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Original

Dose-Volume Histogram Analysis in Point A-based Dose Prescription of High-dose-rate Brachytherapy for Cervical Carcinoma

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Abstract : Traditionally, cervical brachytherapy has been prescribed to point A. However, since the Groupe Européen de Curiethérapie and European Society for Radiotherapy & Oncology guidelines were published, image-guided brachytherapy has become an emerging technique. The purpose of this study was to evaluate the high-risk clinical target volume (HR-CTV) coverage and analyze dose-volume histograms for organs at risk in point A prescription of high-dose-rate brachytherapy. A total of 68 patients with locally advanced cervical cancer were treated with three-dimensional conformal external beam radiation therapy and brachytherapy from December 2012 to March 2017. Fractions of 6 Gy for a total of 12–24 Gy were delivered at point A by brachytherapy to all patients. Following each brachytherapy application, a pelvic computed tomography scan was performed and imported into a three-dimensional brachytherapy treatment planning system. In this study, the HR-CTV, bladder, and rectum were re-delineated according to Report 89 of the International Commission on Radiation Units and Measurements using the magnetic resonance images at the time of diagnosis, and the dose-volume histogram of each structure was analyzed. The median age of patients at diagnosis was 67 years (range, 31–91 years). Mean HR-CTV D_{90} for all patients was 558.3 cGy (range, 228.7–1005.1 cGy) and the mean HR-CTV D_{90} within each clinical T stage was : Ib, 646.4 cGy ; 2a, 579.3 cGy ; 2b, 545.2 cGy ; 3a, 556.6 cGy ; 3b, 451.3 cGy ; and 4, 497.9 cGy. HR-CTVD_{90} was correlated with HR-CTV. The mean D2 cm^3 was 678.1 cGy for the bladder and 511.9 cGy for the rectum. Using point A-based dose prescription, HR-CTV coverage was insufficient, especially in cases with a large tumor volume or a high T stage. Image-guided brachytherapy is expected to improve HR-CTV coverage while keeping rectal and bladder doses within acceptable levels.

Key words : cervical carcinoma, image-guided brachytherapy, point A, dose-volume histogram, high-risk clinical target volume

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Introduction

Standard treatment for cervical cancer is a combination of external beam radiation therapy (EBRT), chemotherapy, and intracavitary brachytherapy[1]. Intracavitary radiation, which is especially important for locally advanced cancer, has been performed since the 1900's and has been shown to contribute to improvement in local control, survival rate, and disease-free period, more in combination with EBRT than when using EBRT alone[2–4]. The Manchester system was developed in the 1930's, and is based on prescription to point A : 2 cm lateral to the central canal of the uterus and 2 cm up from the mucous membrane of the lateral fornix, in the axis of the uterus[5]. It has yielded comparatively good treatment results. However, this prescribed dose point is based on two-dimensional (2D) X-ray films and it cannot visualize the cervical tumor. Furthermore, the dose coverage is insufficient in patients with a large tumor, narrow vagina, cervical canal where insertion is impossible, parametrial invasion, pelvic wall invasion, or infiltration of the vagina[6].

In the 1980's, with advanced radiotherapy techniques, it became possible to make plans based on 3D-images, such as computed tomography (CT) and magnetic resonance imaging (MRI). The International Commission on Radiation Units and Measurements (ICRU) Report 38, issued in 1985, recommended an irradiation target volume rather than point A, and specified reference points for the rectum and bladder[7]. The switch to image-guided brachytherapy (IGBT) , using CT or ideally MRI, indicated an advancement in brachytherapy.

The Groupe Européen de Curiethérapie and the European Society for Radiotherapy & Oncology (GEC-ESTRO) guidelines were published in 2005 to aid with the implementation of IGBT, and in 2013, Report 89 of the ICRU further defined and formalized the principles of the GEC-ESTRO guidelines[8]. Prescribed doses of D_{90} for cervical tumors and D2 cm^3 for organs at risk (OARs) have been employed. Many studies recommended D_{90} for cervical tumors ; D_{90} is defined as the minimum dose delivered to 90% of the high risk clinical tumor volume (HR-CTV) with a correlation with the regional tumor control rate[9]. The HR-CTV is defined as the CTV including the residual tumor at the time of brachytherapy, the whole cervix, and adjacent residual pathologic tissue if present. It is the volume bearing the highest risk of recurrence[9]. The evaluation of OARs has shifted away from the ICRU Report 38 reference points towards a dose-volume histogram (DVH) approach. D2 cm^3 for the bladder and rectum, which is defined as the minimum dose delivered to 2 cm^3 of the organ volume, is used as an indicator of toxicity[9].

IGBT combined with radio-chemotherapy is known to improve local control and overall survival[10–12]. However, point A represents the most-used parameter in gynecologic brachytherapy worldwide including Japan, but it is now a transition period to IGBT. Our hospital is also considering switching to IGBT. In order to prepare for this transition, we examined the problems of the conventional treatment by re-evaluating cases of point A prescription, from the viewpoint of IGBT, by analyzing the dosimetric results of point A-based prescription, according to Report 89 of the ICRU. To our knowledge, there are few reports which analyzed the

dosimetric coverage of HR-CTV in patients treated with point A-based prescription.

Materials and methods

Patients

Patients with locally advanced cervical cancer treated with 3D-conformal EBRT and high-dose-rate brachytherapy (HDR-BT) between December 2012 and March 2017 were analyzed in order to evaluate dose distribution.

Treatment

All patients had an MRI of the pelvis taken before treatment. The EBRT prescription dose was 50–60 Gy delivered to the whole pelvis and pelvic para-aortic region in 25–30 fractions using 10 MV X-rays. A midline block was inserted after delivering 30–40 Gy. HDR-BT was performed using the 192Ir remote-controlled afterloading system. A CT scanner was installed in the brachytherapy treatment room, and after each brachytherapy application, a pelvic CT was performed. The images were imported into a 3D brachytherapy treatment planning system and a plan was made.

All patients had 6 Gy per fraction delivered to point A by brachytherapy, with a total dose of 12–24 Gy. The iridium source strength was 370 GBq. HDR-BT was performed once a week with concurrent central shielding EBRT. Vaginal packing was used to reduce rectum irradiation.

Dose evaluation

After the first HDR-BT fraction, HR-CTV, bladder, and rectum contours were re-delineated according to Report 89 of the ICRU by two radiation oncologists using the MR images available at the time of diagnosis. HR-CTV was presumed to be palpable and visible by clinical examination and detectable using MRI (high intensity in T2-weighted images). A DVH plan, which is a histogram relating radiation dose to tissue volume, was generated for each structure. From the DVH analysis, HR-CTV D_{90}, and D2 cm^3 for the rectum and bladder were obtained. These parameters were analyzed for each T subgroup. Correlations between HR-CTV D_{90} or OAR D2 cm^3 and HR-CTV were performed using Spearman's rank correlation coefficient.

Results

Patient characteristics (*Table 1*)

Sixty-eight patients with cervical cancer were eligible for this analysis. Their median age was 67 years (range, 31–91 years). The numbers of patients per clinical T stage are shown in Table 1. Pelvic lymph node metastases were found in 27 patients. Eight patients had distant metastasis. Sixty-five patients had squamous cell carcinoma and three patients had adenocarcinoma. Forty-nine patients were treated with chemotherapy concurrently.

Dose evaluation

All patients received 600 cGy per fraction delivered to point A. The mean HR-CTV D_{90} for

Table 1. Patient characteristics

Patients, n	68
Age, mean (range), y	67 (31-91)
Stage (TNM), n	
T	
1a	0
1b	13
2a	5
2b	21
3a	7
3b	21
4a	1
N	
0	41
1	27
M	
0	60
1	8
Stage (FIGO), n	
Ⅰ B1	11
Ⅰ B2	2
Ⅱ A1	3
Ⅱ A2	2
Ⅱ B	21
Ⅲ A	7
Ⅲ B	21
Ⅳ A	1
Histology, n	
Squamous cell carcinoma	65
Adenocarcinoma	3
Tumor size at maximum, cm	
＜4	24
4-6	31
＞6	13
Concurrent chemotherapy	
Yes	49
No	19

all patients was 558.3 cGy. The mean HR-CTV D_{90} values for each T classification subgroup are shown in Table 2. Except for the T4 classification, the HR-CTV D_{90} value tended to decrease as the T stage increased (Table 2, Fig. 1). It was difficult to cover the HR-CTV with sufficient dose, especially in patients with Stage T3b tumors. The mean OAR D2 cm^3 was 667.8 cGy for the bladder (range, 316.2-1272.5 cGy) and 511.9 cGy for the rectum (range, 202.8-852.7 cGy) (Table 2). There was no significant difference between HR-CTV and OAR dose.

Table 2. Minimum dose delivered to 90% of the high-risk clinical target volume (HR-CTV D_{90}), and minimum dose delivered to 2 cm^3 (D2 cm^3) of organs at risk in brachytherapy

	N	HR-CTV D_{90} (cGy)	Rectum D2 cm^3 (cGy)	Bladder D2 cm^3 (cGy)
All patients	68	558.3 (229-1,005)	511.9 (203-853)	678.1 (316-1,273)
T1b	13	646.4 (594-732)	418.6 (203-603)	704.3 (316-884)
T2a	5	579.3 (375-694)	477.1 (424-816)	711.1 (649-775)
T2b	21	545.2 (297-1,005)	578.6 (262-853)	681.2 (525-1,137)
T3a	7	556.6 (229-636)	572.7 (337-675)	576.7 (500-1,098)
T3b	21	451.3 (311-761)	504.1 (302-831)	687.9 (320-1,273)
T4	1	497.9	724.8	1,069.9

Values are mean (range) unless specified otherwise. T, TNM stage T.
HR-CTV D_{90} values in stages T2a to T3b were below 600 cGy. HR-CTV D_{90} values decreased as T stage increased.

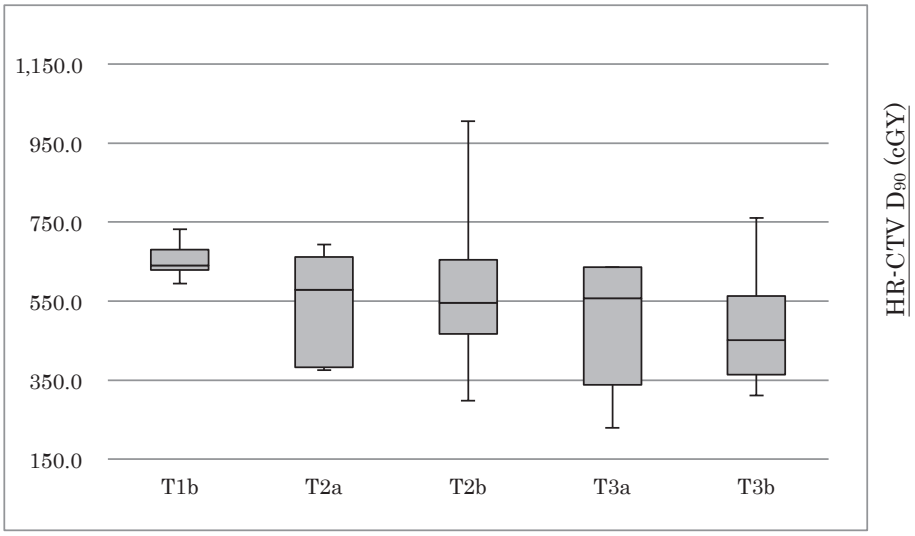

Fig. 1. Comparison of the dose delivered to 90% of the high-risk clinical target volume (HR-CTV D_{90}) in each T stage classification subgroup. Box plot of HR-CTV D_{90} in each T stage. Minimum and maximum value of HR-CTV D_{90} are depicted by a short black line outside the box. The box signifies the upper and lower quartiles, and the median is represented by a black line within the box. The HR-CTV D_{90} value decreases as the T stage progresses, especially in T3b cases.

HR-CTV D_{90} was correlated with HR-CTV, with the HR-CTV D_{90} value decreasing as the HR-CTV increased ($P < 0.001$, $r = -0.5836$, Spearman's correlation; Fig. 2). The HR-CTV D_{90} value was often less than 600 cGy when HR-CTV exceeded 40 cm^3 (Table 3). We present a case of Stage Ⅲ B cervical cancer with a large tumor volume (Fig. 3, Table 4). This case shows a low HR-CTV D_{90} value and the 600 cGy dose line does not cover the HR-CTV.

Discussion

In our study, the HR-CTV D_{90} values obtained for Stages T2a to T3b were below 600 cGy,

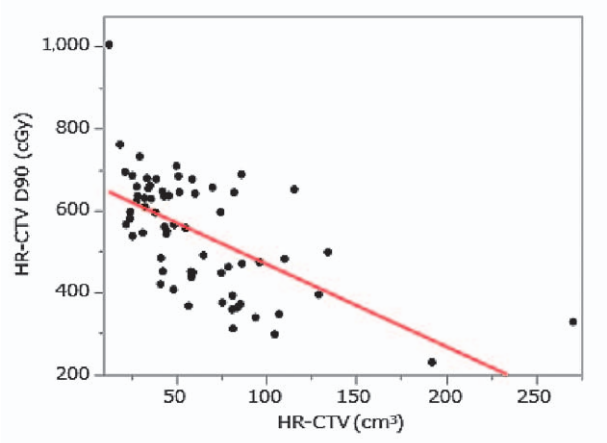

Fig. 2. Correlation between the dose delivered to 90% of the high-risk clinical target volume (HR-CTV D_{90}) and the HR-CTV. There was a significant correlation between HR-CTV D_{90} and HR-CTV (R2 = 0.36, $P < 0.001$, Spearman rank correlation test), with the HR-CTV D_{90} value decreasing as HR-CTV became larger.

Table 3. Comparison of volume and dose parameters among high-risk clinical target volume (HR-CTV)

HR-CTV	Number	HR-CTV D_{90} (cGy)
$< 40\ cm^3$	21	635.4 (537.2–1,005.1)
$\geq 40\ cm^3$	47	477.5 (228.7–708.4)

Values are mean (range) unless specified otherwise. HR-CTV D_{90}, minimum dose delivered to 90% of the HR-CTV.
The HR-CTV D_{90} value was often less than 600 cGy when the HR-CTV was greater than 40 cm^3.

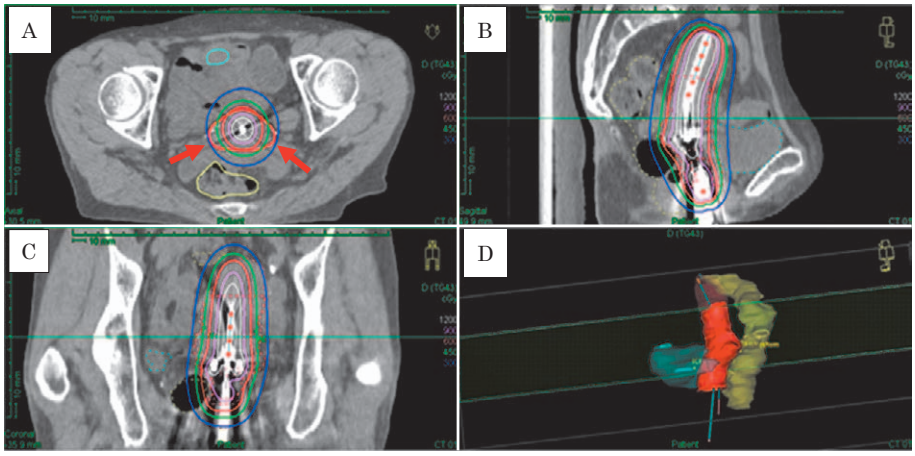

Fig. 3. A case of Stage III B cervical cancer. Distribution of brachytherapy.
Axial (A), Sagittal (B), Coronal (C) view of the dose distribution of brachytherapy. Panel D is the 3D view of HR-CTV (red), Bladder (blue) and Rectum (yellow). The red line in panel A-C is the 6 Gy isodose line, which could not cover the high-risk clinical tumor volume at both posterior sides (arrows).

Table 4. A case of Stage Ⅲ B cervical cancer. Dose-volume parameters in brachytherapy

HR-CTV D_{90} (cGy)	HR-CTV D_{50} (cGy)	Rectum D2 cm^3 (cGy)	Bladder D2 cm^3 (cGy)	HR-CTV (cm^3)
469.89	754.75	462.53	614.50	86.53

HR-CTV, high risk-clinical target volume; D_{90}, minimum dose delivered to 90% of the HR-CTV; D_{50}, minimum dose delivered to 50% of the HR-CTV; D2 cm^3, minimum dose delivered to 2 cm^3 of organ at risk.
The HR-CTV was 86.53 cm^3 which is over 40 cm^3 and the HR-CTV D_{90} did not reach 600 cGy.

which is the dose value prescribed to point A. Moreover, there was a significant correlation between HR-CTV D_{90} and HR-CTV. These results show that HR-CTV coverage is insufficient using a point A-based dose prescription, especially in patients with a highly invasive tumor or large HR-CTV. IGBT, which uses evaluation of tumor volume and 3D-planning, allows for treatment individualization with better HR-CTV coverage, as well as the ability to account for larger tumor sizes while simultaneously sparing OARs. Many studies have shown that IGBT combined with radio-chemotherapy leads to better local control, overall survival, and cancer-specific survival in patients with cervical cancer[10–12].

GEC-ESTRO recommends using MR images for CTV delineation as they are superior to CT images. In studies by Kim *et al*[13] and Viswanathan *et al*[14], the CT-defined HR-CTV was observed to be larger than for MRI scans. This might be one of the reasons for the low HR-CTV D_{90} values in our study. However, MRI use is limited because it is not easily accessible and there is a risk of applicator displacement. Recent surveys of IGBT demonstrated that CT images are commonly used. Thus, Ohno *et al*[15] recently introduced a guideline for CT-based HR-CTV delineation in order to standardize 3D-IGBT applications. The use of this guideline would help in better coverage of the CTV.

When external irradiation is performed, some institutions use a central shielding technique, which is commonly used in Japan and Southeast Asia. This allows for the delivery of high doses to pelvic nodes and lowers the irradiation doses to the bladder and rectum, while permitting an increased dose to the cervix using intracavitary brachytherapy. However, it is unclear whether this central shielding technique allows for accurate DVH assessment, which is emphasized with IGBT. Furthermore, Tamaki *et al*[16] reported that the central shielding technique is able to provide tumor coverage in the right-left directional plane but requires an adequately high dose to the tumor volume in the anterior-posterior direction, especially in the case of a large tumor. Intensity-modulated radiation therapy (IMRT) might allow for precise assessment and could also reduce doses to the rectum, small bowel, and bladder. Kidd *et al*[17] have shown that IMRT has improved survival and reduced treatment-related toxicity compared with non-IMRT radiotherapy. According to a report by Macdonald *et al*[18], a combination of pseudo-split-field IMRT and brachytherapy delivers a significantly higher dose to the primary tumor and lymph nodes compared to a four-field box plan or IMRT not using a split field.

Sun *et al*[19] demonstrated the possibility of performing 2 Gy-per-fraction equivalent dose accumulation by combined split-field IMRT and brachytherapy. These findings support the next transition to using IMRT for cervical cancer.

The present results indicate that, although it is a time-consuming process requiring individualized contouring and planning, the shift from 2D point A prescription to 3D-IGBT is necessary, along with the preparation of environmental factors for this transition. In addition, 3D-IGBT in combination with IMRT would provide a better dose distribution. However, further study is required to determine how these techniques perform in relation to the local control and improvement in adverse events.

Conclusion

Point A-based dose prescription provided insufficient HR-CTV coverage, especially in patients with highly invasive or large-volume tumors. IGBT is expected to improve HR-CTV coverage while keeping rectal and bladder doses within acceptable levels. The transition to IGBT for intracavitary brachytherapy and IMRT for EBRT should be considered.

Conflict of interest disclosure

The authors have no conflicts of interest to disclose.

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