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ORIGINAL ARTICLE

Concomitant chemoradiotherapy with high dose rate brachytherapy as a definitive treatment modality for locally advanced cervical cancer

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KEYWORDS

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Abstract *Purpose:* This study aims to report the incidence of treatment-induced acute toxicities, local control and survival of patients with cervix cancer treated by external beam radiotherapy (EBR) and high-dose-rate (HDR) brachytherapy concomitant with weekly Cisplatin chemotherapy. *Methods:* Forty patients with FIGO Stages IB2 and II were treated. The mean age was 48.49 years. EBR to the whole pelvis TO 45 Gy in 25 fractions was given to all patients. A parametrial boost was given in 60% of patients, to a median dose of 9 Gy. Brachytherapy with HDR was performed during or after completing EBR with a dose of 24 Gy in four fractions of 6 Gy delivered weekly to point "A" or in some patients who were planned on MRI image guided brachytherapy with dose prescribed to high risk clinical target volume (CTV). Patient age, tumor stage, and presence or absence of comorbid conditions as diabetes mellitus, ischemic vascular disease and collagen disease

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and total dose to right and left point "A" were variables analyzed for treatment induced toxicities, survival and local control.
Cumulative biologic effective dose (BED) at rectal and bladder reference points were correlated with treatment complications in these organs.
Results: The most common acute toxicities included grade 1 and 2 fatigue (30%), diarrhea (25%), decreased neutrophil count (25%) and anemia (22.5%). Only 5% of the patients developed grade 3 rectal complications (proctitis and rectal bleeding) and 10% developed grade 1 or 2 rectal complications. Regarding urinary complications, 12.5% developed grade 1 or 2 toxicities.
Mean follow-up time was 20 months. Overall survival, disease-free survival, and local control were 100%, 92.5 %, and 95%, respectively. One patient developed bone metastases and two patients developed local relapse.
Conclusion: This study suggests that concomitant chemoradiotherapy with 45 Gy to the whole pelvis concomitant with cisplatin chemotherapy and four fractions of 6 Gy to point "A" with HDR brachytherapy is an effective and tolerable fractionation schedule in the treatment of Stages IB2 and II cervix cancer.

1. Introduction

It is estimated that 12,200 women will be diagnosed with and 4210 women will die of cancer of the cervix uteri in 2010 X CLOSE Table I-1 (http://seer.cancer.gov/scr/1975_2007/results_single/sect/sect_01_table.01.pdf). Incidence and mortality associated with cervical cancer are higher among minorities, as illustrated by the American Cancer Society Statistics. The incidence of cervical cancer for Hispanics (14.2/100,000) is almost double that for non-Hispanic whites (7.3/100,000), and 3% of cancer deaths in Hispanics are due to cervical cancer. The incidence of cervical cancer is about 30% higher in African Americans (11.5/100,000) than in whites, with about twice the mortality (5.0 versus 2.4/100,000), representing 2% of cancer deaths in African American women.[1]

Global incidence and mortality rates are even more disparate. However, there has been a 75% decrease in the incidence and mortality of cervical cancer over the past 50 years in developed countries. The cervical cancer is the second most common cause of cancer-related morbidity and mortality among women in developing countries. In 2002, in developing countries, 493,243 new cases were observed and 273,606 deaths, with a 55% mortality rate. Eighty-three percent of all cases of cervical cancer worldwide occur in developing countries, resulting in a cumulative risk of 1.5 percent for developing cervical cancer by age 65 years.[2] Approximately 70% of cervical cancers are squamous cell carcinomas (SCCs), 25% adenocarcinomas, and 3–5% adenosquamous carcinomas.[3]

The risk of metastasis to lymph nodes in patients with stages IB2 and II cervical cancer is much higher than that in patients with stage IB1 disease (30–50% versus 15–25%) and the subsequent 5 year survival rate is lower (60–70% versus 80–90%).[4,5]

Until recently, women with cancer with these stages underwent radical hysterectomy or received radiation therapy alone. To improve these incomes, chemotherapy has been added to radiation therapy. Concurrent chemotherapy with radiation treatment is now standard treatment in these stages of disease. The synergistic effect of chemotherapy and radiation therapy reduces the tumor hypoxic fraction, synchronizes cell cycles, inhibits cellular repair, and recruits non-proliferating cells into cell cycles. These effects account for the improved treatment efficacy obtained with concurrent chemo-radiation as opposed to irradiation alone.[6–10]

In 1999, the US National Cancer Institute announced its support of concurrent cisplatin-based chemotherapy and radiation therapy in women with cervical treated with radiation therapy. This was based on data from five randomized controlled trials that showed a significant benefit of concurrent chemo-radiation either as postoperative adjuvant therapy in patients with high risk factors or primary therapy in patients with locally advanced cervical cancer. All five trials utilized concurrent cisplatin either alone or in combination with 5-fluorouracil (5-FU) or 5-FU and hydroxyurea.[6–10]

Generally, radiation therapy for cervical cancer consists of a combination of external whole pelvic irradiation (ERT) and intracavitary irradiation (ICRT). The aim is to eradicate cancer in the primary site, paracervical tissue, and regional pelvic LNs.[11] ERT is given initially to decrease the bulk of the tumor, which in turns allows better geometric anatomy to allow optimal dose delivery in ICRT. ERT also covers parametrium, pelvic side wall and regional lymph nodes. ICRT is often delivered with uterine tandem and vaginal ovoids to provide a high radiation dose to the cervix tumor after it is partially shrunken by ERT. This application of ICRT has been proven by many authors to reduce the rate of local failure and to improve the survival rate compared with ERT alone: 78% versus 53% for local control[12] and 43–87% versus 21.0–60.5% for survival.[12–14]

Low-dose-rate brachytherapy has long been used,[15] but immobilization and hospitalization of patients and exposure of medical personnel to radiation have been by-products. There has been increasing use of the high-dose-rate technique in the recent years which reduces hospitalization, takes advantage of continuous reduction in size of the tumor target, allows variation in dosimetry, and reduces radiation exposure to treating personnel.[16,17] It remains difficult to compare the superiority of either methods due to lack of randomized trials, poor methodology in reporting complications, and loss of a large number of patients to follow-up in most studies.[18] In a study of approximately 2000 patients, Lorvidhaya et al.[19] reported similar survival and complications at each disease stage between patients undergoing high- and low-dose-rate brachytherapy. Conventional high-dose radiation therapy for bulky

tumors certainly results in a high rate of complications, such as rectovaginal fistula, vesicovaginal fistula, stricture ureter, and vaginal necrosis and stenosis, due to the need higher doses and/or tumor invasion.[11]

Pulsed Dose Rate (PDR) brachytherapy attempts to improve upon the unfavourable radiobiology of the high dose rate brachytherapy which delivers radiation in high fraction sizes while maintaining the ability to finely optimize dose distribution and eliminate the personnel exposure to radiation through remote afterloading. Treatment is delivered frequently, often once per hour for each treatment course. Biologically, since each fraction comes before the complete repair of the sublethal cellular damage, the tissue experience the radiation as almost continuous, mimicking LDR brachytherapy Although, this approach incorporates the biological advantage of LDR brachytherapy and the optimization advantage of the HDR brachytherapy, it also has many disadvantages including frequent treatments requiring inpatient admission for each applicator insertion, lack of applicator stabilization, and possibility of mechanical failure. Although PDR has prospered in Europe and Asia, in the USA it has floundered due to regulations by the Nuclear Regulatory Commission (NRC) that require that a physicist and/or radiation oncologist be present for each fraction, which is almost impossible to accomplish in a long schedule in a hospital setting.[20]

In spite of implementing HDR brachytherapy strategy for the treatment of cervical cancer for more than four decades, wide variations in treatment modalities including different fractionations, applicators and planning modalities still exist and subsequently the optimum treatment scheme still remains controversial. This observational study aimed to report the experience of HDR brachytherapy in the treatment of patients with cervical cancer, evaluating treatment induced toxicities and treatment outcomes.

2. Methods

2.1. Patients

From June 2008 to June 2009, 40 patients with squamous cell carcinoma of cervix were treated with definitively concomitant chemo-radiotherapy.

Clinical stage distribution of patients according to the International Federation of Gynecology and Obstetrics (FIGO) criteria was as follows: IB2 (25%), IIA (12.5%) and IIB (62.5%). ECOG Performance status ranged from 0 to 2. Nineteen of 40 patients (47.5%) had pretreatment examination under anesthesia. Mean age was 48.5 years (range from 31 to 70 years). Sixty percent of the patients had grade 2 disease, 37.5% had grade 3 disease and only one patient (2.5%) had grade 1 disease. Forty-five percent of the patients were smokers. Two patients (5%) were diabetic, one patient had Ischemic vascular disease and one patient had collagen–vascular disease.

Staging was performed in all patients through clinical examination and was complemented by abdomino-pelvic computed tomography (CT) and MRI. PET scan was not routinely used. The initial complaint of most patients was post-coital bleeding or abnormal vaginal spotting.

At presentation median hemoglobin was 11.4 (range 6.6–13.7) 10–13 gm/dl. The range was 6.6: 13.7 gm/dl group with median 11.4 gm/dl. The median white blood cell count was 7.3 K (range 2.2 –17.6 k). The median platelet count was 325 k (range 87 –670 K): The median SGOT was 20 U/dl (range 14–34) the median SGPT was 23 U/dl (range 14–55).

The mean creatinine level is 0.8 mg/dl, ranging from 0.4 to 1.1 mg/dl. All patients had normal liver function tests, sodium and potassium levels in blood and fasting blood sugar levels. No patients had HIV infection or uncontrolled co-morbidities.

No patients had prior invasive malignancy, prior radiotherapy to the region of the study cancer, initial surgical treatment, excluding diagnostic biopsy of the primary site, diagnostic laparoscopy or nodal sampling, severe, active co-morbidity, defined as follows: unstable angina and/or congestive heart failure requiring hospitalization in past 6 months, left ventricular ejection fraction $< 50\%$, transmural myocardial infarction within the last 6 months, acute bacterial or fungal infection requiring intravenous antibiotics at the time of registration, respiratory illness requiring hospitalization or precluding study therapy at the time of registration, or any uncontrolled condition, which in the opinion of the investigator, would interfere in the safe and timely completion of study procedures.

2.2. External beam radiation therapy (EBRT)

Pelvis was treated to a total dose of 45 Gy in 5 weeks with a four-field technique (*AP-PA* and lateral opposed fields), using beam energies of 10 to < 15 MV. Patients were treated once a day, 5 days a week with a fraction size of 1.8–2 Gy. Involved lateral parametrium and/or involved pelvic nodes were boosted with fields tailored to encompass known areas of disease to achieve a total parametrial dose (*including* the intracavitary treatment) of $60\,\text{Gy} + 5\%$. A minimum source-axis distance of 100 cm and a minimum source-to-skin distance of 80 cm were used.

2.3. Radiation therapy fields

2.3.1. Simulation

All treatment fields were simulated and portal verifications were done on the treatment unit. Treatment was delivered in the prone or supine position at the discretion of the treating physician. Techniques to limit irradiation of the small bowel were employed including treatment with a full bladder and selective use of a bellyboard, and use of small bowel contrast during simulation. The distal aspect of cervico-vaginal disease was marked with radio-opaque seeds or a radio-opaque vaginal tampon. Barium or another radio-opaque device was used to localize the rectum. CT scan (including treatment planning CT) or MRI was used in for treatment planning. The tumor target volume including gross nodal disease was indicated on the simulation films or digitally reconstructed radiographs if CT planning is utilized. Blocking was used in all fields to shield small bowel and femoral heads while maintaining a margin of at least 1 cm from common iliac nodes. The following borders were used:

2.3.2. AP-PA portals

Superior: One centimeter above the inferior aspect of the sacroiliac joints, extended field up to a line splitting T11-T12 were considered in selected patients.

Inferior: Transverse line below the obturator foramen or 3 cm below the most distal vaginal disease, to include the introitus if necessary.

Lateral: Two centimeter lateral to widest true pelvic diameter unless the distal 1/3 of the vagina is involved; then the inguinal lymph nodes should also be treated.

2.3.3. Lateral portals

Superior/inferior borders: Identical to AP-PA fields: Anterior border: A line drawn anterior to the symphysis pubis and at least 1 cm anterior to common iliac nodes at L4-L5.

Posterior border: A line through the posterior sacrum to include the cervical disease with a margin of 3–4 cm.

Parametrial boost: AP-PA fields with inferior and lateral borders identical to pelvic fields. Superior border was 1 cm above the inferior aspect of the sacro-iliac joints with central blocking which measured at least 4.5 cm in width at mid plane and tailored to the position of the intra-cavitary system. A Parametrial boost was performed in 24 patients (60%) with gross Parametrial invasion. Dose of Parametrial boost ranged from 3.6 to 10.8 Gy, with a median of 9 Gy.

Dose specifications: Dose was prescribed at the isocenter of the beams; the maximum and minimum doses in the target volume should be within ±5% of the dose at the isocenter.

2.4. Brachytherapy

HDR brachytherapy preferably started as early as week two, based on tumor geometry. Once HDR brachytherapy begun, at least one insertion was performed per week, with no external beam therapy or chemotherapy given on the day of the insertion. If the majority of the external beam radiation was completed, then two insertions per week could be done separated by at least 48 h in order to complete all treatment within eight weeks. Chemotherapy could be given with one HDR fraction delivered after the completion of all the external beam irradiation.

In cases of unsuitable conditions for intracavitary insertion mainly due to poor tumor geometry, HDR brachytherapy was performed after completion of EBRT. Conditions that prevented the timely initiation of brachytherapy include hysterometry not easily performed, the os not visible, the lateral extent of the tumor not be covered by effective dose, the colpostats available not be accommodated due to the tumor volume, or possibility of perforation due to the cervical canal destruction by tumor. Twenty-four Gray to point "A" in four weekly fractions of 6 Gy was planned for all patients.

The dose to points A, B, rectum, bladder were defined as follows: point "A"*:* The point 2 cm along the intrauterine tandem from the cervical os or flange of the tandem and then 2 cm laterally in the plane of the intra-cavitary system. *Point "B":* The point 5 cm lateral from a point 2 cm vertically superior to the cervical os or flange of the central tandem along the patients' midline. *Bladder Dose:* the point in the center (in the superior–inferior plane) of a contrast-filled balloon of a Foley catheter and closest to the applicator system on a lateral view, as defined by ICRU 38. *Rectal Dose:* the dose at a point 0.5 cm posterior to the vaginal ovoid or vaginal packing in the lateral projection, defined by ICRU 38.

HDR brachytherapy was applied using an Iridium-192 source (Ir-192) with nominal activity of 10 Ci. The applicator system consisted of an intrauterine tandem with three different angles and paired colpostats (Fig. 1). Types of colpostats were selected based on the individual's anatomy. Tandem and ring applicators were used in some patients (Fig. 2).

Figure 1 The applicator system consisted of an intrauterine tandem with three different angles and paired colpostat.

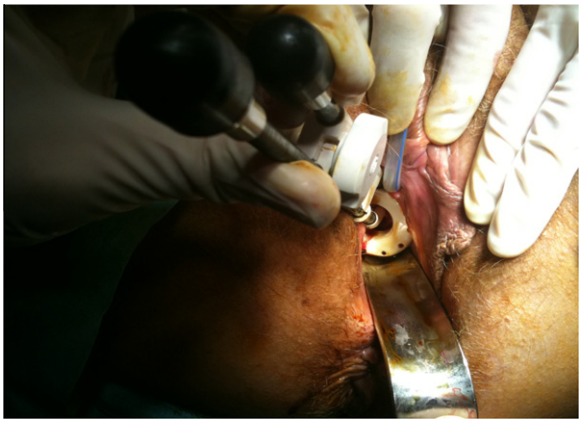

Figure 2 Tandom and ring application.

During each insertion, whenever possible, a rectal retractor and an anterior vaginal packing were used to maximize the distance between the sources and the anterior rectal wall and posterior bladder. When the placement of rectal retractor was not possible, both the posterior and anterior vaginal walls were packed with radio-opaque gauze to reduce rectal and bladder doses and to visualize the posterior vaginal septum.

HDR brachytherapy dosimetric planning was performed using PLATO system developed by Nucletron. Orthogonal films were taken to verify the placement of the applicators and to perform the dosimetric plan. The prescribed dose was computed to point "A". Based on linear quadratic model, biologic effective dose (BED) to point "A", resulting from contribution of EBRT and HDR brachytherapy, was determined for all patients, using a tumor α/β value of 10. The rectal and bladder reference points were determined according to the International Commission of Radiation Units and Measurements (ICRU), Report 38, guidelines for rectal and bladder doses. Total BED at rectal and bladder reference points were determined by adding the components of EBRT and HDR brachytherapy, with an α/β value of 3, which is used for late-responding tissues.

MRI image guided brachytherapy planning based on GEC ESTRO Guidelines were used in four patients. The dose was prescribed to High Risk CTV and Intermediate Risk CTV based on the initial tumor burden shown in pre-treatment MRI and the residual tumor burden shown in Post-External Beam Radiation Therapy MRI. (Fig. 3).

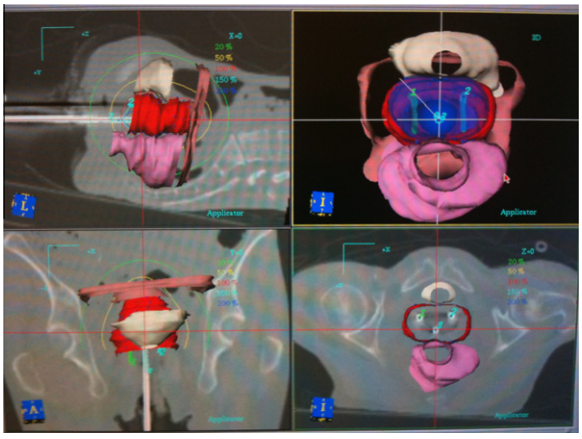

Figure 3 Different view for plan evaluation.

PLATO planning system was used in planning all the cases. Dose volume histograms (DVH) were used for plan evaluation with ultimate goal of delivering 85 Gy to High Risk CTV and 60 Gy to Intermediate Risk CTV while delivering less than 100% of the prescribed dose to less than 2 cc of Organs At Risk (OAR) which were considered to be the rectum, bladder and sigmoid. As per our predesigned clinical protocol; the dose was recorded in all patients to point "A" right, point "A" left, point "B" right, point "B" left, bladder and rectum.

2.5. Chemotherapy

All patients underwent cisplatin chemotherapy concurrent with Radiation Therapy. The cisplatin was administered weekly for 5 or 6 weeks with dose 40 mg/m^2. Before chemotherapy administration, physical examinations, complete blood counts, and liver and renal function tests were performed. If the absolute neutrophil count was $<1500/mm^3$ or the platelet count was $<75{,}000/mm^3$, chemotherapy was delayed or interrupted until the patient recovered. Patients were prehydrated with two liters of D5/1/2 NS and 40 mEq KCL or NS. Cisplatin was given over 30–60 min followed by 1L of D5/1/2/NS. At least three liters of fluids over the ensuing 24 h either parenterally or orally was delivered.

Acute treatment-related toxicities, measured from the initiation of chemo-radiotherapy to 3 months after completion, were assessed using patient history, physical examination findings, and complete blood count results, using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.1.

2.6. Follow-up

Patient follow-up was performed every 3 months. Clinical examination and cervical cytology were taken at each follow-up. Chest radiograph and abdomino-pelvic CT were done every 6 months. Local recurrence was defined as disease was detected centrally or in the parametrium within the true pelvis.

Recurrences were defined as distant if they occurred in the para-aortic lymph nodes or elsewhere outside the pelvis. Follow-up time was defined by the interval between the first day of radiotherapy and the last information about the patient. Patients considered lost to follow-up were those known to be disease free when last seen and who did not return for their scheduled follow up visits.

3. Results

The total doses delivered to point "A" and B on the left and right are listed in Table 1. As the dose and the number of fractions of HDR brachytherapy were the same for all patients, the variation of BED to point "A" was due to the different doses of EBR and applicators positioning. Table 1 summarizes the doses delivered to these reference points.

Total BED at rectal and bladder reference points were determined by adding the components of EBRT and HDR brachytherapy, considering an α/β value of 3, which is used for late-responding tissues. The rectal point ranged from 5884.109 cGy to 7377.72 cGy, with a mean of 6198.22 cGy, and the total dose at the bladder point ranged from 6288 cGy to 8297.7 cGy, with a mean of 7090.26 cGy.

Median follow-up time for all patients was of 20 months (range 8–28 months, mean 19.5 months). At the time of this analysis, 37 patients (92.5%) were alive with no evidence of disease, one patient (2.5%) was alive with distant metastasis, two patients (5%) was alive with local recurrence, and none of the patients died due to either recurrent or inter-current disease nor complications. (Table 2).

Overall survival and disease-free survival at a mean of 20 months for all patients was 100% and 92.5%, respectively. Local control was continued until the time of the analysis in 38 patients (95%). Two patients (5%) developed recurrent disease and one patient out of forty patients (2.5%) developed distant metastases. Bone was the site of distant metastases. Table 3 shows the patterns of failure.

3.1. Treatment induced complications

The most common reported side effect was fatigue that was experienced by 30% of the patients. Grade 1 or 2 anemia and neutropenia were present in 22.5% and 25% of the patients. Grade 1/2 vomiting was reported in 22.5% of the patients that was tolerated and most probably related to chemotherapy administration. Diarrhea was of significant impact – Grade 3/4 – in 5% of the patients while Grade 1/2 diarrhea was reported in 20% of patients.

Table 1 Dose delivered to ICRU 38 reference points.

	Point "A" right total dose	Point "A" left total dose	Point "B" right total dose	Point "B" left total dose
Mean	85.15	85.58	63.08	63.72
STD	1.65	2.21	2.58	3.45
SEM	0.26	0.35	0.41	0.54
Median	85.13	85.13	63.50	62.30
Range	80.1: 90.0	80.1: 90.3	57.7:69.1	58.8:73.8

Table 2 Follow up.

Patient status at analysis	Number of patients	Percentage (%)
Alive without disease	37	92.5
Alive with distant disease	1	2.5
Alive with local recurrent disease	2	5
Died of recurrent/ intercurrent disease	0	0
Died of complication	0	0
Total	40	100

Table 3 Pattern of failure.

Patterns of failure	Number of patients	Percentage (%)
Local failure	2	5
Distant metastases	1	2.5
Both	0	0
Total	3	7.5

Regarding rectal complications; two patients – 5% – developed grade 3/4 proctitis that led to grade 3/4 rectal bleeding that required medical intervention while four patients – 10% – had Grade 1/2 proctitis that led to grade 1/2 rectal bleeding. Five patients – 12.5% – reported grade 1/2 urinary frequency that was correlated to the effect of radiation on urinary bladder. The total BED to rectum and bladder reference points at different levels was the predictive factor analyzed for incidence of treatment induced complications in rectum and bladder, respectively (see Table 4).

4. Discussion

This study aimed to determine the feasibility and tolerance of Intracavitary High Dose Rate brachytherapy after External Beam Radiotherapy to the pelvis with or without Para-aortic region combined with weekly cisplatin. The target population was female patients diagnosed with Stage IB2 and Stage II cervical cancer that is confirmed histopathologically and assigned for concomitant chemoradiotherapy definitive treatment.

Concomitant radiotherapy and platinum-based chemotherapy is the standard of care for patients with locally advanced cervical. Based on randomized studies that showed a 12% benefit of the addition of chemotherapy to radiotherapy, this combination has been implemented since 1999.[21]

Chemoradiotherapy reduced local and distant recurrence and progression and improved disease-free survival. There was a suggestion of a difference in the size of the survival benefit with tumor stage, but not across other patient subgroups. Acute hematologic and GI toxicity was increased with chemoradiotherapy, but data were too sparse for an analysis of late toxicity. There is no solid data regarding increased late toxicity after chemoradiation compared with radiotherapy alone.[22–24]

This study included 40 patients in total who were treated with High Dose Rate brachytherapy after External Beam Radiotherapy concomitant with Cisplatin Chemotherapy.

All the patients had thorough laboratory evaluation prior to treatment start that included Complete Blood Picture, Renal Function Tests, Liver Function Tests, Fasting Blood Glucose and Electrolytes.

All the patients had pretreatment MRI for accurate evaluation of tumor topography. Some of the patients had pretreatment PET scan in the suspicious cases.

Initial whole pelvis treatment to both groups ranged from 44 to 50 Gy. The parametrial boost to patients in both groups was usually according to initial parametrial infiltration or residual gross disease after whole pelvis external beam radiation therapy. Whole pelvis External Beam Radiation Therapy was the standard as per the predesigned protocol of this study. Para Aortic Field was used only if histopathologically confirmed Para Aortic LN involvement in the PDR arm and for PET positive Para Aortic LN in the HDR arm.

All the patients received weekly concomitant chemotherapy cisplatin 40 mg/m^2. Chemotherapy was well tolerated and was not interrupted in any of the patients. All the patients in both treatment groups had Partial Response after External Beam Radiation Therapy concomitant with chemotherapy. The most common system still in use for treating cervical cancer with brachytherapy is the Manchester system. Using this system, it was recognized that cervical cancers with larger primary tumors and higher International Federation of Gynecology and Obstetrics (FIGO) stage require higher doses of radiation to point "A" for locoregional control[24] in comparison with lower stages.

Conformal brachytherapy has been made possible with advances in both imaging and treatment delivery technology. It is now possible to locate and assess tumor bulk using magnetic resonance imaging (MRI).25 This provides the ability to accurately estimate the tumor volume with MRI.[26,27]

Radiotherapy and in particular brachytherapy (BT) have been major treatment modalities for cervical cancer for 100 years. Despite major breakthroughs in other areas of BT, there has been, until relatively recently, little technological development in gynaecological BT. BT in cervical cancer is still widely based on 2D X-ray imaging, limited individualization, and prescription of dose according to point "A". We believe that brachytherapy practice is very diverse across different countries and institutions. However, in the late 1990s MR image guided BT (IGBT) was initiated,[28,29] and recommendations from the GEC-ESTRO working group introduced MRI-based target concepts and 3D dose volume evaluation and reporting.[30,31] Implementing MRI image guided brachytherapy into practice have significantly improved the possibilities to optimize, to record and report doses in a reproducible way as already demonstrated in a number of institutional reports.[28,32,33]

A common language has been developed that allows different BT traditions to communicate. Important steps and challenges in MRI-based IGBT have been investigated and described in several publications with regard to: contouring,[34–36], dose optimization[28,32,34,37,33,36] and applicator reconstruction.[38–43]

Based on the clinical experience collected so far, the MRI-based IGABT approach is expected to have a major impact on the clinical outcome with a concomitant decrease in the rates of both local failure and morbidity.[44]

With the introduction of an MRI-based target concept it is possible to move from prescription at point "A" to prescription of dose to a 3D target volume in terms of dose volume histogram (DVH) parameters. Furthermore, dose optimization can be performed based on MR image guidance, whereby

Table 4 Treatment induced toxicities.

Toxicity	Grade 1/2		Grade 3/4	
	Crude incidence	Percentage (%)	Crude incidence	Percentage (%)
Anemia	9	22.5	–	–
Neutropenia	10	25	–	–
Diarrhea	8	20	2	5
Vomiting	9	22.5	–	–
Fatigue	12	30	–	–
Rectal bleeding	4	10	2	5
Proctitis	4	10	2	5
Urinary frequency	5	12.5	–	–

standard loading patterns are modified to come to an individually sculpted pear-shaped isodose which is tailored to target and organs at risk at the time of BT.[45]

In the process of moving from 2D (X-ray and standard loading) to 3D (MRI) target definition and dose optimization it is essential to relate the classical dose prescription and standard loading patterns to the new routes of 3D dose prescription and dose optimization. In our study we assessed the relation between point doses and 3D DVH parameters that resulted in statistically significant differences in all the reference point doses "Points A right, A left, B right and B left" and to evaluate the improvement of DVH parameters when applying MRI-based IGBT and its impact on treatment toxicity and outcome that revealed better toxicity profile when applying the MRI image guided brachytherapy and similar treatment response including Response Rate, Disease Free Survival and Overall Survival.

In this study, tandem and ovoid applicators were used in most of the HDR applicators. A tandem and ring applicator was used in few cases according to the tumor geometry and availability. The tandem and cylinder was never applied.

MRI image guided brachytherapy planning based on GEC ESTRO Guidelines were used in few patients. The dose was prescribed to High Risk CTV and Intermediate Risk CTV based on the initial tumor burden shown in pre-treatment MRI and the residual tumor burden shown in Post-External Beam Radiation Therapy MRI.

PLATO planning system was used in planning all the cases. Dose Volume Histograms – DVH – were used for plan evaluation with ultimate goal of delivering 85 Gy to High Risk CTV and 60 Gy to Intermediate Risk CTV while delivering less than 100% of the prescribed dose to less than 2 cc of Organs At Risk "OAR" namely; Rectum, Bladder and Sigmoid. As per our predesigned clinical protocol; the dose was recorded to point "A" right, point "A" left, point "B" right, point "B" left, bladder and rectum.

Regarding the treatment induced hematological toxicities; the treatment was well tolerated where 77.5% of all the patients did not experience any grade of anemia during the treatment. Seventy-five percent of all the patients did not experience any grade of neutropenia during the treatment. Regarding platelets count, 98.75% of all the patients did not experience any grade of thrombocytopenia during the treatment.

Twenty percent of the patients reported a grade 1/2 diarrhea compared to only 5% experienced grade 3/4 diarrhea. Thirty percent of the patients had fatigue and 22.5% had vomiting. Four patients experienced grade 1/2 rectal hemorrhage compared to only two patients who had grade 3/4.

Our results are comparable to those reported in two randomized trials conducted by the Gynecology Oncology Group[7,9] and in the study of the National Cancer Institute of Canada Clinical Trials Group (NCIC CTG).[46] In the study by Rose et al.[9] grade 3 and 4 leukopenia occurred in 21% and 2% of patients, grade 3 and 4 GI toxicity in 8% and 4% patients, and genitourinary grade 3 and 4 adverse effects occurred in 3% and 2% of patients, respectively. In the trial by Keys et al.[7] using preoperative EBRT and brachytherapy combined with weekly cisplatin, grade 3 and 4 hematologic toxicities were observed in 18% and 3% of patients and GI toxicities in 9% and 5% of patients, respectively, compared with 2% moderate hematologic and 2% and 3% moderate and severe GI toxicity, respectively, in the group assigned to RT alone. These adverse effects were almost exclusively transient.

In the trial by Pearcey et al.[46] the significant (grade 3 or worse) acute side effects, most commonly GI, hematologic, and genitourinary toxicity, were observed more frequently but still occasionally in the combined modality arm and this was not associated with clinically important treatment delays. In our study, we report better toxicity profile that is most probably correlated to the advanced conformal brachytherapy utilized in this study and the improvement in planning and sparing of Organs at Risk. There might be an element of potential underreporting of some toxicities owing to some files based data collection.

Good tolerance of concurrent cisplatin and RT has also been reported in smaller series.[47–49] Malfetano et al.[47] combined weekly cisplatin at a dose of 1 mg/kg (up to 60 mg) with extended-field RT (including para-aortic lymph nodes) and brachytherapy. Administration of cisplatin (mean five cycles, range one–six) was accompanied by minimal morbidity (no grade 4 neutropenia or thrombocytopenia) and no nephrotoxicity, ototoxicity, or neurotoxicity. Of 67 patients, 10 had their chemotherapy withheld secondary to leukopenia. RT was not interrupted in any patient. Boronow[48] observed no Grade 4 hematologic toxicity during postoperative chemoradiotherapy with cisplatin (20 mg/L/24 h for a 96-h infusion during weeks 1, 4, and 7) and extended-field RT. All patients completed their treatment schedule without breaks. Omura et al.[50] observed only occasional Grade 3 or 4 hematologic, GI, and renal toxicity (0.7%, 0.7%, and 1.5%, respectively) in the group of patients treated with RT and cisplatin (50 mg/m^2 every 3 weeks, up to six cycles). In their study, Grade 1–3 neurotoxicity (both peripheral and central, all reversible) occurred in 5% of patients. In another study, RT with concurrent cisplatin (50 mg/m^2 every 10 days) was accompanied by Grade 4 acute

bowel toxicity in 1 of 60 locally advanced cervical cancer patients.[53]

A review of treatment induced acute toxicity included 4590 cervical cancer patients enrolled in 19 randomized trials, of which 12 used platinum based chemotherapy revealed on average GI and genitourinary toxicity incidence of grade 3 and 4 (8.0% and 1.5%, respectively) that is considerably higher to the respective figures in our study, same for grade 3–4 leukopenia (16.4%) and thrombocytopenia (1.7%) that occurred more frequently.[52]

Hypomagnesemia caused by enhanced renal excretion of magnesium is reported as cisplatin induced toxicity. These sequelae may lead to secondary hypocalcemia with subsequent tetany symptoms. Hypomagnesemia is reported in up to 90% of patients if no corrective measures are undertaken. However, the clinical relevance of this finding remains uncertain.[53] grade 3 and 4 hypomagnesemia, possibly accompanying cisplatin administration, was reported in 3 of 176 patients treated in the GOG trial.[9] In this trial, hypomagnesemia occurred in 48% of patients assigned to RT and weekly cisplatin. However, in our study pretreatment serum electrolyte assay did not included magnesium measurements, myoclonia after cisplatin infusions was never reported.

The short follow-up for most of the patients analyzed in this study – median of 20 months – did not allow for a reliable assessment of late toxicity. No apparent difference in late adverse effects between RT alone and RT plus weekly cisplatin was reported in either the GOG trial[7] or the NCIC CTG trial.[46]

In the former, the most common Grade 3 and 4 side effects were those from large bowel or rectum, small bowel, and bladder. In the study by Pearcey et al.[51] the most common was genitourinary toxicity, but, again, no statistically significant difference was found in the incidence of late effects between the two arms. No increased risk of late complications associated with the addition of cisplatin and 5-fluorouracil to RT was also reported in a Radiation Therapy Oncology Group study, although acute toxicity was much greater in the patients who underwent chemoradiotherapy.[8]

The median follow up that was 20 months in the HDR arm shows three patients failed during the follow up; two local failures and one distant metastasis were. There was no statistical significant probability of correlation between total dose delivered to point ''A'' and treatment failure.

In an analysis that included 141 patients with cervix cancer (stages IB–IVA) treated with 45–50.4 Gy EBRT ± cisplatin plus 4_7 Gy IGBT. Gross tumour volume (GTV), high risk clinical target volume (HR CTV) and intermediate risk CTV (IR CTV) were delineated and DVH parameters (D90, D100) were assessed. Groups of patients were formed according to tumour size at diagnosis (GTVD) of 2–5 cm (group 1) or >5 cm (2), with subgroups of the latter for HR CTV size at first IGBT 2–5 cm (2a) or >5 cm (2b). Eighteen local recurrences in the true pelvis were observed. Dose–response analyses revealed a significant effect of HR CTV D100 ($p = 0.02$) and D90 ($p = 0.005$). The authors concluded that significant dependence of local control on D100 and D90 for HR CTV was found. Tumour control rates of $>90\%$ can be expected at doses >67 Gy and 86 Gy, respectively.[54] This data is relevant to our findings where we had 92.5% local control of tumor over a median follow up of 18 months.

So far, no solid data on statistically significant large population and long term follow up is available for the MRI image guided brachytherapy in cervical cancer. Further data on dose volume relationships in cervical cancer radiotherapy are expected from an ongoing prospective multicentre study on MRI-guided BT in cervical cancer: EMBRACE (www.clinicaltrials.org, www.embracestudy.dk). This study will hopefully for the first time make it possible to reach a critical mass of patients which will be large enough to obtain credible data on key volumetric, dosimetric, clinical and biological parameters.

Another important factor that might be contributing to treatment outcome is the tumor molecular profiling and its impact on treatment response, disease free survival and overall survival. Being able to predict which patients are likely to have a recurrence after standard therapy through tumor molecular profiling and biomarker studies is likely to improve overall outcome in these patients by helping to select those who may benefit from individualized targeted therapies.

Nuclear factor kappa B (NF-κB) is a transcription factor whose role in the pathogenesis of a wide variety of tumor types including cervical cancer has been well described.[55–57] Cumulative evidence suggests that this protein functions as a mediator of cellular survival, inflammation, angiogenesis, and treatment resistance through regulation of the transcription of over 200 target genes. Nuclear factor kappa B has recently become a major target for cancer drug development, as shown by the many nonspecific natural and synthetic compounds shown to exert their therapeutic effects at least in part through the inhibition of NF-κB.[58,59] Furthermore, recent preclinical and clinical studies that combine these agents with radiation and chemotherapy have shown promising results.[58–60]

The role of NF-κB as a potential prognostic biomarker has only recently been explored. In several cancers including breast, prostate, skin, lung, and pancreas, NF-κB nuclear expression has correlated with poor clinical outcome.[61–65]

Recently, eighteen patients with locally advanced cervical cancer were enrolled in a study in which cervical biopsy specimens were obtained before radiation therapy and 48 h after treatment initiation. Matched biopsy specimens from 16 of these patients were available and evaluated for the nuclear expression of NF-κB protein by immunohistochemical staining. After a median follow-up of 43 months, there were nine total treatment failures. Nuclear staining for NF-κB was positive in 3 of 16 pretreatment biopsy specimens (19%) and 5 of 16 postradiation biopsy specimens (31%). Pretreatment expression of NF-κB nuclear staining correlated with increased rates of local–regional failure (100% versus 23%, $p = 0.01$), distant failure (100% versus 38%, $p = 0.055$), disease-specific mortality (100% versus 31%, $p = 0.03$), and overall mortality (100% versus 38%, $p = 0.055$).[66]

The authors suggested that pretreatment nuclear expression of NF-κB may be associated with a poor outcome for cervical cancer patients treated with chemoradiation. Although these data require validation in a larger group of patients, the results support the continued study of the relationship between NF-κB and outcome in patients treated for carcinoma of the cervix.[66] Unfortunately, our study did not put into consideration the molecular profiling of the enrolled patients; however we will be strongly endorsing future research and clinical trials in this direction.

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