41	21.12		
Bladder dose (Gy)	Retroverted	20	26.85	9.41	**0.001**
	Anteflexed	11	22.64		
	Stenosis	5	21.40		
	Atrophy	5	20.00		
	Total	41	24.22		

Conclusions

ICRT application in anatomically distorted uteri is a challenge with higher complication rates and higher incidences of perforation compared to an anteverted uterus. Certain modifications in procedure may yield better results and help in limiting the number of perforations. Ultrasound guidance may further decrease the rate of complications and improve applications.

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