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Factors affecting the dosimetry of high-dose rate intracavitary brachytherapy in cervical cancer

Bikash Ranjan Mahapatra, Sandip Kumar Barik, Deepak Kumar Das, Saroj Kumar Das Majumdar, Dillip Kumar Parida, Mathan Kumar Ramasubbu, Avinash Badajena, Bijay Kumar Barik, Minakshi Mishra, Ashutosh Pattanaik, Satyabrata Kanungo, Anupam Muraleedharan ⓘ, Sk Soel Ahmed, Priyanka Mukherjee, Shaha Sheik Abdulla, Ankur Mahajan and Arnab Sarkar

All India Institute of Medical Sciences, Bhubaneswar, Odisha, India

Abstract

Background: Intracavitary brachytherapy (ICBT) is essential in managing locally advanced cervical cancer. Brachytherapy as a modality has the advantage of a higher dose to the tumour with a dose fall off at the periphery as per the inverse square law. The dose per fraction is much higher than external beam radiotherapy. So proper application and dosimetry are of paramount importance to reduce late toxicity.

Methods: A retrospective analysis of 69 patients who underwent three ICBT applications of 7 Gray in each fraction was done. The factors under consideration were the type of pain management (spinal anaesthesia (SA) versus conscious sedation (CS)), the initial size of the disease (bulky and non-bulky) and subsequent fractions (first fraction versus third fraction). The dosimetric parameters analysed were the doses received by points A, B and P and that of the critical organs (bladder, rectum and sigmoid colon).

Results: The dose received by critical organs was comparable concerning all the factors under consideration. The dose to point P on the left side was significantly lower in the CS group than in the SA group (p-value = 0·031). Also, the dose to point P on the right side was significantly lower in the third fraction compared with the first fraction (p-value = 0·016).

Conclusions: ICBT under spinal anaesthesia resulted in a higher dose to the pelvic wall. The initial size of the tumour or the subsequent fractions does not significantly affect the dose received by critical organs.

Introduction

The cancer burden is rising throughout the world.[1] This has been attributed to the increasing age of the population as well as the change in lifestyle and the environment. In countries with robust screening systems and vaccination, many cancers, such as breast and cervical cancers, get diagnosed early. On the contrary, middle- and low-income countries still face a considerable burden of such preventable cancers.[2] Cervical cancer constitutes 6·5% of all new cancer cases in females worldwide and 18·3% in India.[1,3] It's a harsh reality that 60% of cervical cancer in India gets diagnosed at a locally advanced stage.[4] So, the definitive management revolves around chemoradiation and brachytherapy.[5] Intracavitary brachytherapy (ICBT), a highly conformal radiation delivery mode, offers many advantages. Most important is the sharp dose fall-off beyond the target. This ensures that there is no compromise in the dose to the target while the critical organs are spared. The number of sessions of ICBT depends on the dose per fraction and the External Beam Radiotherapy (EBRT) dose. The goal is to give a total of 80–90 Gy equivalent dose (EQD2) to point A (The point A, as defined by the Manchester system, being the point that is 2 cm lateral to the central canal of the uterus and 2 cm above the mucous membrane of the lateral fornix, in the plane of the uterus).

The proper intracavitary application provides a better dose distribution. Various factors are expected to influence the same. As it is an invasive procedure, pain management is an essential factor. This has been duly addressed in the latest guidelines also.[6,7] Other probable factors could be the size of the tumour. Bulky tumours (> 4 cm) are more likely to leave a residual disease post-EBRT, which can affect the placement of the applicators. Finally, previous knowledge about the patient's anatomy (length of the uterine canal, position of the uterus, relative location of the organs at risk) may also improve the applicator placement. This may translate into a better dose profile in later fractions of ICBT than the earlier. In this retrospective study, we try to analyse the
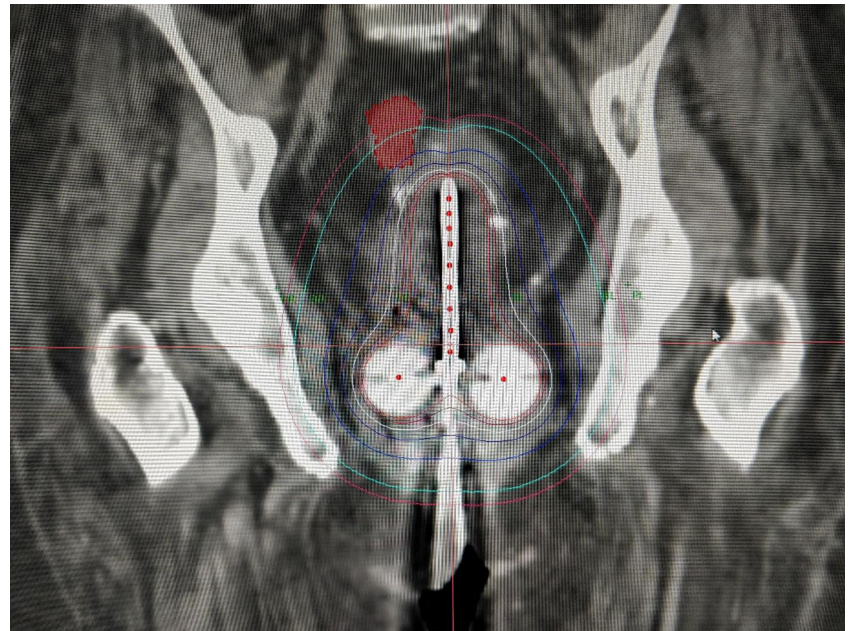
Figure 1. Coronal image of pelvis with brachytherapy plan showing isodose lines and points A, B and P.

dose distribution using dose-volume histograms (DVH) during different brachytherapy sessions and its association with the type of anaesthesia and the initial size of the tumour.

Material and Methods

This is a retrospective study of cervical cancer patients who underwent concurrent chemoradiotherapy for a dose of 50 Gy with intravenous Cisplatin 40 mg/m^2 followed by three sittings of ICBT from August 2018 to June 2022. The ICBT dose per sitting was 7 Gy to point A. The total number of patients was 69. Due to the lack of workforce, anaesthesia assistance for ICBT procedures was available only for half the days of a week. The rest of the patients underwent the procedure under conscious sedation (CS). The patients who received anaesthesia had to clear the anaesthesia fitness before the process. Workup for ICBT included a complete blood count, Hepatitis B, C, HIV I & II serology and coagulation profile. All patients were admitted admission one day before the procedure. Shaving from the umbilicus to mid-thigh and bowel preparation was done. For bowel preparation, 10 mg Bisacodyl tablet was given the night orally before the procedure, followed by proctoclysis enema the next morning. The patients were kept fasting overnight.

For spinal anaesthesia (SA), the drugs used were intravenous Bupivacaine heavy 5 mg per ml and Inj Fentanyl, and for CS, intravenous Promethazine 25 mg, intravenous Tramadol 50 mg infusion and 2% lignocaine solution for local anaesthesia. The patients were kept in a lithotomy position, and 0·5% povidone-iodine solution was used to paint the perineum. Urinary catheterisation was done using a Foley catheter, and the balloon was inflated with 7cc Iohexol contrast. Per vaginal examination was done to assess the residual disease and the position of the cervical os and vaginal space. Serial dilation of the cervical os was done using Hegar's dilator, and the uterine cavity length was assessed using uterine sound. Then, central tandem of the same length was inserted into the uterine cavity, and the ovoids, selected based on vaginal space, were placed into the bilateral fornices. The applicators (modified Fletcher suit) were fixed, and thorough

posterior vaginal packing followed by anterior packing was done. Non-contrast computerised tomographic simulation scans were taken in GE & Optima CT580. The images were sent to Oncentra brachytherapy planning system V 4.6.01. The Organs at Risk, like the rectum, sigmoid colon and bladder, were contoured according to Radiation Therapy Oncology Group guidelines. In the next step, catheter reconstruction and generation of reference points like point A, point B (5 cm from the midline of the patient) and point P (6 cm from the midline of the patient) were done, followed by dwell points activation, optimisation and the dose prescription of 7 Gy to point A. The plan evaluation was done with the help of the DVH, the doses received by points A, B and P and that of the Organs at risk (D2cc and D0·1cc)[8,9] (Figure 1). After approval of the plan, the treatment is delivered using an Iridium-192 high-dose-rate brachytherapy machine (Nucletron & Microselectron HDR v3). Throughout the procedure, the vital signs of the patient were monitored. The applicators were removed post-treatment delivery, and per vaginal examination was done to assess for bleeding.

The collected data were analysed using IBM SPSS Version 26. The categorical variables were described by percentage or proportion, and continuous variables by mean and standard deviation. The paired *t*-test was used for the dosimetric analysis between the first and the third fractions. When the data were non-parametric, analysis was done by Wilcoxon signed-rank test. The unpaired t-test was used to analyse the dosimetric difference between the bulky and non-bulky groups, spinal anaesthesia and conscious sedation. When the data were non-parametric, analysis was done using the Mann-Whitney *U* test.

Results

The number of patients enrolled in the study was 69, and the total number of plans evaluated was 207. The median age group was 50–59 years and the most common histopathology was squamous cell carcinoma. In this study population, stage II was found to be the most common (52·1%) (Table 1). The dose to points A, B and P on both sides and the dose received by the critical organs (bladder, rectum and sigmoid colon) were analysed concerning the type of

Table 1. Shows the baseline characteristics of the study population

Number of patients		69
Total number of ICBT applications		207
The age group of patients (In years)	30–39	5 (7·2%)
	40–49	16 (23·2%)
	50–59	23 (33·3%)
	60–69	19 (27·5%)
	70–79	6 (8·7%)
FIGO Stage	Stage I	2 (2·9%)
	Stage II	36 (52·1%)
	Stage III	30 (43·4%)
	Stage IV	1 (1·4%)
Histopathology	Squamous cell carcinoma	62 (89·8%)
	Adenocarcinoma	3 (4·3%)
	Adenosquamous carcinoma	4 (5·8%)
Tumour size	Bulky (≥ 4 cm)	43 (62·3%)
	Non-bulky(<4 cm)	26 (37·7%)
Pain management	Conscious sedation	37 (53·6%)
	Spinal anaesthesia	32 (46·4%)

Table 2. Shows the dose received by points A, B and P and critical organs between CS and SA

Dose (% of Point A)		SA	CS	p-value
Left	Point A	98·85 ± 2·35	99·64 ± 2·16	0·228
	Point B	28·70 ± 2·72	28·01 ± 2·13	0·087
	Point P	20·90 ± 2·12	20·22 ± 1·64	**0·031**
Right	Point A	99·95 ± 2·31	99·79 ± 2·57	0·965
	Point B	28·83 ± 2·65	28·34 ± 2·34	0·211
	Point P	20·93 ± 2·10	20·47 ± 1·85	0·258
Bladder	0·1 cc	113·48 ± 27·70	113·15 ± 31·41	0·714
	2 cc	84·20 ± 15·64	83·71 ± 17·41	0·958
Rectum	0·1 cc	100·62 ± 29·22	97·80 ± 25·07	0·914
	2 cc	74·19 ± 16·69	72·53 ± 16·29	0·601
Sigmoid	0·1 cc	93·20 ± 40·86	89·45 ± 36·14	0·794
	2 cc	60·52 ± 18·70	60·91 ± 21·73	0·496

Table 3. Shows the dose received by points A, B and P and critical organs between the bulky and non-bulky disease

Dose (% of Point A)		Bulky (≥4 cm)	Non-bulky (<4 cm)	p-value
Left	Point A	99·33 ± 2·35	99·38 ± 2·11	0·530
	Point B	28·30 ± 2·47	28·21 ± 2·23	0·812
	Point P	20·46 ± 1·93	20·49 ± 1·75	0·856
Right	Point A	99·85 ± 2·56	99·85 ± 2·33	0·982
	Point B	28·50 ± 2·46	28·56 ± 2·50	0·876
	Point P	20·61 ± 1·96	20·70 ± 1·95	0·639
Bladder	0·1 cc	114·47 ± 29·06	111·29 ± 31·73	0·325
	2 cc	83·90 ± 16·36	83·86 ± 16·84	0·775
Rectum	0·1 cc	100·47 ± 24·40	96·14 ± 29·91	0·080
	2 cc	74·68 ± 15·47	70·59 ± 17·67	0·076
Sigmoid	0·1 cc	93·05 ± 38·96	87·13 ± 35·98	0·697
	2 cc	61·88 ± 18·99	58·95 ± 23·11	0·774

Table 4. Shows the dose received by points A, B and P and critical organs between the first and the third fractions

Dose (% of Point A)		First fraction	Third fraction	p-value
Left	Point A	99·30 ± 1·96	99·87 ± 2·51	0·081
	Point B	28·40 ± 2·05	28·05 ± 2·47	0·253
	Point P	20·63 ± 1·60	20·22 ± 1·91	0·067
Right	Point A	99·96 ± 2·21	99·58 ± 2·94	0·557
	Point B	28·66 ± 2·38	20·09 ± 2·44	0·085
	Point P	20·81 ± 1·88	20·22 ± 1·92	**0·016**
Bladder	0·1 cc	113·50 ± 33·71	109·77 ± 29·50	0·349
	2 cc	83·52 ± 16·93	82·77 ± 16·70	0·712
Rectum	0·1 cc	96·88 ± 28·08	100·33 ± 24·08	0·364
	2 cc	72·82 ± 18·37	74·05 ± 15·75	0·611
Sigmoid	0·1 cc	91·82 ± 43·51	88·14 ± 37·05	0·601
	2 cc	60·44 ± 19·48	60·21 ± 22·73	0·935

anaesthesia (37 patients in CS versus 32 patients in SA), the initial size of the disease and subsequent fractions (first and third) (Tables 2–4). The dose to point P on the left side was significantly lower in the CS group than in the SA group (20·22 ± 1·64 and 20·90 ± 2·12, p-value = 0·031). Also, the dose to point P on the right side was significantly lower in the third fraction compared with the first fraction (20·22 ± 1·92 and 20·81 ± 1·88, p-value = 0·016).

Discussion

Carcinoma cervix is the fourth most common cancer worldwide. In India, it is the third most common malignancy, with an annual incidence is to the tune of 0·12 million.[3] Our pool of patients also reflects the national trend of the disease.[10] In this study, cervical cancer is more prevalent in the age group of 50–59 years. Squamous cell carcinoma was the predominant histology; more than 90% of the patients belonged to stages II and III.

ICBT is an integral part of the management paradigm of cervical cancer. The dose received by the critical structures is an essential predictor of late toxicity and invariably affects the therapeutic index. The purpose of this retrospective study was to analyse the influence of various factors towards dosimetry in ICBT. Earlier studies have shown that using longer tandem and larger ovoids results in better dose distribution.[11,12] Also, with an increase in the curvature of tandem, there is a significant increase in bladder dose with a decrease in rectal dose.[11] The position of the patient, too, could affect dosimetry. The ICBT plans in the lithotomy position were superior to those in the supine position concerning doses to the critical organs.[13]

The factors considered in this study were the type of sedation, initial tumour size and the impact of subsequent fractions—i.e., first and third. The literature on these factors is few and is based on a set of 2D dosimetry. Also, the samples studied were fewer in number. These studies did not include sigmoid colon as a critical structure in the ICBT plan.[11,12,14–18] So, we embarked on a comprehensive analysis of multiple factors affecting dosimetry on a robust sample in high-dose rate brachytherapy using 3D dosimetry.

The management of pain is of prime importance in ICBT application. This can be achieved by general anaesthesia, spinal anaesthesia, conscious sedation or paracervical block (ABS). It is assumed that with the use of anaesthesia, there will be more relaxation of perineal muscles, which helps in better application and improved vaginal packing. In our study, doses received by critical organs such as the bladder, rectum and sigmoid colon and points A, B and P on the right side in SA and CS were comparable. However, the dose received by point P on the left side was found to be more in the SA group. This implies that SA may help achieve an increased pelvic wall dose, which indicates a slight improvement in plan quality under SA. In patients having contraindications to spinal anaesthesia such as severe spinal deformity, left ventricular outflow obstruction, demyelinating lesions, patient refusal, increased intracranial tension, infection at the site of injection, coagulopathies, conscious sedation provides an alternative.

It is seen in previous studies that the adequacy of packing and anaesthesia was in favour of general anaesthesia over conscious sedation.[16,17] Anker et al. found that the use of anaesthesia showed no improvement in implant technique. The multivariate analysis showed a decrease in ovoid size and a significantly higher bladder dose with intravenous anaesthesia.[11] Similarly, another study showed an unexpectedly higher dose to the rectum with GA/SA over conscious sedation.[14] In the anaesthesia group, the maximum dose to the bladder was significantly more, but the mean dose was comparable in an analysis by P C Bana et al.[15] A previous study by the same author with a smaller sample size and addressing only the dosimetric effect of anaesthesia had shown no significant difference in all the dosimetric parameters between the CS and SA groups.[19]

Our study showed that most (62%) of our patients presented with a bulky disease. After EBRT, a complete response (no clinically visible/palpable disease) was seen in 23 patients. Further analysis showed that 15 of the 23 patients belonged to the non-bulky group (>50%). Residual disease was the norm in the bulky group (>80%) post-EBRT. The dosimetric parameters showed no significant difference between the bulky and non-bulky groups. These are the findings of Anker et al.[11]

The third factor that was considered in the study was the effect of subsequent fractions on dosimetry. It was assumed that better knowledge of anatomy and the impact of the previous brachytherapy doses in case of residual disease might lead to better application and better dosimetry. In this study, it was seen that the dose to point P on the right side was significantly higher in the first fraction compared to the third fraction. It was also noticed that the dose to the bladder and sigmoid was numerically higher in the first fraction, and that of the rectum was higher in the third fraction, but both were statistically non-significant. These may be due to changes in bladder and bowel filling. Senkus-Konefka et al., too, ventured into this premise in their study. There was a decrease in both ovoid size and tandem length with subsequent implants with an associated increase in dose to critical organs (bladder and rectum).[12] Another study by Anker et al. showed a decrease in

ovoid size and curvature of the tandem over time, but the tandem length was intentionally decreased to reduce the dose to the sigmoid colon, which correlated with an increase in rectal dose in subsequent fractions.[11] In the study by Menhel et al., it was found that individual fraction optimisation was superior to treating all fractions based on the dosimetry of the first fraction. This was attributed to the interfraction fluctuation of the position of critical organs.[18]

Conclusion

ICBT under spinal anaesthesia resulted in a better dose to the pelvic wall. If the logistics permits, all patients should be offered ICBT under anaesthesia. The initial size of the tumour does not affect dosimetry in ICBT planning. With subsequent fractions of ICBT, there is no significant difference in the dose received by the critical organs. Further studies are required to validate the findings in a prospective setting.

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