

Dosimetric Investigation of Interstitial Versus Combined Intracavitary with Interstitial High Dose Rate Brachytherapy for Cervical Cancer

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Abstract

The aim of brachytherapy treatment planning is to archive curative uniform dose to the target volume and at the same time reduce unnecessary dose to the organs near to target area. The purpose of the study was to evaluate clinical target (HR-CTV) coverage and organ at risk (OAR) doses of interstitial brachytherapy (ISBT) and combination of intracavitary and interstitial brachytherapy (IC/ISBT) techniques for cervix cancer. As this is a retrospective study, 11 patients treated from 2018 to 2022 were identified, ISBT (n=4) and IC/ISBT (n=7). Dose-volume histogram (DVH) from Oncentra Masterplan Treatment Planning System (TPS) and dosimetric parameters were analysed and evaluated. The results showed the mean equivalent dose to 2 Gy (EQD₂) of HR-CTV was 89.1 ± 11.71 Gy while the mean EQD₂ of D_{2cc} for bladder, rectum and sigmoid were 88.9 ± 16.71 Gy, 81.2 ± 12.63 Gy, and 70.1 ± 15.95 Gy, respectively. For IC/ISBT technique, the mean EQD₂ of HR-CTV was 91.5 ± 8.4 Gy which was exceeded the dose constraint based on American Brachytherapy Society (ABS) recommendations. The mean of coverage index (CI) was 0.90 and the mean of dose heterogeneity index (DHI) for this technique was 0.36 ± 0.06 . Meanwhile for ISBT technique, the mean EQD₂ of HR-CTV was at 85.1 ± 16.75 Gy. However, the mean EQD₂ of D_{2cc} for rectum (81.2 Gy) was slightly exceeded the constraints while for the mean EQD₂ of D_{2cc} for bladder and sigmoid still in tolerance. The mean DHI values showed slightly equal when comparing in both techniques. As a conclusion, the IC/ISBT technique showed superior in term of dose coverage to HR-CTV based on higher CI value compared to ISBT technique. It is feasible to have a better knowledge of the effect of the dose to the HR-CTV and OARs by analysing the various brachytherapy applicators and techniques. This could aid in improving the management of the cervix cancer disease.

Keywords

Interstitial brachytherapy, hybrid applicators, coverage index, organs at risk doses

Introduction

Cervical cancer is the fourth most common malignancy in women intercontinentally [1]. Predominantly, it is caused by Human Papilloma Virus infections [2]. Cervical cancer can be treated with various approaches, but its standard treatment is the integration of external beam radiotherapy (EBRT) concurrent with chemotherapy and followed by brachytherapy especially for later stages (locally advanced) cervical cancer [3].

For the brachytherapy of cervical cancer, various hybrid applicators (combination of intracavitary applicators and interstitial needles) had been introduced in the market. Vienna ring applicator is a hybrid applicator system that combines tandem and ring applicator. The surface of ring applicator is used as the anchor for needle placement. 2 mm of diameter holes that were drilled parallel to the ring axis which is 2 mm from the outer ring surface for allowing the needles insertion [4]. These applicators and needles are the computed tomography/magnetic resonance (CT/MR) compatible (Nucletron, Veenendaal, The Netherlands). The use of Vienna ring applicator for treatment of cervical cancer improve the target coverage to the clinical target (HR-CTV), reduces doses to organ at risk (OAR) and easily reproducible for needle insertion (interstitial technique) to enable covers more targeted area.

The combination of tandem and ovoid Utrecht applicator (Elekta, Veenendaal, The Netherlands) also a type of hybrid technique and a CT/MR compatible system. Utrecht applicator consists of an intra-uterine tube and a pair of ovoid. It is a renewed version of the tandem-ovoid applicator where there are 10 drilled holes on the ovoid which provides CT/MR compatible plastic bold or sharp needles passing through it for interstitial placement. The angle of the intra-uterine tubes varies and the ovoid also had different sizes. Each ovoid contains five needle holes in a 15° angle which facilitates the placement of the needles more or less parallel to the tandem.

There is also another type of technique which is interstitial brachytherapy for cervical cancer using a prostate stepper template as a guide. Prostate stepper template is a square light-weighted that has a universal 5 mm grid array and a single action locking system that locks all implanted needles in a single movement. This system helps in accelerating the procedure and it was designed to eliminate accidental movement of the individual needles. It consists of rows and columns of holes spaced 5 mm apart. As its name suggests, this template was used mainly for interstitial brachytherapy for prostate cancer. However, it is very flexible where it also can be used for treatment of cervical cancer. The application of this template for cervical cancer brachytherapy utilizes perineal template technique where the needles were placed transperineally and fixed with the template. The placement of the needles was usually guided by ultrasound probe inserted through the rectum, or also known as trans-rectal ultrasound (TRUS). The guidance helps in ensuring accurate and precise position of the needles within the tumour volume which helps in improving the target coverage and reducing exposure to the healthy surrounding tissues which is the organ at risks (OARs).

In this study, the HR-CTV coverage and OAR doses of Interstitial brachytherapy alone (ISBT) and combined intracavitary/interstitial brachytherapy (IC/ISBT) for cervical cancer were assessed. By using various brachytherapy applicators and procedures, it is possible to acquire a better understanding of the effect of the dose. This could aid in improving the management of the cervix cancer disease.

Materials and Methods

This study protocol has been reviewed and granted approval from Human Research Ethics Committee USM (HREC) under study protocol code (USM/JEPeM/22010026) that was issued on 10th of March 2022.

Patient selection

The inclusion criteria were as followed:

- i. Patients diagnosed with cervix carcinoma with the International Federation of Gynaecology and Obstetrics (FIGO) IIB to IVA;
- ii. Patients completed concurrent chemo radiotherapy before brachytherapy;
- iii. Patients who did not undergo hysterectomy.

This is a retrospective study where the data were obtained from the existing data in the Oncentra Masterplan Brachytherapy Treatment Planning System (TPS) Ver. 4.5.3 (Elekta, Veenendaal, The Netherlands). From the TPS, the cervical cancer patients that had undergone interstitial high-dose rate (HDR) brachytherapy using hybrid applicators (Vienna ring applicator and tandem-ovoid Utrecht applicator) and interstitial alone using prostate stepper template were selected. From the databases, patients that used related technique as in the list; Vienna (n=7), Utrecht (n=1) and interstitial (n=4) which totalled to 11 patients. The patients are ranged from 41 to 84 years old.

3-D Brachytherapy treatment planning

The CT data of 11 patients plan using three-dimensional (3D) brachytherapy on the TPS were re-evaluated. The HR-CTV and OARs were contoured by medical doctor (oncologist) according to European Gynaecological Groupe European de Curietherapie-European Society for Radiotherapy and Oncology (GEC-ESTRO) GYN working group guidelines and planned brachytherapy using the Oncentra TPS. Then the treatment was planned using the methodology of graphical optimization (GrO) as regular optimization method. Dose volume histogram (DVH) summarised the information of three dimensional (3-D) dose distribution and was used to evaluate the radiation dose to HR-CTV and OARs.

Dosimetry analysis

The treatment plans were assessed for respective IC/ISBT and ISBT techniques. The doses to HR-CTV and OARs which are bladder, rectum and sigmoid were evaluated using DVH parameters from the Oncentra software for both techniques according to GEC-ESTRO recommendations. Dosimetric comparison of D_{90} for the HR-CTV and D_{2cc} for OARs between IC/ISBT and ISBT technique was also performed. D_{90} is the parameter collected for analysis of HR-CTV coverage from the DVH of each treatment plan. Meanwhile, D_{2cc} was the parameter used to calculate the doses to the OARs. D_{90} is the minimum dose delivered to 90% target volume. D_{2cc} is the minimum dose in the most irradiated 2cm³ of the volume.

GEC-ESTRO also recommended another 2 dosimetry indicators for assessment and comparison of the brachytherapy plans. The indicators are the dose homogeneity index and coverage index. Dose homogeneity index (DHI) is the ratio of target volume receiving a dose in the range of 1.0 to 1.5 times of reference dose. The ideal value for DHI is 1. It was calculated using formula in Equation 1 [5,6]:

$$DHI = \frac{(TVD_{ref} - TV1.5D_{ref})}{TVD_{ref}} \quad \text{(Equation 1)}$$

Where, TVD_{ref} refer as the volume of the target that received 100% of the prescribed dose and $TV1.5D_{ref}$ mean the volume of the target that received 1.5 times the reference dose (100% of prescribed dose). Coverage index (CI) is the fraction of the target volume that receives a dose equal to or greater than reference dose. CI gives an estimate of how much the target volume that received 100% of the prescribed dose. The ideal value for CI is 1. It can be presented by Equation 2 [5,6,7]:

$$CI = \frac{TVD_{ref}}{TV}$$

For the equation, TVD_{ref} mean the target volume that receives reference dose which is 100% of the prescribed dose while TV refer as the volume of the target. The ratio between D_{2cc} of OAR and D_{90} of HR-CTV were calculated for both technique and were compared. The ratio is used as a measure of the DVH favourability. A low ratio shows a low OAR D_{2cc} and a high HR-CTV D_{90} (A low ratio shows a favourable situation of low doses to the OAR and high dose to HR-CTV) [8]. The data were presented in mean standard deviation.

A cumulative dose summation was used to track cumulative biologically effective doses (BED) and EQD2 from EBRT and each fraction of HDR brachytherapy for the targets and the OARs. The equivalent doses to 2 Gy (EQD2) were calculated using α/β of 10 and 3 for HR-CTV and OARs, respectively [9,10]. The formula used to calculate the EQD2 is as the Equation 3 [11]:

$$EQD2 = nd \left(\frac{d + \left(\frac{\alpha}{\beta} \right)}{2 \text{ Gy} + \left(\frac{\alpha}{\beta} \right)} \right) \quad (\text{Equation 3})$$

Where, n is the number of fractions, d is the dose per fraction and α/β refer to property of the irradiated tissue. The expected total dose to 90% of the HR-CTV (D_{90}) is at least 90 Gy of EQD2₁₀ (≥ 80 Gy to ≤ 90 Gy EQD2). As for the organ at risks (OARs) which are the rectum, bladder and sigmoid, the prescribed dose limits were: a total dose to 2 cm³ (D_{2cc}) of the bladder of no more than 90 Gy EQD2₃ (≤ 90 Gy EQD2), and for the rectum and sigmoid D_{2cc} of no more than 75 Gy EQD2₃ based on the American Brachytherapy Society (ABS) consensus guideline for locally advance carcinoma of the cervix [12].

Results and Discussion

Table 3.1: The EQD2 dose of D_{90} (HR-CTV) and D_{2cc} (OARs) for each brachytherapy plan.

No	EQD2 (Gy)			
	HR-CTV	Bladder	Rectum	Sigmoid
1	93.6	81.9	74.9	56.7
2	104.7	106.3	81.4	98.0
3	82.3	79.7	68.4	-
4	98.5	96.1	86.5	64.9
5	82.7	93.0	77.6	53.0
6	109.4	108.8	108.1	83.8
7	74.0	96.7	90.2	60.9
8	82.9	52.5	60.1	-
9	74.0	98.5	87.8	60.7
10	92.8	90.3	83.9	89.1
11	85.6	74.3	74.1	64.0
MEAN	89.1	88.9	81.2	70.1
SD	11.71	16.11	12.63	15.95

- Patient no 6 to 9 was using interstitial technique

Table 3.2: The mean of EQD2 (EQD2 calculated from EBRT plus EQD2 from brachytherapy) for all selected patients.

Parameter		Total EQD2 (Gy)					
		All Patient (n=11)		ISBT Technique (n=4)		IC/ISBT Technique (n=7)	
		Mean	SD	Mean	SD	Mean	SD
HR-CTV	D ₉₀	89.1	11.71	85.1	16.75	91.5	8.4
Bladder	D _{2cc}	88.9	16.11	89.1	24.99	88.8	11.0
Rectum	D _{2cc}	81.2	12.63	86.6	19.82	78.1	6.3
Sigmoid	D _{2cc}	70.1	15.95	68.5	13.28	71.0	18.3

The mean of EQD2 of D₉₀ (HR-CTV) and D_{2cc} (OARs) based on DVH for each brachytherapy plan was shown in Table 3.1. The mean D₉₀ of HR-CTV was 89.1 ± 11.71 Gy EQD2₁₀ and within the limits of 80 – 90 Gy EQD2₁₀. The mean EQD2 of D_{2cc} for bladder, rectum and sigmoid are 88.9 ± 16.12 Gy, 81.2 ± 12.63 Gy and 70.1 ± 15.95 Gy, respectively. The mean EQD2 of D_{2cc} for bladder and sigmoid were within the limits but not for rectum. 2 patients which are patient no.7 and patient no. 9 were received mean D₉₀ of HR-CTV of 74 Gy which is less than 80 Gy (EQD2₁₀). Both of them received the same technique which are the ISBT technique. Based on Table 3.1., there are five patients who received mean HR-CTV D₉₀ that exceeds more than 90 Gy. Out of 5, 4 of them received IC/ISBT technique and the rest received ISBT technique. 7 out of 11 patients were received bladder D_{2cc} that exceeds the dose constraints of EQD2₃ more than 90 Gy. For rectum, 7 the patients received EQD2₃ of D_{2cc} dose exceeding 75 Gy. For sigmoid, there are 3 patients received EQD2₃ of D_{2cc} more than 75 Gy.

Table 3.3: Summary of CI and DHI values calculated for both IC/ISBT and ISBT techniques.

INDICES	ISBT Technique		IC/ISBT Technique	
	Mean	SD	Mean	SD
CI	0.85	0.16	0.90	0.07
DHI	0.37	0.10	0.36	0.09

Table 3.4: The ratio of D_{2cc} of OAR to D₉₀ of HR-CTV between IC/ISBT and ISBT techniques.

	Bladder	Rectum	Sigmoid
ISBT	1.047605	1.017338	0.80478
IC/ISBT	0.970947	0.854108	0.775773

Table 3.4 showed the ratio of OAR D_{2cc} to D₉₀ of HR-CTV for IC/ISBT technique is lower compared with the ratio for ISBT technique. It showed that IC/ISBT technique gave more favourable situations of higher doses to the HR-CTV while lower dose to the OARs.

Comparison of mean EQD2, CI, and DHI of HR-CTV between IC/ISBT technique and ISBT technique

The EQD2 calculation was based on the linear quadratic model (LQ) and was performed using formula in Equation 3. The α/β ratio that was used for the calculation of EQD2 of HR-CTV D₉₀ was 10. The α/β ratio is defined as a measure of the fractionation sensitivity of the cells. It indicates how resistant is the cells towards radiation damage. Cells that has high α/β ratio are less sensitive to the sparing effect of fractionation. On the cell survival plot, the high α/β ratio indicates a linear plot. A tissue that has high α/β ratio are relatively less resistant to low doses. Usually, a high α/β ratio was used to represent a high proliferating tissue such as the tumour cells. Higher α/β ratio was used because it reduces normal tissue

toxicity without significant reduction in tumour lethality [13,14]. This technique was better in delivering higher dose to the HR-CTV. This can be observed from the result of the analysis in Table 3.2. where the average of D_{90} HR-CTV for IC/ISBT technique is higher than the ISBT technique (91.5 ± 8.4 Gy of EQD2₁₀). It means that the HR-CTV received an adequate dose. As mentioned, patients who received treatment using IC/ISBT technique had a HR-CTV volume that ranged from 34.93 - 168.33 cm³. The analysis also proved that IC/ISBT technique gives higher doses to the HR-CTV with distal parametrium extension [8,15,16]. The CI for this technique was 0.90 which means that at least 90% of the HR-CTV was covered by 100% of the prescribed dose. Meanwhile, the mean DHI for this technique was 0.36 ± 0.06 . It means that only 35% of the target volume received a homogenous dose distribution. However, the mean D_{90} of HR-CTV for IC/ISBT technique slightly exceeds the dose constraints of 80 to 90 Gy EQD2₁₀. Vienna group has demonstrated that the minimum dose to the HR-CTV should be greater or equal than 87 Gy to achieve an effective local control rate [17,18]. Local control was defined as the stopping of cancer growth at the origin. Thus, to achieve better local control rate, it might be necessary for the HR-CTV to received higher doses above the constraints.

As for the ISBT technique, the mean total HR-CTV D_{90} was at 85.1 ± 16.75 Gy of EQD2₁₀ which is within the recommended dose constraints. However, out of 4 patients, 2 of them received D_{90} of HR-CTV below the dose constraints which were 74 Gy EQD2₁₀. The EQD2₁₀ dose received were not met the recommendation tolerance. One patient had a D_{90} of HR-CTV that exceeding the dose constraint of 109.4 Gy. This is because, this patient had a history of receiving boost EBRT. ISBT had become a more systematic and safe methods in treatment of cancer due to advancement of imaging method from two-dimensional (2D) to three-dimensional (3D) imaging. This is due to a superior access to the target volume and other surrounding organs making it's easier for the placement of needle inside the tumour. This technique makes it an effective method to treat larger tumour as the needles can be placed at various angles and location depending on the extent of the tumour. Based on Table 4.3, the mean DHI for the ISBT technique was 0.37 ± 0.1 which means that 37% of the target volume received homogeneous dose. Other than that, the mean CI was at 0.85 ± 0.16 . The result indicates that 85% of the target volume received 100% of the prescribed dose. The CI value was lower than the CI for IC/ISBT technique. As the DHI value was quite low, it means that the planning must be further optimised to achieve better dose homogeneity within the target volume and to reduce the non-homogenous area [7]. The further optimisation will not use the standard GrO, another advanced optimisation needed to archive higher DHI such as combination of point optimisation with graphical optimisation (PGO) or inverse optimisation known as Inverse Planning Simulated Annealing (IPSA). As mentioned before, the ideal value for CI and DHI is 1. Despite that, due to high levels of dose around the needles, it is quite not practically possible to achieve the ideal value. The study also concludes that the increase in CI values, the DHI values will be reduced [7].

Comparison of mean EQD2 dose of OAR between IC/ISBT technique and ISBT technique

The mean D_{2cc} of OAR, rectum and sigmoid met the dose constraints (90 Gy EQD2₃ and 71.0 Gy EQD2₃, respectively). However, the mean D_{2cc} of rectum (78.1 Gy EQD2₃ $\pm$ 6.3 Gy EQD2₃) slightly exceeded the dose constraints. Calculation of EQD2 of D_{2cc} of the organ at risks was performed using α/β ratio 3. For organ at risks, lower α/β ratio was used to indicate that the accumulation of multiple single hits produces increased damage for higher doses. It is said the cells with lower α/β ratio are more sensitive to the sparing effect of fractionation. For lower α/β ratio, the cell survival curve plots a greater curvature which means that increases in doses may kill more cells. Tissues with low α/β ratio are relatively resistant to low doses compared to high α/β ratio. As bladder, rectum and sigmoid are late responding tissue, they were entitled to lower α/β ratio [13,14]. The overexposure to the OAR might be necessary to ensure that the target coverage was adequate enough for an effective cancer treatment. From Figure 3.3., where the ratio of average OARs D_{2cc} with D_{90} of HR-CTV were portrayed, it can be seen that the ratio for IC/ISBT technique was indeed lower than the ISBT technique. It means that by using the IC/ISBT technique, higher doses were delivered to the HR-CTV while the dose to the organ at risks were minimised. The same pattern was seen

as the IC/ISBT technique. The mean D_{2cc} for rectum ($86.6 \pm \text{Gy EQD}_{23}$) exceeds the dose constraints for OAR. The dose constraints for bladder and rectum were well met on average. For ISBT technique, the D_{2cc} for bladder and sigmoid were at $89.1 \pm 24.99 \text{ Gy EQD}_{23}$ and $68.5 \pm 13.28 \text{ Gy EQD}_{23}$, respectively. Both well met the dose constraints on average. However, the mean D_{2cc} for rectum exceeded the dose constraints ($86.6 \pm \text{Gy EQD}_{23}$). This is probably due to the location of the rectum that are very close to the HR-CTV. Thus, it is inevitable that the rectum received higher dose compared to other organs.

Conclusion

From the study, the mean D_{90} based on calculated EQD_{210} for both techniques met the ABS recommendations in order to provide high dose to the HR-CTV. As for the organs at risk, only the mean D_{2cc} of rectum (81.2 Gy) was slightly exceeded the dose constraints for both techniques. The mean DHI value was not significantly different in both techniques. However, the IC/ISBT technique was more superior in conforming dose to HR-CTV based on higher CI value compared to ISBT alone. It is feasible to have a better knowledge of the effect of the dose to the HR-CTV and OARs by analyzing the various brachytherapy applicators and techniques. This could aid in improving the management of the cervix cancer disease.

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Declaration of competing interest

The authors declared no competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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