

Inter-institutional comparison of treatment practice for cervical cancer with special emphasis on brachytherapy

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Abstract

Purpose: To compare the cervical cancer treatment outcome and toxicities between two different institutions.

Material and methods: We analysed the clinical outcome of cervical cancer patients treated at two different centres from January 2015 to December 2016. Centre A treated 72 patients by external beam radiotherapy (EBRT) to a dose of 45 Gy in 25 fractions followed by intracavitary brachytherapy (ICBT) 6.5 Gy × 4 fractions and centre B treated 89 patients by EBRT to a dose of 50.4 Gy in 28 fractions followed by ICBT 9 Gy × 2 fractions. The local control, distant metastases and treatment toxicities were compared.

Results: The median follow-up in centre A was 12 months and in centre B was 18 months. The median overall treatment time in centre A was 52 days and in centre B was 61 days. The mean equieffective doses in 2 Gy (EQD₂) for high risk target volume (CTV_{HR}) and point A in centre A were 84.59 and 64.5 Gy, respectively. The mean EQD₂ for point A in centre B was 78.5 Gy. One patient out of 72 (1.38%) had local recurrence in centre A and five patients out of 89 (5.6%) had local recurrence in centre B. Local control in centre A was 98.6% and in centre B was 94.3%. The local recurrence rate was higher in centre B but it was not statistically significant ($p = 0.15$). One patient developed brain metastasis in centre B. One patient developed grade 3 proctitis in centre A.

Conclusions: A high dose rate brachytherapy fractionation schedule of 6.5 Gy × 4 fractions over 2 days for CTV_{HR} is associated with reduced overall treatment time, a slightly higher local control rate and lesser dose to OARs compared to 9 Gy × 2 fractions given one week apart to point A.

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Purpose

Cervical cancer is the fourth most common cancer among women and eighty percent of the cases of cervical cancer are recorded in developing countries [1]. The majority of the patients present with a locally advanced stage and hence concurrent chemoradiation is the standard of care for them [2]. Radiotherapy is administered in the form of external beam radiotherapy (EBRT) and brachytherapy (BT). The commonly used dose in EBRT is 45 Gy to 50.4 Gy at the rate of 1.8 Gy to 2 Gy per fraction over five weeks. In the era of low-dose-rate (LDR) brachytherapy there was uniformity in the dose delivery but different fractionation schedules are practised in high-dose-rate (HDR) brachytherapy. The choice of the schedule in an institute mainly depends on logistic issues such as the patient load, availability of resources and proximity of the patients to the hospital. Commonly used

HDR brachytherapy schedules are 5.5 Gy × 5 fractions, 6.5 Gy × 4 fractions, 7 Gy × 4 fractions, 7.5 Gy × 3 fractions and 9 Gy × 2 fractions. Each of these has its own advantages and disadvantages. This study is focussed on the clinical outcome of two different dose schedules used by two different institutions for cervical cancer patients.

Aim of the study was to compare the treatment outcome and toxicities between two different institutions treating cervical cancer.

Material and methods

In the present study we analysed retrospectively the treatment outcomes and toxicities of cervical cancer patients treated between January 2015 and December 2016 at centre A (medical teaching hospital located in an urban locality) and centre B (medical teaching hospital lo-

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cated in a rural locality). Patients who were treated with concurrent chemoradiation followed by intracavitary brachytherapy were included in the study. Patients who did not receive concurrent chemotherapy and patients who had interstitial implantation were excluded from the study. All patients had undergone detailed gynaecological examination, punch biopsy from the growth, complete blood count, liver function tests, renal function tests and serum electrolytes. Plain radiography of thorax and contrast enhanced computed tomography (CT) scan of the abdomen and pelvis were done to rule out distant metastases before starting the treatment.

External beam radiotherapy

In centre A all patients received EBRT of 45 Gy in 25 fractions by four field three dimensional conformal radiotherapy (3DCRT) technique using standard contouring guidelines on an Elekta Synergy linac with a 6 MV photon beam. In centre B all patients were treated on a Varian C linac with a 6 MV photon beam for a dose of 50.4 Gy in 28 fractions by parallel opposed anteroposterior fields by conventional technique. The upper border of the field was at the junction of the 4th and 5th lumbar vertebra and the lower border of the field was at the lower border of the obturator foramen or 2 cm below the vaginal extension of the disease. None of the patients underwent midline shielding or parametrial boost irradiation in both centres.

Chemotherapy

Injection of cisplatin 40 mg/m² was given weekly for three to five cycles in both centres and no chemotherapy was given during brachytherapy.

Brachytherapy

In centre A two weeks after the completion of EBRT and concurrent chemotherapy, intracavitary brachytherapy (ICBT) applicators (uterine tandem with flange and two vaginal ovoids) were inserted under spinal anaesthesia or mild sedation. CT scan simulation with 50 ml of diluted contrast in the bladder and 20 ml in the rectum without intravenous contrast was done after insertion of the applicators. Axial CT slices of 3 mm thickness were taken from the upper border of the third lumbar vertebra to the middle of the shaft of the femur. The CT images were transferred to the HDR plus treatment planning system, which uses the Task Group 43 dose calculation algorithm. The organs at risk (OARs) such as the bladder, rectum, sigmoid and high risk clinical target volume (CTV_{HR}) were contoured according to the guidelines published by Viswanathan *et al.* [3]. CTV_{HR} was defined based on the findings of examination under anaesthesia and the CT image. The dose was prescribed to CTV_{HR}. Plan was evaluated and optimized to achieve more than 80 Gy of D₉₀ (dose received by 90% CTV_{HR}) and to restrict the dose to 2 cm³ of rectum less than 4.5 Gy per fraction and 2 cm³ of bladder less than 5 Gy per fraction. Four fractions of 6.5 Gy at a 6-hour interval on two consecutive days were delivered using a Multisource remote after-

loader from BEBIG with a cobalt-60 radioactive source. In centre B, the first application of ICBT was done ten days after the completion of EBRT and concurrent chemotherapy. CT scan simulation was done without any intravenous or bladder contrast and images were transferred to the treatment planning system BrachyVision-11, which uses the Task Group 43 dose calculation algorithm. OARs were contoured and the dose was prescribed to point A, which was marked 2 cm above and lateral to the flange at the level of the cervical os. Two fractions of 9 Gy with separate plans were delivered with a one-week gap between the fractions by a Varian gamma Med plus machine with an iridium-192 (¹⁹²Ir) radioactive source. The BED (biologic effective dose) and EQD₂ (equieffective dose in 2 Gy) for both schedules were calculated using the formula $BED = nd(1 + d/\alpha/\beta)$ and $EQD_2 = BED/[1 + (2/\alpha/\beta)]$, where n is the number of fractions; d is the dose per fraction. The α/β ratios of 3 and 10 were considered for normal tissue and tumour respectively [4].

Follow-up

All patients were followed up once in two to three months up to two years. Clinical examination was done for all the patients during the follow-up visits. Biopsy and intravenous contrast CT scans were done for patients with recurrent lesions. Sigmoidoscopy was done for patients with the symptom of bleeding per rectum.

Analysis

The treatment outcome such as local control, recurrence and toxicities were listed and analyzed between the centres by the chi-square test using the statistical software SPSS version 18.0 (SPSS Inc., IBM, Chicago, USA). The values were considered to be statistically significant when $p \leq 0.05$.

Results

The patient characteristics are summarised in Table 1. Seventy-two patients were treated in centre A and eighty-nine patients were treated in centre B. The median overall treatment time in centre A was 52 days and in centre B was 61 days. The median follow-up in centre A was 12 months and in centre B was 18 months. The mean EQD₂ for CTV_{HR} and point A in centre A are 84.65 Gy and 64.50 Gy, respectively. The mean EQD₂ for point A in centre B was 78.5 Gy. The mean EQD₂ of 2 cm³ of bladder was 73.75 Gy and 77.76 Gy in centre A and centre B, respectively. The mean dose to 2 cm³ of rectum was 67.57 Gy and 71.18 Gy in centre A and centre B, respectively. One patient out of 72 (1.38%) had local recurrence in centre A and five patients out of 89 (5.6%) had local recurrence in centre B. Local control in centre A was 98.6% and in centre B was 94.3% ($p = 0.15$). Though the χ^2 test did not show any statistical significance, the recurrence rates were higher in centre B. The patients with local recurrence were treated by palliative chemotherapy in both the centres. One patient developed brain metastases in centre B and received palliative whole brain radiotherapy. One patient developed grade 3 proctitis in centre A and was

treated by argon photo coagulation therapy and none developed any rectal complications in centre B.

Discussion

This study is a retrospective reflection of two dose schedules used for cervical cancer at two different institutes. This work is an attempt to decide which fractionation of ICBT will be better based on the patient convenience, patients load and other factors peculiar to a particular cancer centre. We have also made an attempt to compare the EQD₂ of different fractionation schedules.

The process of HDR brachytherapy is elaborate in terms of the procedure, imaging, planning and multiple treatment fractions. Though MRI is superior in delineating the target in cervical brachytherapy, many centres in developing countries are unable to perform MRI-based brachytherapy because of financial constraints. Worldwide, many fractionation schedules have been used such as 5.5 Gy × 5 fractions, 6.5 Gy × 4 fractions, 7 Gy × 4 fractions, 7.5 Gy × 3 fractions and 9 Gy × 2 fractions. The image-guided intensity-modulated external beam radio chemotherapy and MRI-based adaptive brachytherapy in locally advanced cervical cancer (EMBRACE II) study aimed at achieving 65 Gy to 75 Gy EQD₂ to point A [5]. In the present study the mean EQD₂ of point A in centre A with prescription of 6.5 Gy × 4 fractions to CTV_{HR} was 64.5 Gy whereas in centre B with dose prescription of 9 Gy × 2 fractions to point A it was 78.5 Gy. Tanderup *et al.* in their study reported > 94 % of local control with D₉₀ CTV_{HR} of 85 Gy and more [6]. Johannes *et al.* in their study reported more than 95% local control when D₉₀ is greater than 87 Gy [7]. In our study the mean EQD₂ of CTV_{HR} in centre A was 84.65 Gy. Though there was no statistically significant difference we observed higher local control in centre A and centre B reported higher local recurrence. This may be because of lower EQD₂ delivered to the target with prescription of 9 Gy × 2 fractions as observed in our previously published dosimetric study on different dose prescription schedules for cervical brachytherapy [8]. Centre B also had more frequent stage III disease and overall treatment time was longer compared to centre A.

Rectum and bladder are the main dose limiting organs in the brachytherapy of cervical cancer. We have summarised the EQD₂ of different studies in Table 2 [9,10,11,12,13]. According to ICRU 89 and the American Brachytherapy Society (ABS) the recommended EQD₂ for 2 cm³ of bladder and rectum is < 90 Gy and < 75 Gy, respectively [14,15]. In the present study no major bladder or rectal toxicities were reported in either centre but the dose delivered to 2 cm³ of bladder and rectum by 9 Gy × 2 fractions was higher compared to 6.5 Gy × 4 fractions. In a retrospective study by Kazi *et al.* it was recommended to restrict the dose between 64 to 69 Gy for 2 cm³ of the rectum to avoid grade 3 proctitis [16]. Mazon *et al.* reported increased grade 3 and higher rectal complications for a dose > 75 Gy for 2 cm³ of rectum [17]. Georg *et al.* reported in their study that there is an increased probability of grade 3 rectal toxicities for a dose greater than 76 Gy to 2 cm³ of the rectum [18]. In the present study the

Table 1. Patient characteristics

Variable	Institute	
	Centre A	Centre B
Total no. of patients	72	89
Age		
Median (range)	49 (34-75)	52 (35-85)
Stage		
IB	2 (2.77%)	18 (20.22%)
IIA	4 (5.55%)	7 (7.86%)
IIB	50 (69.44%)	37 (41.57%)
IIIA	2 (2.77%)	8 (8.98%)
IIIB	14 (19.47%)	19 (21.37%)
Histology		
Squamous cell carcinoma	71 (98.62%)	87 (97.75%)
Adenocarcinoma	1 (1.38%)	2 (2.25%)
Follow-up in months		
Median (range)	12 (10-30)	18 (12-38)
Overall treatment time in days		
Median (range)	52 (49-72)	61 (54-85)

mean EQD₂ of 2 cm³ of rectum was 67.57 Gy and 71.18 Gy in centre A and centre B, respectively. Ghosh *et al.* in their study observed higher incidence of late toxicities of bladder and rectum in patients treated with 9 Gy × 2 fractions compared to 7 Gy × 3 fractions [13].

Centre A treated patients with a single application, single plan and multiple fractions whereas centre B did multiple applications with a single fraction each time with a separate plan for the second fraction. The mean overall treatment time was 52 days in centre A and 61 days in centre B. Petereit *et al.* observed that a delay in overall treatment time in cervical cancer beyond 56 days reduces the overall survival by 0.6% and pelvic control by 0.7% per day [19]. The fractionation schedule of 6.5 Gy × 4 fractions delivered in two consecutive days would be better in keeping the overall treatment time to less than 56 days.

The relatively small number of patients and shorter follow-up durations are the main limitations of this study to compare the disease status and delayed complications. The other limitations are CT-based volume delineation and comparison of CTV_{HR} prescription in one centre with point A prescription in another centre. Long-term follow-up studies are recommended to analyse the tumour control and toxicities in detail. Both 6.5 Gy × 4 fractions over two days and 9 Gy × 2 fractions over two weeks are comparable to those widely used brachytherapy schedules. In a busy institute with a shortage of resource persons and dedicated operation theatre treating with four fractions of 6.5 Gy within two days may be appropriate for better treatment compliance.

Table 2. Equieffective dose in 2 Gy of available fractionation schedules

Author No. of patients	Dose fraction- ation	Bladder 2 cm ³ (Gy ₃)	Rectum 2 cm ³ (Gy ₃)	D ₉₀ CTV _{HR} (Gy ₁₀)	Local control at 2 years	Grade 3 or higher rectal and bladder complications
Pötter <i>et al.</i> [9]						
156 patients	7 Gy × 4	86	65	93	95%	2/156
Beriwal <i>et al.</i> [10]						
44 patients	5-6 Gy × 4	79.7	57.5	83.3	88%	–
Tharvichitkul <i>et al.</i> [11]						
47 patients	6.5-7 Gy × 4	88.2	69.6	93.1	97.1%	2/47
Nomden <i>et al.</i> [12]						
46 patients	7 Gy × 4	83	66	84	93%	–
Ghosh <i>et al.</i> [13]						
62 patients	7 Gy × 3		EQD ₂ point A 74 Gy		88.5%	1/62
62 patients	9 Gy × 2		EQD ₂ point A 72.75 Gy		91.5%	
Present study						
Centre A – 72 patients	6.5 Gy × 4	73.75	67.57	84.6	95.4%	1/72
Centre B – 89 patients	9 Gy × 2	77.76	71.18	–	93.2%	

CTV_{HR} – high-risk clinical target volume, D₉₀ – dose received by 90% of the CTV_{HR}

Conclusions

A high dose rate brachytherapy fractionation schedule of 6.5 Gy × 4 fractions over 2 days for CTV_{HR} is associated with reduced overall treatment time, a slightly higher local control rate and a smaller dose to OARs compared to 9 Gy × 2 fractions given one week apart to point A.

Disclosure

The authors report no conflict of interest.

References

1. Latest Global Cancer Data. World Health Organization Press Release No 263, 12 September 2018.
2. Chemoradiotherapy for Cervical Cancer Meta-analysis Collaboration (CCCMAC). Reducing uncertainties about the effects of chemoradiotherapy for cervical cancer: individual patient data meta-analysis. *Cochrane Database Syst Rev* 2010; 1: CD008285.
3. Viswanathan AN, Dimopoulos JC, Kirisits C et al. Computed tomography versus magnetic resonance imaging-based contouring in cervical cancer brachytherapy: Results of a prospective trial and preliminary guidelines for standardized contours. *Int J Radiat Oncol Biol Phys* 2007; 68: 491-498.
4. Hall EJ, Giaccia AJ. Radiobiology for the radiologist. 6th ed. Lippincott Williams & Wilkins, Philadelphia 2006.
5. Pötter R, Tanderup K, Kirisits C et al. The EMBRACE II study: The outcome and prospect of two decades of evolution within the GEC-ESTRO GYN working group and the EMBRACE studies. *Clin Transl Radiat Oncol* 2018; 9: 48-60.
6. Tanderup K, Fokdal LU, Sturdza A et al. Effect of tumor dose, volume and overall treatment time on local control after radio chemotherapy including MRI guided brachytherapy of locally advanced cervical cancer. *Radiother Oncol* 2016; 120: 441-446.
7. Demopoulos JC, Lang S, Kirisits C et al. Dose-volume histogram parameters and a local tumor control In magnetic resonance image-guided cervical cancer brachytherapy. *Int J Radiat Oncol Biol Phys* 2009; 75: 56-63.
8. Mohan K, Revathy T, Ram C et al. Impact of different dose prescription schedules on EQD2 in high-dose-rate intracavitary brachytherapy of cervix carcinoma. *J Contemp Brachytherapy* 2019; 11: 189-193.
9. Pötter R, Georg P, Dimopoulos JC et al. Clinical outcome of protocol-based image (MRI) guided adaptive brachytherapy combined with 3D conformal radiotherapy with or without chemotherapy in patients with locally advanced cervical cancer. *Radiother Oncol* 2011; 100: 116-123.
10. Beriwal S, Kannan N, Kim H et al. Three-dimensional high dose rate intracavitary image-guided brachytherapy for the treatment of cervical cancer using a hybrid magnetic resonance imaging/computed tomography approach: Feasibility and early results. *Clin Oncol* 2011; 23: 685-690.
11. Tharavichitkul E, Chakrabandhu S, Wanwilairat S et al. Intermediate-term results of image-guided brachytherapy and high-technology external beam radiotherapy in cervical cancer: Chiang Mai University experience. *Gynecol Oncol* 2013; 130: 81-85.
12. Nomden CN, De Leeuw AA, Roesink JM et al. Clinical outcome and dosimetric parameters of chemo-radiation including MRI guided adaptive brachytherapy with tandem-ovoid applicators for cervical cancer patients: A single institution experience. *Radiother Oncol* 2013; 107: 69-74.
13. Ghosh S, Rao P. High-dose-rate orthogonal intracavitary brachytherapy with 9 Gy/fraction in locally advanced cervical cancer: Is it feasible? *J Obstet Gynecol India* 2016; 66: 452-458.

14. International Commission on Radiation Units and Measurements Report. Prescribing, recording, and reporting brachytherapy for cancer of the cervix (ICRU report 89), Bethesda 2013.
15. Viswanathan AN, Beriwal S, de los Santos JF et al. American brachytherapy society consensus guidelines locally advanced carcinoma of the cervix. Part II: High dose rate brachytherapy. *Brachytherapy* 2012; 11: 47-52.
16. Kazi S, Niladri B, Patra M et al. A retrospective study of correlation between reported dose volume parameters for urinary bladder, rectum & sigmoid colon with clinical outcome in high dose rate brachytherapy of carcinoma cervix. *IOSR Journal of Dental and Medical Sciences* 2016; 15: 14-23.
17. Mazon R, Fokdal LU, Kirchheiner K et al. Dose-volume effect relationships for late rectal morbidity in patients treated with chemo radiation and MRI-guided adaptive brachytherapy for locally advanced cervical cancer: Results from the prospective multi center EMBRACE study. *Radiother Oncol* 2016; 120: 412-419.
18. Georg P, Lang S, Dimopoulos JC et al. Dose-volume histogram parameters and late side effects in magnetic resonance image-guided adaptive cervical cancer brachytherapy. *Int J Radiat Oncol Biol Phys* 2011; 79: 356-362.
19. Peterit DG, Sarkaria JN, Chappell R et al. The adverse effect of treatment prolongation in cervical carcinoma. *Int J Radiat Oncol Biol Phys* 1995; 32: 1301-1307.