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The promise of image-guided brachytherapy of better clinical outcomes in treatment of cervical cancer: Does it deliver? An Indian scenario

Richa Tiwari [a,*], Geeta S. Narayanan [a], Vijetha Jayakumar [a], Sowmya Narayanan [b], Bhaskar Vishwanathan [a], Sanjeet K. Mandal [a], Suresh Babu [b], Ramya V. [b], Daicy George [b]

[a] Department of Radiation Oncology, Vydehi Institute of Medical Sciences and Research Centre, Bengaluru, India
[b] Department of Radiation Physics, Vydehi Institute of Medical Sciences and Research Centre, Bengaluru, India

HIGHLIGHTS

- Maximum burden of cervical cancer in developing countries like India
- Image-based brachytherapy – tumour dose escalation, sparing of normal structures
- Even in advanced stages and large tumours- excellent control rates
- One of the first review of this approach from India

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ABSTRACT

Purpose. The purpose of this series is to study the effectiveness of MRI based image-guided brachytherapy (IGBT) in Indian patients with cervical cancer who mostly present in later stages with bulky diseases.

Patients and methods. 151 cervical cancer patients treated at our institution in last four years, with definitive chemoradiation followed by MRI-based brachytherapy were reviewed. With median follow up of 26 months, Kaplan Meier estimates at two years were calculated for local control (LC), pelvic control (PC), disease-free survival (DFS) and overall survival (OS). Also, severe late sequelae were reported.

Results. The patients predominantly presented with locally advanced cervical cancer in FIGO stages IIB (53.6%) and IIIB (23.2%). Tumour dimensions at diagnosis were ≥5 cm in 56.3% and pelvic nodal involvement was found in 38.4% of the patients. 94% of the patients received curative chemoradiation. Mean HRCTV volume at the time of brachytherapy was 42.2 ± 19 cm^3 and mean cumulative dose to HRCTV was 78.9 ± 5.6 Gy. Overall LC, PC, DFS and OS at 2 years were 88.7%, 88.1%, 82.2% and 94% respectively. The predictors for local failure were FIGO stage ($p = 0.002$) and tumour size at diagnosis ($p = 0.009$). Late grade 3–4 bladder and bowel toxicities were observed in 3.8% of the patients.

Conclusion. Our review demonstrates that IGBT is an effective strategy to improve locoregional control with limited long-term sequelae in patients with locally advanced extensive cervical cancer in the setting of a developing country.

1. Introduction

With 122,844 new cases diagnosed every year- India has the largest burden of cervical cancer in southern Asia [1]. Even with its declining global incidence and improvement in control rates with widespread use of concurrent chemoradiation, India still loses >60,000 women every year to this potentially curable disease.

Brachytherapy is an integral part of definitive treatment regimen for locally advanced cervical cancer (LACC). Incorporation of image guidance in brachytherapy, especially MRI, promises significant improvement in local control. It does so by allowing individual dose adaptability and possible dose escalation to the visualized target volume while reducing dose to critical normal structures [2]. Though robustness of 3D volume-based brachytherapy in terms of better clinical response rates has been proven in many large western case series, conventional point-based brachytherapy remains the most commonly practiced form in India. We report our institutional experience with MRI-guided

* Corresponding author at: Dept of Radiation Oncology, Vydehi Institute of Medical Sciences and Research Centre, 82, Nallurahalli, Whitefield, Bengaluru, Karnataka 560066, India.
E-mail address: radiotherapy_richa4647@vimsmail.com (R. Tiwari).

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brachytherapy for treatment of cervical cancer and its clinical impact in an Indian scenario.

2. Materials and methods

151 patients of newly diagnosed cervical carcinoma treated at our institution with curative intent in last 4 years (January 2014 to August 2017) were found eligible for this retrospective analysis.

2.1. Patient & tumour specifics

The diagnostic evaluation to assess the extent of the disease included thorough clinical examination and abdomino-pelvic cross-sectional imaging either with MRI (1.5 T, Phillips Activa) or contrast enhanced CT (128 slice, Siemens Somatom) or PET/CT (Siemens Biograph mCT 128 slice). The lymph nodes were considered involved if they had any one of the following features on imaging (a) short axis diameter > 1 cm with loss of their normal shape (b) evidence of necrosis irrespective of size (c) diffusion restriction on diffusion weighted MR images (d) PET uptake present. Final staging of the disease was done in accordance to FIGO (2009) and AJCC (2017) TNM classification. Clinical and pathological characteristics of the tumour and patients are summarized in Table 1.

2.2. Treatment details

2.2.1. External beam radiotherapy (EBRT) and chemotherapy (ChT)

The initial pelvic irradiation to the primary tumour and the regional nodes was delivered by 3D conformal technique (3DCRT) or volumetric arc therapy (VMAT) to a dose of 45 to 50 Gy in 1.8–2 Gy per fraction. The primary target included whole cervix, uterus and vagina up to 2–3 cm below the inferior extent of the disease. The regional target included common iliac, external and internal iliac, obturator and presacral group of lymph nodes. Inguinal lymph nodes were also contoured when lower third of vagina was involved. Pelvic nodal boost of 5–10 Gy was allowed to positive nodes. Extended field RT was planned, in case para-aortic nodes were involved, extending up to the inferior border of 12th thoracic vertebra. Concurrent weekly intravenous infusion of cisplatin 40 mg/m^2 was administered along with EBRT. Carboplatin was used to patients who had deranged renal parameters.

2.2.2. Brachytherapy (BT)

Brachytherapy was undertaken under spinal anaesthesia after 3rd week of EBRT if the patients were suitable. After assessing the extent of residual disease under anaesthesia, appropriate MR-compatible intracavitary applicators (tandem-ovoids/tandem-ring/tandem with ring & interstitial needles/tandem with cylinder & interstitial needles) were used for the procedure. The 1st fraction of BT in all patients was planned on MRI and the subsequent fractions on CT simulated images. The planning system used for this purpose was Brachyvision system v11.1 (Varian) and Oncentra planning system v4.53 (Elekta).

All target volumes- high risk clinical target volume (HRCTV), Intermediate risk clinical target volume (IRCTV) and organs at risk (OAR)- rectum, bladder, sigmoid & small bowel were delineated according to GYN GEC-ESTRO Guidelines and recommendations I [3]. Doses to these structures were derived using manual optimization following normalization to point-A and reported following GYN GEC-ESTRO Guidelines and recommendations II [4].

Absorbed doses to these volumes were converted into radiobiological equivalent of 2 Gy per fraction (EQD2) with α/β value of 10 for tumour and 3 for organs at risk (OAR).

Dose fractionation used for BT was: 21 to 30 Gy in 3–5 fractions in one to three applications.

2.2.3. Follow up

All patients were clinically evaluated for tumour response and toxicities at 3 monthly intervals for the first two years and biannually for next three years. Radiological assessment with abdomen & pelvic MRI was done at the 3rd month follow up and yearly thereafter or earlier if clinically indicated.

2.2.4. Statistical endpoints

Local control (LC) i.e. absence of disease on clinical, radiological and histopathological (in suspicious cases) examination was our primary aim.

Secondary endpoints were pelvic control (PC), disease free survival (DFS), overall survival (OS) and severe late toxicity assessment. PC was defined as no disease either locally or regionally in pelvis, DFS as absence of loco-regional and distal evidence of disease or any death. The late toxicities were graded using CTC (Common Toxicity Criteria) v3.0.

All statistical analyses were done with the help of IBM, SPSS v20 (Chicago, IL) using the Kaplan Meier survival analysis and log rank test was used for statistical significances. Time intervals for LC, PC, DFS and OS were computed from the date of diagnostic biopsy to the date of event or the last follow-up.

3. Results

3.1. Tumour and treatment factors

Median age of presentation was 46.5 (range 26–71) years. 89.4% (135) of the patients presented with LACC (stages IIB-IVA). The squamous cell carcinoma was the most common histology reported in 94% (142) of the cases while adenocarcinoma was diagnosed in 4.6% (7). Diagnostic evaluation was done using MRI in 86% (130), contrast enhanced CT in 13.9% (21) and PET/CT in 5.2% (8) of the patients. Median size of tumour at presentation was 5.9 ± 3.6 cm. 56.3% (85) of the patients had tumour diameter ≥ 5 cm in at least one dimension on diagnostic axial MRI/CT and 39.7% (60) had ≥7 cm. 39.7% (60) of the patients had evidence of pelvic lymph node positivity and para-aortic nodes were significantly enlarged on imaging in ~10% (15) of patients.

EBRT was delivered by conformal 3DCRT in 91.4% (138) cases and by VMAT in 8.6% (18). Mean EBRT dose delivered was 46.9 Gy EQD2$_{(10)}$. 9.9% (15) of the patients received extended field EBRT and nodal boost was given in 11.2% (17). 98.7% (149) of the patients received concurrent platin-based chemotherapy and 86% (130) were able to tolerate 3 or more cycles.

Most common dose fractionation used for BT was 7 Gy for 3 fractions in 71.5% (108) of the patients. Median HRCTV volume was 42.2 cm^3 and it was >35 cm^3 in 59.6% (90). Mean cumulative dose to 90% (D90) of HRCTV volume was 78.9 Gy EqD2$_{(10)}$ and 24.5% (37) of the patients received ≥85 Gy. Combined IC-ISBT was used in 16.5% (25) of the patients

Table 1
Patient and disease characteristics.

Factor		No. of patients: N (%)
Median age in years	46.5 (range 26–71)	151
FIGO stage	IB2	02 (1.3)
	IIA	14 (9.3)
	IIB	81 (53.6)
	IIIA	11 (7.3)
	IIIB	35 (23.2)
	IVA	08 (5.3)
Histology	Squamous cell carcinoma	142 (94)
	Adenocarcinoma	7 (4.6)
	Others	2 (1.3)
Tumour size at diagnosis in centimetre (cm)	≥5 cm	89 (59)
	<5 cm	62 (41)
Nodal status	Pelvic lymph nodes+	60 (39.7)
	Para-aortic+	15 (9.9)

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