Dosimetric analysis between Manchester points “A” and high-risk clinical target volume in the three-dimensional image-guided brachytherapy for uterine cervical cancer

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Abstract

Background: Gynecological brachytherapy has evolved from the concept of punctual prescription (Manchester) to treatment volumes. **Objective:** To analyze the dosimetric result between the prescription at point A and high-risk clinical target volume (HR-CTV). **Methods:** Both plans were performed in 28 patients with stage IB2-IVA cervical cancer (112 applications), the dose used was 4 fractions of 5.62 Gy. **Results:** The mean D90 (dose to 90% volume) and its standard deviation for HR-CTV: 92.1 ± 2.7 Gy, was lower ($p < 0.008$) than at points A (103.4 ± 21.6 Gy). HR-CTV coverage: $97.8 \pm 7.3\%$ was higher ($p < 0.00000000043$) than with points A ($86.6 \pm 14.7\%$). The bladder D2 cc was: 83.8 ± 22.4 Gy vs. ICRU 38 bladder point (66.1 ± 7.6 Gy) ($p < 0.0057$), demonstrating the underestimation of the dose in the punctual planning. The D2 cc of the rectum was: 73.6 ± 12.7 Gy vs. ICRU 38 straight point (75.1 ± 11.9 Gy) ($p < 0.4857$), not differing significantly. **Conclusions:** 3D brachytherapy provides greater dose coverage for HR-CTV compared to the traditional system, with an underestimation of the dose received in the bladder in the punctual system.

Key words: Cervical cancer. Brachytherapy. Intracavitary. Manchester. Volumetric.

Análisis dosimétrico entre puntos «A» de Mánchester y volumen blanco clínico de alto riesgo en braquiterapia 3D guiada por imagen para el cáncer cervicouterino

Resumen

Introducción: La braquiterapia ginecológica ha evolucionado desde el concepto de prescripción puntual (Mánchester) a volúmenes de tratamiento. **Objetivo:** Analizar el resultado dosimétrico entre la prescripción a puntos A y volumen blanco clínico de alto riesgo (CTV-HR). **Métodos:** Se realizaron ambas planeaciones en 28 pacientes con cáncer cervicouterino estadio IB2-IVA (112 aplicaciones), la dosis utilizada fue cuatro fracciones de 5.62 Gy. **Resultados:** La dosis media al 90% del CTV-HR y desviación estándar: 92.1 ± 2.7 Gy fue más baja ($p < 0.008$) que a puntos A (103.4 ± 21.6 Gy). La cobertura al CTV-HR: $97.8 \pm 7.3\%$ fue mayor ($p < 0.00000000043$) que con puntos A ($86.6 \pm 14.7\%$). La D2 cc de vejiga fue: 83.8 ± 22.4 Gy vs. punto vejiga ICRU 38 (66.1 ± 7.6 Gy) ($p < 0.0057$), demostrando la subestimación de la dosis en la planeación puntual. La D2 cc de recto fue: 73.6 ± 12.7 Gy vs. punto recto ICRU 38 (75.1 ± 11.9 Gy) ($p < 0.4857$), no difiriendo significativamente. **Conclusiones:** La braquiterapia 3D proporciona una mayor cobertura de dosis al CTV-HR comparándolo con el sistema tradicional, existiendo una subestimación de la dosis recibida en vejiga en el sistema puntual.

Palabras clave: Cervicouterino. Braquiterapia intracavitaria. Mánchester. Volumétrica.

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Introduction

Cervical cancer ranks fourth in worldwide cancer incidence and mortality in women¹. External beam radiation therapy and brachytherapy have been the mainstay of radical treatment for more than half a century at locally advanced stage².

Intracavitary brachytherapy consists of placing an intrauterine tube and two vaginal ovoids, with subsequent loading of radioactive sources^{3,4}. The Manchester system, which is the most widely used in the world, started with the use 2D (two-dimensional) imaging^{5,6}, using orthogonal radiographies, in which the dose was prescribed to Manchester points A^{7,8}. Currently, with the advance in technology, 3D image-guided brachytherapy (IGBT), with the use of computed tomography (CT) and magnetic resonance imaging (MRI), have enabled tumor contouring in cervical cancer and healthy organs: bladder, rectum and sigmoid colon, with a more accurate technique, offering improvements in dose-volume parameters and in clinical outcome^{9,10}.

In this study, the differences in the percentage of tumor doses coverage and radiation doses received by the tumor and organs at risk rectum and bladder will be compared and determined with two types of planning: dose prescription at Manchester points A vs. prescription to high-risk clinical target volume (HR-CTV) in patients treated with high-dose rate gynecological brachytherapy.

Material and methods

In 28 patients with stage IB2-IVA cervical cancer (112 gynecological brachytherapy applications), treated at the radiotherapy unit of Hospital General de México Dr. Eduardo Liceaga Oncology Department during the period encompassed from November 1, 2017 to September 1, 2018, with high-dose rate brachytherapy (HDR-BCT) with simultaneous arrangement (intrauterine tube with pair of ovoids) using CT for simulation in 2D planning⁸; alternately, each already-treated patient had another volumetric planning performed, using the GYN GEC-ESTRO Guidelines recommendations⁹; the prescribed dose was four 5.62-Gy fractions, twice weekly, for a dose equivalent to 2 Gy/day (EQD2) with an alpha/beta of 10 = 29.3 Gy; for the calculation of organs at risk EQD2, an alpha/beta of 3 was used. The brachytherapy equipment used was ECLIPSE™: BrachyVision 3D-gammaMedPlus iX HDR/PR (Varian), using the Iridium-192 radioisotope. In the planning with prescription to Manchester points A, reference "A"

points were determined based on the system developed by Tod and Meredith in 1938⁵, and the reference points of the rectum and bladder according to ICRU 38 (International Commission on Radiation Units and Measurements Report 38)¹¹. In the planning with volumetric prescription, HR-CTV and organs at risk were contoured according to the GYN GEC-ESTRO guidelines. These guidelines determine that gross tumor volume (GTV, volume of gross disease visible by imaging techniques) and CTV outlining should be performed for each brachytherapy application, taking into account T2-weighted MRI images both at diagnosis and at every brachytherapy application. Diagnostic GTV is defined as tumor macroscopic extension at diagnosis detected by clinical examination and by T2-weighted MRI. Brachytherapy GTV is defined as tumor macroscopic extension at the time of brachytherapy application detected by clinical examination and T2-weighted MRI. HR-CTV (high risk) includes brachytherapy GTV with the entire cervix and tumor extracervical extension without safety margins being added⁹. They also mention that both MRI and CT provide similar quality for discrimination of organs at risk such as the bladder, rectum, sigmoid colon, small intestine and vagina, but with regard to GTV and adjacent normal uterine tissue discrimination MRI is superior¹⁰.

Eskander et al. performed HR-CTV and organs at risk contouring with CT and MRI following the aforementioned recommendations, showing that although CT overestimates HR-CTV at its coronal axis, dose parameters did not show significant differences between MRI and CT and, similarly, in organs at risk, no significant differences were found, concluding that 3D image-guided brachytherapy application is feasible using TC¹².

In our study, images for treatment planning were obtained by means of CT equipment with 3-mm slices along the pelvis. HR-CTV contouring was performed including the entire cervix and its extracervical extension, both visible in the CT images of each brachytherapy application and in physical examination findings. For the organs at risk, contouring was carried out of the rectum, sigmoid colon, bladder and small intestine. The bladder was contoured from base to dome; the rectum was contoured from the ischial tuberosities to the sigmoid flexure; the sigmoid colon was contoured from the sigmoid flexure to 2 cm above the applicator; and the small intestine was contoured from its appearance in the lowest CT slice to up to 2 cm above the applicator.

An observational, descriptive, retrospective, cross-sectional study was carried out, where the data yielded by

Table 1. Planning with prescription to high-risk clinical target volume (HR-CTV)

Variables' average total dose: EBRT + HDR-BCRT (EQD2)						
No. of patients	Tumor Volume (cc)	D90 dose received by the tumor (HR-CTV) (Gy)	Percentage of dose coverage to the tumor (HR-CTV) (%)	Dose to Manchester points A (Gy)	Dose to 2 cc of bladder (Gy)	Dose to 2 cc of rectum (Gy)
28	43.0 ± 12.9	92.1 ± 2.7	97.8 ± 7.3	103.4 ± 21.6	83.8 ± 22.4	73.6 ± 12.7

EBRT: external beam radiation therapy; HDR-BCT: high-dose rate brachytherapy; EQD2: dose equivalent to 2 Gy per fraction; D90: dose received by 90% of tumor volume; cc: cubic centimeters; Gy: Gray.

the dose and volume histograms were recorded. Total overall dose (external beam radiotherapy + brachytherapy) of each variable per patient was obtained by adding external radiation therapy dose to brachytherapy EQD2 dose.

The sample size was determined by the method of two means' difference for paired samples with a two-tailed hypothesis, with a sample size with Cohen's d effect = 0.2, 80% power and 95% reliability. The estimate of this sample size was determined using the G power statistical software, version 3.1.9.2.

An analysis of the obtained data was carried out using the SPSS program and Stata 10, comparing variables in the volumetric vs. punctual planning: dose received by 90% of tumor volume, percentage of tumor coverage (HR-CTV), bladder point vs. bladder D2 cc (dose in 2 cubic centimeters), rectum point vs. rectum D2 cc.

Results

In a period of nine months, clinical and digital files from 28 patients (112 brachytherapy applications) with stage IB2-IVA cervical cancer, treated with HDR-BCT, with the traditional punctual prescription system (Manchester A points and ICRU 38-defined organs at risk), and who underwent simulation with CT, were collected. Mean age was 46.39 years, with a standard deviation of ± 10.45 . According to the histopathological report, squamous cell carcinoma was diagnosed in 22 patients (78%), adenocarcinoma in 5 patients (18%) and signet ring cell carcinoma in 1 patient (4%). International Federation of Gynecology and Obstetrics (FIGO) staging was I in 2 patients (7%), II in 14 patients (50%), III in 5 patients (18%) and IV in 7 patients (25%). External beam radiation therapy dose was 50 Gy in 23 patients (82%) and 45 Gy in 5 patients (18%). The five patients who received 45 Gy had para-aortic lymph node involvement. Concomitant cisplatin-based chemotherapy

(40 mg/m²) with external beam radiation therapy was administered to 26 patients (93%), one patient did not receive chemotherapy (4%) and whether one patient received chemotherapy is not known (4%). Mean tumor volume at the time of brachytherapy was 43.03 cc with a standard deviation of ± 12.95 cc; tumor volume was less than 20 cc in one patient (4%), 20-40 cc in 10 patients (36%) and larger than 40 cc in 17 patients (61%).

In all 112 CT-guided HDR-BCT planning procedures, dose prescription was 5.62 Gy per fraction, for a total of 22.48 Gy in four fractions. The dose to 90% of the high-risk clinical target volume (HR-CTV D90) was 74.26-79.26 Gy, while the dose to 2 cc of bladder and rectum was limited to 90 and 75 Gy, respectively. The dose to Manchester points A was 74.26-79.26 Gy, and the dose to ICRU 38 bladder and rectum points was limited to 80 and 75 Gy, respectively.

In the volumetric planning, mean D90 dose to HR-CTV was 92.1 Gy with a standard deviation of ± 2.7 Gy, which was significantly lower ($p < 0.00816$) than the mean dose to Manchester point A, which was 103.4 ± 21.6 Gy (Table 1). In the volumetric planning, the percentage of tumor dose coverage (HR-CTV) was $97.8 \pm 7.3\%$, which was significantly higher ($p < 0.00000000043$) than the tumor dose coverage (HR-CTV) with the planning to Manchester points A: $86.6 \pm 14.7\%$ (Tables 1 and 2).

Dose ranges for the organs at risk were within acceptable limits. Mean dose to 2 cc of rectum was 73.6 ± 12.7 Gy. It was lower and non-significant ($p < 0.48572$) vs. mean dose to the rectum point (ICRU 38), which was 75.09 ± 11.9 Gy. Mean dose to 2 cc of bladder was 83.8 ± 22.4 Gy, and was significantly higher ($p < 0.00022$) than the dose to the bladder point (ICRU 38), which was 66.1 ± 7.6 Gy (Tables 1 and 2).

Discussion

3D image-guided brachytherapy, with the use CT and MRI, is a recommended clinical practice for the

Table 2. Planning with prescription to Manchester points A

Variables' total average dose: EBRT + HDR-BCT (EQD2)				
No. of patients	D90 dose received by the tumor (HR-CTV) (Gy)	Percentage of dose coverage to the tumor (HR-CTV) (%)	ICRU 38 bladder point (Gy)	ICRU 38 rectum point (Gy)
28	80.2 ± 8.2	86.6 ± 14.7	66.1 ± 7.6	75.9 ± 11.9

EBRT: external beam radiation therapy; HDR-BCT: high-dose rate brachytherapy; EQD2: dose equivalent to 2 Gy per fraction; D90: dose received by 90% of tumor volume; HR-CTV: high-risk clinical target volume; Gy: Gray; ICRU 38: International Commission on Radiation Units and Measurements Report 38.

treatment of cervical cancer, since it allows us to carry out treatment planning and assess the doses delivered to tissues more precisely and accurately. Current publications support that MR images are superior to CT images, due to better soft tissue resolution when evaluating residual disease and cervicouterine anatomy; however, when contouring organs at risk, both imaging studies were found to be equivalent, as demonstrated by the San Diegogroup¹². GEC-ESTRO currently recommends using MR imaging for tumor volume outlining; however, given that in many institutions this imaging technique is not available, CT is being used for 3D treatment planning^{9,10}.

In this study, CT images were used to perform HR-CTV and organs at risk contouring, with mean tumor volume ($43.03 \pm 12.95 \text{ cm}^3$) being found to be higher than that reported in other studies in which contouring was carried out with MRI ($34 \pm 17 \text{ cm}^3$ and $36 \pm 23 \text{ cm}^3$)^{13,14}; thus concluding that contouring with CT tends to overestimate HR-CTV. However, coverage of this volume increase was achieved without exceeding the dose restrictions for organs at risk.

When 3D planning was carried out, mean dose to 90% of HR-CTV ($92.1 \pm 2.7 \text{ Gy}$) was compared with the dose received by Manchester points A ($103.4 \pm 21.6 \text{ Gy}$) ($p < 0.008$), with D90 for HR-CTV being found to be lower in 3D planning, but within limits recommended by the literature, since based on the study by Dimopoulos et al., they reported that a D90 EQD2 = 87 Gy for HR-CTV is associated with approximately 95% of disease local control (Fig. 1)¹³, while with planning to Manchester points A, high radiation doses are correlated with higher toxicity and irradiation to adjacent healthy tissues.

These results are associated with tumor volumes larger than 40 cm^3 , which were found in 61% of patients in this study, in whom the use of interstitial brachytherapy is recommended, which allows to obtain adequate dose coverage to HR-CTV, without increasing the dose to adjacent healthy tissues^{13,14}. According to observations

reported by Derks et al.¹⁵, when comparing 2D brachytherapy vs. 3D image-guided brachytherapy, the use of interstitial needles was associated with a larger high-risk clinical target volume, higher dose to HR-CTV and lower dose to the bladder. When both treatment techniques were compared, a trend was shown for 3D brachytherapy towards greater local control (93% at 1 year and 88% at 3 years) and better overall survival (75% at 3 years and 66% at 5 years) with reduced toxicity (17 vs. 12%), in comparison with the conventional 2D brachytherapy technique.

The percentage of tumor volume coverage with 100% of the prescribed dose for each brachytherapy fraction (5.62 Gy) with planning to HR-CTV ($97.8 \pm 7.3\%$) was significantly higher ($p < 0.000000000043$) than with the planning to Manchester points A ($86.6 \pm 14.7\%$), with 3D image-guided brachytherapy being observed to provide better tumor coverage for HR-CTV in comparison with prescription to Manchester points A.

Ha et al. group¹⁶ found a relationship between tumor size and HR-CTV coverage, reporting that D90 mean value for HR-CTV was approximately 10% lower for 2D-based plans than for 3D plans (88.4 vs. 97.7%; $p = 0.068$) with tumors $\leq 4 \text{ cm}$, but when tumors were $> 4 \text{ cm}$, values were significantly higher for patients based on 3D than for 2D-based plans (96.0 vs. 78.1%; $p = 0.017$).

Regarding the organs at risk, the observed dose ranges were within acceptable limits and were comparable to the doses reported by Kim¹⁷. Mean dose to ICRU 38 bladder point ($66.1 \pm 7.6 \text{ Gy}$) was markedly underestimated in comparison with the mean dose to 2 cc of bladder ($83.8 \pm 22.4 \text{ Gy}$) with statistically significant results ($p < 0.00577$) (Fig. 2). However, mean dose to ICRU 38 rectum point ($75.1 \pm 11.9 \text{ Gy}$) did not significantly differ ($p < 0.48572$) from the dose to 2 cc of the rectum ($73.6 \pm 12.7 \text{ Gy}$) (Fig. 3).

With the results obtained, the viability of CT-based planning approach to IGBT according to GEC-ESTRO recommendations is demonstrated. However, due to

Patient	Dose points A (Gy)	HR-CTV D90 dose (Gy)
1	90.86	90.02
2	80.81	85.68
3	73.68	84
4	63.78	88.74
5	121.26	91.43
6	80.31	92.34
7	83.7	91.57
8	111.08	92.43
9	146.81	94.98
10	70.69	92.69
11	135.16	92.67
12	111.7	89.62
13	98.71	94.81
14	112.49	89.7
15	101.59	90.54
16	107.56	93.55
17	154.6	91.93
18	123.24	95.96
19	113.84	92.7
20	87.96	95.51
21	91.41	94.33
22	99.09	94.24
23	111.06	92.33
24	98.55	92.79
25	89.26	92.76
26	111.27	94.37
27	108.32	92.78
28	116.8	94.02

Figure 1. Comparison between the dose received by Manchester points A and HR-CTV, in 3D planning, for each patient. EBRT: external beam radiation therapy; HR-CTV: high risk-clinical target volume; BCT: brachytherapy; D90: dose received by 90% of tumor volume.

PACIENTE	3D plan: Total dose EBRT + HDR BCT	2D plan: Total dose EBRT + HDR BCT
	2cc of bladder	ICRU38 bladder point
1	77.03	64.9
2	68.45	62.21
3	67.57	66.74
4	61.29	83.6
5	109.8	67.32
6	67.78	69.69
7	84.19	83.02
8	94.91	67.04
9	160.88	65.29
10	54.93	61.31
11	73.19	58.9
12	87.55	70.77
13	57.02	59.54
14	65.9	60.19
15	60.69	63.11
16	79.41	78.86
17	112.46	62.34
18	101.89	75.74
19	96.89	74.53
20	90.05	74.24
21	68.83	57.83
22	85.83	65.18
23	85.38	56.29
24	95.09	62.18
25	60.91	56.32
26	91.38	60.3
27	79.43	59.95
28	107.91	63.11

Figure 2. Total dose (EBRT + BCT) to 2 cc vs. dose to ICRU 38 point for the bladder. EBRT: external beam radiation therapy; HDR-BCT: high-dose rate brachytherapy; ICRU 38: International Commission on Radiation Units and Measurements Report 38.

PACIENTE	3D plan: Total dose EBRT + HDR BCT	2D plan: Total dose EBRT + HDR BCT
	2 cc of rectum	ICRU38 rectum point
1	63.62	60.59
2	55.3	55.69
3	51.64	55.55
4	55.93	65.33
5	63.44	63.84
6	56.15	67.78
7	62.49	69.89
8	84.15	67.66
9	72.36	64.08
10	63.11	75.7
11	82.47	82.43
12	84.8	80.53
13	86	70.14
14	84.3	81.24
15	82.74	69.32
16	86.79	92.15
17	76.58	75.74
18	88.54	89.32
19	89.18	91.18
20	85.01	95.99
21	65.62	99.01
22	78.65	94.8
23	69.55	74.89
24	67.49	70.72
25	56.47	79.54
26	97.92	83.75
27	79.04	73.68
28	72.2	75.93

Figure 3. Total dose (EBRT + BCT) to 2 cc vs. dose to ICRU 38 point for the rectum. EBRT: external beam radiation therapy; BCT: brachytherapy; ICRU 38: International Commission on Radiation Units and Measurements Report 38.

variations in contoured tumor volume, in institutions that have sufficient means, performing the simulation with MRI is recommended in order for greater accuracy in HR-CTV contouring to be obtained.

We conclude that, in institutions where MRI is unavailable, applying 3D image-guided brachytherapy using CT is feasible, since 3D planning, when compared to 2D planning, shows to be superior in tumor coverage and outlining with higher accuracy of the doses received by organs at risk.

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Conflict of interests

The authors declare that they have no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this research.

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