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Clinical Outcomes and Toxicity of CT-guided High Dose-rate Brachytherapy in Women With Locally-advanced Cervical Cancer

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Abstract. *Background/Aim: To evaluate the outcome and toxicities in patients with locally advanced cervical cancer (LACC) treated with radiochemotherapy and intracavitary brachytherapy. Patients and Methods: This study included 67 patients with LACC treated between 2010 and 2018. The most represented stage was FIGO IIB. The patients were treated with external beam radiotherapy (EBRT) to the pelvis and boost to the cervix and parametrials. Concomitant chemotherapy (CHT) with cisplatin (CDDP) 40 mg/mq was planned. Subsequently, the patients underwent CT-based endouterine brachytherapy (BT). The response was evaluated at 3 months with PET-CT and/or pelvic magnetic resonance imaging (MRI). Since then, the patients have been followed with clinical instrumental controls every 4 months for the first 2 years and every 6 months for the following 3 years. Local response was assessed with pelvic MRI and/or PET-CT scan at the end of intracavitary BT) according to RECIST 1.1 criteria. Results: The median duration of treatment was 55 days (range=40-73 days). The prescription dose to the planning target volume (PTV) was delivered in 25 to 30 (median 28) daily fractions. The EBRT median dose to the pelvis and gross tumor volume were 50.4 Gy (range=45-56.25) and 61.6 Gy (range=45-70.4), respectively. The 1-year, 2-year, 3-year, and 5-year overall survival rates were 92.44%, 80.81%, 78.84%, and 76.45% respectively. The actuarial 1-year, 2-year, 3-year, and 5-year disease-free survival rates were 89.5%, 83.6%, 81%, and 78.2% respectively. Conclusion: This study analyzed acute and chronic toxicity, survival, and local control in cervical cancer patients treated with IMRT followed by CT-planned high dose rate-brachytherapy. Patients demonstrated satisfactory outcomes and incidence of acute and late toxicities.*

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With about half a million cases/year, cervical cancer is the seventh most common cancer in the world. In the least developed countries, the incidence rate is doubled compared to the most developed countries (1). Squamous cell carcinoma (SCC) accounts for about 80% of cervical cancers, while most of the remaining histologies are adenocarcinomas. Brachytherapy (BT) as a boost to external beam radiotherapy (EBRT) is the gold standard in the management of locally advanced cervical cancer (LACC) and significantly improves survival (2-4). However, it can be considered as an alternative to surgery even in the early stages of IB-IIA, as suggested by two significant randomized

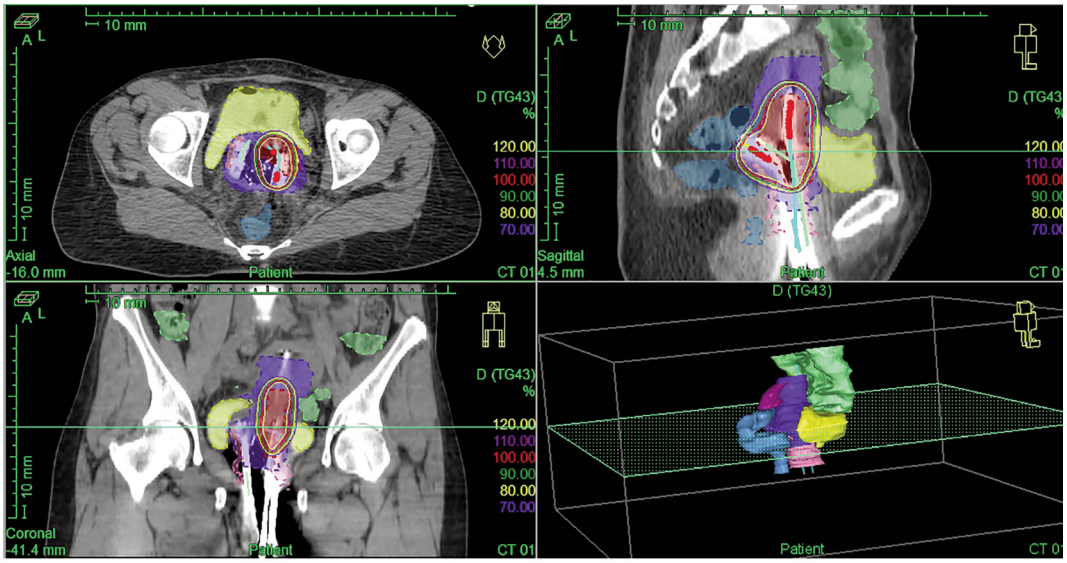

Figure 1. *Representative BT plan dose distribution with Oncentra Brachy (version 4.5.3).*

studies (5, 6). In the modern literature, clinical use of three-dimensional image-guided brachytherapy (3D-IGBT) has been rising (7, 8). 3D-IGBT enables evaluation of the dose–response relationship with the use of dose–volume histogram (DVH) parameters. Due to the use of both computed tomography (CT) and magnetic resonance imaging (MRI), treatment planning drastically shifted to 3D optimization, allowing improved tumor control and a decreased dose to the organs at risk (OARs).

The purpose of this retrospective mono-institutional study was to assess outcome, toxicity, and different prognostic factors in patients with LACC treated with EBRT and intracavitary endouterine high dose rate (HDR) brachytherapy.

Patients and Methods

Patient population. We analyzed all patients with LACC treated with definitive pelvic EBRT with or without concurrent chemotherapy followed by CT-guided HDR intracavitary BT boost at our institution between 2010 and 2018. Tumor characteristics such as histological type and stage have been recorded according to the International Federation of Gynecology and Obstetrics (FIGO) (9). Bulky disease was considered with large tumor diameter greater than 50 mm. Standard imaging staging workup included total body CT scan or positron-emission tomography (PET)/CT and MRI. All patients signed informed consent prior to treatments.

EBRT. All patients underwent CT-based planning in the supine position with a customized immobilization system. The clinical target volume (CTV) included the gross tumor volume (GTV-intended as a clinically visible disease site in available imaging), the uterus, bilateral ovaries, bilateral parametria, superior third of the vagina, presacral region, and common, internal, and external iliac lymph nodes. The lomboaortic lymph node tract was inserted into the CTV when clinically appropriate and treated with an extended-field technique. The CTV was enlarged by an 5-7 mm isotropic margin to the planning target volume (PTV). The OARs considered were the anus and rectum, bladder, both femur, bowel, both kidney, and spinal cord. Treatments were planned with the Eclipse 4.5.5 (Varian Medical Systems, Palo Alto, CA, USA) treatment planning system and delivered by Varian linear accelerator using photons with a nominal energy of 15 MV. All patients underwent image-guided radiotherapy (IGRT) using a cone-beam computed tomography (CBCT) system as daily pretreatment imaging. Any observed set-up error ≥2 mm was corrected prior to treatment. Patients were treated using intensity modulated radiation therapy (IMRT) or 3-dimensional conformal technique (3DRT). When clinically indicated, patients received a boost to the cervix and/or lymph nodes with clinical evidence of involvement using a simultaneous-integrated boost (SIB) or sequential technique.

HDR-BT. MRI was performed after completing EBRT to assess the radiologic response in all patients. T2-weighted axial acquisition was chosen to better draft the target volumes. HDR-BT was performed using a tandem-and-ovoid intracavitary device with a source of iridium-192. The applicator insertion was done in a lithotomy position. Foley's catheter was inserted into the urinary bladder and the bulb was inflated with 5 cc saline. After a thorough pelvic examination, uterine sounding was done, and the length of uterine cavity was measured. A CT compatible applicator consisting of a central tandem and two ovoids (Nucletron, Elekta AB, Stockholm, Sweden) was inserted. Adequate vaginal packing with roll gauze was done to increase the distance between applicator and OARs. The applicator was immobilized with T-bandage. CT-based treatment planning was applied for BT treatment by acquisition of 2.5 mm thicker slice, using a customized immobilization system. Oncentra (version 4.5.3) treatment planning system was used for dosimetric calculations and treatment. One radiation oncologist specialized in gynecologic malignancies contoured all fractions for

Table I. *Patient and tumor characteristics*.

Age	
Median	57 y (29-83)
Stage	
IB	5 (8%)
IIA	4 (6%)
IIB	30 (44%)
IIIA	6 (10%)
IIIB	6 (10%)
IIIC	7 (9%)
IVA	5 (8%)
IVB	1 (2%)
Histology	
Adenocarcinoma	10 (15%)
Squamous	52 (77%)
Papillary serous	1 (2%)
Other	4 (6%)
Tumor diameter	45 mm (19-87)
Bulky tumor	
Yes	14
No	53
Lymph node involvement	
Negative	41 (61%)
Positive	26 (39%)
Chemotherapy	
Cisplatin	53 (79%)
Other	3 (5%)
None	11 (16%)

all patients. The high-risk clinical target volume (HR-CTV) and OARs were contoured on the planning CT according to the GEC-ESTRO guidelines (10, 11). For patients achieving local complete radiological response after EBRT, the HR-CTV was defined as the whole cervix. For patients having residual tumor after EBRT, the HR-CTV included the residual GTV and the whole cervix. The OARs included the rectum, sigmoid colon, urinary bladder, and bowel. The median prescribed dose was 21 Gy (range=10-28 Gy) in 2 to 4 fractions. The most used scheme was 21 Gy in 3 fractions. The prescribed doses were tailored for each patient with the aim of a dose to the OAR-adapted approach, respecting the prescribed oncological dose to the tumor using the ICRU (International Commission on Radiation Units and Measurements) recommendations. The total combined EBRT and brachytherapy doses to CTV and OARs were converted into the 2-Gy equivalent doses (EQD2) using the linear quadratic model (α/β=10 for HRCTV and α/β=3 for OARs) and recorded. Figure 1 shows a representative dosimetric of dose distribution.

Toxicities and follow-up. Acute and late toxicities were reported according to the Radiation Therapy Oncology Group (RTGOG) and the European Organization for Research and Treatment of Cancer scoring system (EORTC) every week during EBRT and HDRBT, 5-6 weeks and 3 months after treatment completion (12). Sexual late toxicities were scored after a minimum 6-month follow-up period according to the Symptoms, Objective, Management, Analytic (SOMA) scoring system (13). All patients were followed by the radiation therapist, medical oncology physician and gynecologist during and after therapy. Local response was assessed with pelvic MRI and/or PET-CT scan at the end of intracavitary BT according to RECIST 1.1 criteria (14). Patients were followed-up with clinical examinations, blood tumor markers, and pelvic MRI performed at 2 months from the end of BT, every 3 months for the next 2 years, and every 6 months for the next 3 years.

Table II. *Treatment characteristics*.

Characteristic	Median (range)
EBRT dose, Gy,	61.6 (45-70.4)
EBRT fractions	28 (25-30)
EBRT technique, n (%)	
IMRT	49 (73%)
3DCRT	18 (27%)
BT prescription dose, Gy	21 (10-28)
BT fractions	3 (2-4)
Total days of treatments	55 (40-73)
Days from EBRT to BT	7 (3-28)

3DCRT: Three-dimensional Conformal Radiotherapy; BT: brachytherapy; EBRT: external-beam radiotherapy; IMRT: intensity-modulated radiotherapy.

Statistics analysis. Statistical analysis was performed using the SPSS statistical software package version 13.0 (SPSS, Chicago, IL, USA). OS was calculated from the date of diagnosis to the date of death from any cause or the date of the last follow-up. Disease-free survival (DFS) and metastasis-free survival (MFS) were calculated from the date of the end of treatment to the date of either distant metastases, locoregional recurrence, or the date of the last follow-up. The Kaplan-Meier method was used to estimate the survival rates.

Results

Patient, tumor, and treatment characteristics. We analyzed 67 patients. Patient and tumor characteristics are shown in Table I. The median age at diagnosis was 57 years (range=29-83 years). The most represented histology was the squamous cell carcinoma, found in 52 patients (77.6%). Fifty-eight (86.5%) patients had FIGO stage IIB or higher before treatment. The clinical tumor size ranged from 19 to 87 mm, with a mean tumor diameter of 45 mm. Fifty-three patients (79%) received weekly cisplatin (40 mg/m^2), and three patients (5%) received another type of systemic therapy. At the time of diagnosis, 26 patients (39%) had lymph node disease, of which 18 had only pelvic lymph nodes affected. Fifty-three (83.6%) patients received concomitant cisplatin-based chemotherapy. The treatment characteristics and dosimetric parameters are summarized in Table II and Table III. The median treatment duration was 55 days (range=40-73 days). The prescription dose to PTV was delivered in 25 to 30 (median 28) daily fractions. Forty-nine and 18 patients were treated with IMRT and 3DRT, respectively. The EBRT median dose to the pelvis and to GTV were 50.4 Gy (range=45-56.25 Gy) and 61.6 Gy

Table III. *Dosimetric data to HR-CTV and OARs.*

	I BT (67 pts)	II BT (67 pts)	III BT (63 pts)	IV BT (16 pts)
D90 HR-CTV, median (range) (cGy)	624 (437-930)	599 (289-839)	633 (259-918)	639 (334-840)
D95 HR-CTV, median (range) (cGy)	556 (364-827)	511 (221-749)	570 (191-815)	578 (294-768)
D2cc bladder, median (range) (cGy)	545 (213-945)	508 (220-1,081)	535 (269-1,031)	431 (219-697)
D2cc rectum, median (range) (cGy)	439 (122-686)	415 (69-812)	399 (62-762)	365 (109-610)

Doses from all fractions of BT calculated in cGy. BT: Brachytherapy; D2cc: dose covering 2 cubic centimeters of OAR; D90-95: minimum dose covering 90-95% of HR-CTV; HR-CTV: high-risk clinical tumor volume; OAR: organ at risk.

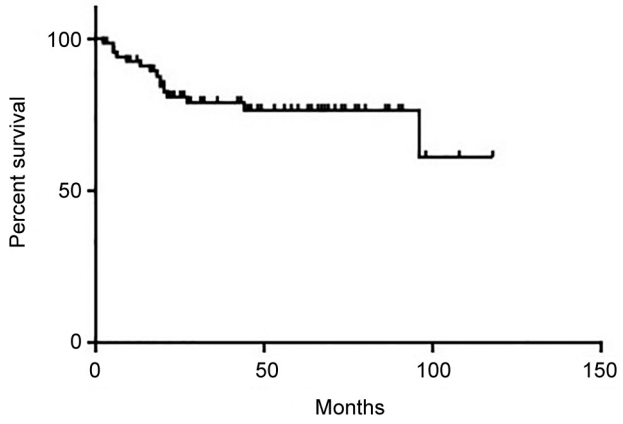

Figure 2. *Kaplan-Meier curves of overall survival of all patients receiving definitive external-beam radiation therapy (EBRT) plus intracavitary brachytherapy.*

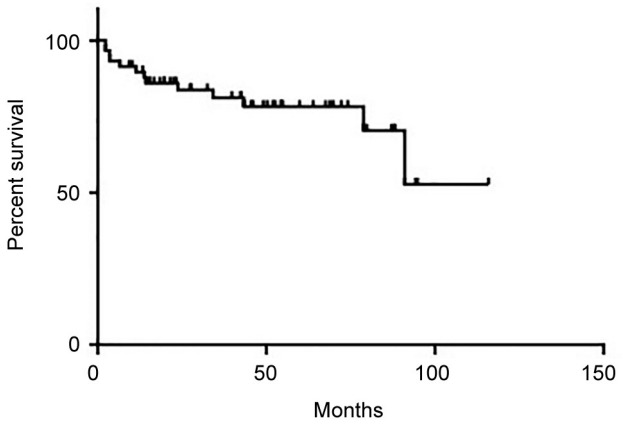

Figure 3. *Kaplan-Meier curves of disease-free survival of all patients receiving definitive external-beam radiation therapy (EBRT) plus intracavitary brachytherapy.*

(range=45-70.4 Gy), respectively. Fifty-three patients received an overdose on the cervix and parametrial using IMRT-SIB (median boost dose 11.2 Gy, range=10-12 Gy) or sequential boost (median boost dose 11.2 Gy range=5-25.2) in 35 and 18 patients, respectively.

The median time between EBRT completion and beginning of BT boost was 7 days (range=3-28 days). All patients (89.5%) had a post-EBRT pelvic MRI done at the time of brachytherapy. All patients received intracavitary HDR-BT at the end of concomitant EBRT-CHT. The median BT dose for patients was 21 Gy (range=10-28 Gy); the median BT dose per fraction was 7 Gy (range=5-7 Gy).

Outcomes. The median follow-up was 43 months (range=2-118 months). The 1-year, 2-year, 3-year, and 5-year OS rates were 92.44%, 80.81%, 78.84%, and 76.45%, respectively (Figure 2). The actuarial 1-year, 2-year, 3-year, and 5-year DFS rates were 89.5%, 83.6%, 81%, and 78.2% respectively (Figure 3). The 1-year and 2-year MFS were 94.7% and 90.2%, respectively. The 2-year, 3-year, and 5-year OS for bulky *vs*. non-bulky disease patients were 79%, 76%, and 71% *vs*. 85%, 85%, and 86%, respectively (95%CI=0.52-4.2; p=0.45). The 2-year, 3-year, and 5-year OS for patients with positive lymph nodes at onset *vs*. negative lymph nodes was 71.3%, 56.1%, and 56% *vs*. 77.4% 74.2%, and 74%, respectively (95%CI=0.30-1.85; p=0.53). Eleven/67 (16.4%) patients were non-responders. We have recorded ten relapses (15%) of which two were local relapses and eight systemic relapses, with a median DFS of 32 months (range=0-116 months) among these patients. At the median follow-up time, 39 (58.2%) patients were alive without disease. Twenty-two patients died (15 due to the disease and 7 due to not cervical cancer-related causes).

Toxicities. Cumulative toxicity assessment showed acute genitourinary complications grade 1 in twenty-two/67 (32.83%) patients and grade 2 in five/67 (7.4%), whereas only one patient complained of acute G3 toxicity (1.49%).

Acute grade 1 gastrointestinal toxicity occurred in twelve/67 (17.91%) patients while six/67 patients (8.95%) complained of acute grade 2 toxicity. Nine/67 patients showed both genitourinary and acute gastrointestinal toxicities, at different stages of severity. Late G3 toxicity occurred in two/67 patients (2.98%), while only one/67 patients developed vaginal stenosis (1.49%).

Discussion

EBRT with concurrent chemotherapy followed by a BT is the gold standard for women with LCC. BT boost represents a crucial part of multimodal treatment and is also a positive prognostic factor for LACC patients (15). The American Brachytherapy Research Group carried out a systematic review with the aim of defining outcomes, toxicity, and local control (LC) results in patients with LACC who have undergone chemo-RT and HDR-BT for LACC. Authors underlined the benefits in survival outcomes related to this combined therapy (16). Prospective and retrospective studies have investigated the results on local disease control. Pötter *et al*. (17) reported 100% LC rates for stage IB, 96% for stage IIB, and 86% for stage IIIB. In addition, compared to previous studies in which BT was performed with 2D technique, patients treated with CT-based 3D-BT seemed to have better survival rates and less serious morbidities. About DFS, prospective studies in the literature report a ≥24 months DFS of 55% in patients untreated with concurrent CT, while patients who received multimodal therapy obtained a ≥24 months DFS of 65% (18-20). As regards BT, there has been a shift from low-dose BT (LDR-BT) to high-dose BT (HDR-BT) while maintaining an overlapping oncological effectiveness, as seen in a large series of randomized studies (21-23). Thanks to the use of CT-BT, planning has dramatically shifted towards 3D optimization, allowing an improvement in the coverage of the tumor, and reducing the dose to the organs at risk (OAR). Further improvements regarding local control and toxicities were related to the introduction of MRI-based BT, which could be now considered the gold standard according to GEC-ESTRO guidelines. However, despite the growing MRI popularity and availability, CT-based BT still represents the most employed IGBT technique for LACC treatments in daily clinical practice, especially in the low-income countries but also worldwide. Although MR imaging is greater in terms of soft tissue delineation and target definition, especially for residual disease after EBRT and parametrial involvement, radiation oncologists may rely on long-term experience with CT utilization in EBRT planning and treatments. Recently CT-based BT target contouring recommendations have been published by IBS-GEC ESTRO-ABS to improve contouring accuracy (10).

Several studies in the last decades have demonstrated the feasibility and safety of CT-based BT as well as the effectiveness of the treatment (24-26). In 2010, Hallock *et al*. published oncological outcomes of 57 patients with LACC treated with 28 Gy/4 fractions CT-based ultrasound guided HDR-BT. Their experience reported 3-year OS and relapse-free survival of 86% and 62%, respectively, and with low toxicity even in bulky tumors, comparable to MRI-based BT (24). A Japanese retrospective study on 84 patients treated with ICBT reported 3-year OS, LC, and PFS rates of 94%, 89%, and 81%, respectively, confirming previous favorable oncological data using CT as image guidance for HDR-BT. Authors remark that in their series, larger tumors were significantly associated with poor LC and an intracavitary/interstitial approach is suggested to gain an appropriate target coverage (25). Simpson *et al*. analyzed clinical outcomes in 76 women with LACC treated with CT based HDR-BT. At median follow-up (17 months) the 2-year cumulative incidences of local, locoregional, and distant failure were 5.8%, 15.1%, and 24.3% respectively, with only 5 cases of G3 toxicities, thereby showing excellent local control, with low rates of acute and late toxicity (26).

A recent study by Yuki *et al*. analyzed 30 consecutive uterine cervical cancer patients treated with IMRT using TomoTherapy followed by HDR-ICBT. The 3-year local control, disease-free survival, and overall survival rates were 89.9%, 83.3%, and 86.3% with a good local control and tolerance of toxicity (27).

Our study aimed to investigate 67 patients with LAAC, treated with RT + BT, which is to date the most common clinical practice in our center. Survival outcomes and toxicity profile were the endpoints of the study. Five-years OS and DFS rates of 76.45% and 78.2%, respectively, were comparable with other recent studies from literature.

The cumulative acute GU toxicity rates revealed are Grade 1 32.83%, Grade 2 7.4%, and Grade 3 1.49%. As for late GU toxicity assessment, only 2.98% of patients complained of Grade 3 complications. 17.91% of patients complained of acute Grade 1 GI toxicity and 8.95% of Grade 2. We did not detect acute Grade 3 GI toxicity or late GI toxicity. Only one/67 patients developed vaginal stenosis (1.49%). Literature on the late effects of HDRBT in cervical cancer patients is even more sparse. In the absence of evidence-based guidelines, it is important to report all toxicities with an appropriate description of the regimen used. The data reported in this cohort showed excellent local control and low incidence of toxicities, comparing very favorably with other published reports. Further prospective studies should be considered to validate our outcomes.

Conclusion

In this patients' cohort, we analyzed the toxicity profile, survival outcome, and LC disease in cervical cancer patients treated with IMRT and CT-planned HDR-BT. Patients have shown excellent results in terms of local control and toxicity

in the treatment of cervical cancer. In recent literature, the use of advanced techniques has been increasingly recommended to improve the quality of treatments and survival outcomes.

Conflicts of Interest

The Authors have no conflicts of interest to declare in relation to this study.

Authors' Contributions

VDS, GF and GV were major contributors in writing the manuscript, analyzed the data and drafted the article. DA and GS made substantial contributions to conception of the study. AN, LM, FT, PCG, IA, VD, CC, VT, FDF, MV, MFO provided clinical expertise in this project. All Authors contributed to the article and approved the submitted version.

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