Dosimetry of the bowel as a risk organ in intracavitary gynecologic image guided 3D brachytherapy

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Abstract

Introduction: Image-guided 3D brachytherapy (IGBT) contemplates the volumetric definitions for the calculation of the dose to clinical target volume and the risk organs, such as bladder, rectum and sigmoid, but the value of contouring the bowel has not been proven. **Objective:** To determine the doses received at the D2cc (dosage in 2 cubic centimeters) bowel in IGBT. **Methods:** Retrospective study including 117 applications of intracavitary gynecological IGBT of high dose rate carried out in the General Hospital of Mexico, evaluating the bowel D2cc. **Results:** 117 applications of IGBT were made by computed tomography, 61 simultaneous arrangements (tandem and ovoids), and 56 vaginal cylinders. In the simultaneous arrangement group, the values of the bowel D2cc were in the range of 53 to 1153 cGy, mean 324 cGy; in the vaginal cylinder group, the range obtained was 36 to 549 cGy, with a mean of 224 cGy. Applying a multiple linear regression model, larger doses to the bowel were observed (86.4 cGy) in the simultaneous arrangement group compared to the vaginal cylinder group, with statistical significance. **Conclusion:** The bowel dosimetry shows higher doses in simultaneous arrangements, but studies are required that evaluate the dosimetry obtained with acute and late clinical toxicity.

Key words: HDR brachytherapy. Cervix cancer. 3-D Image-based brachytherapy. Volume dose parameters.

Dosimetría del intestino delgado como órgano de riesgo en la braquiterapia ginecológica intracavitaria 3D guiada por imagen

Resumen

Introducción: La braquiterapia 3D guiada por imagen (BTGI) contempla definiciones volumétricas para cálculo de dosis a volumen blanco clínico y órganos de riesgo como vejiga, recto y sigmoides, pero no se encuentra definida la importancia de la dosimetría en intestino delgado. **Objetivo:** Determinar las dosis recibidas a la D2cc (dosis en 2 centímetros cúbicos) intestino delgado en BTGI. **Métodos:** Estudio retrospectivo, incluye 117 aplicaciones de BTGI ginecológica intracavitaria de alta tasa de dosis en el Hospital General de México evaluándose la D2cc intestino. **Resultados:** Se realizaron 117 aplicaciones de BTGI mediante tomografía computarizada, 61 arreglos simultáneos (sonda intrauterina y par de colpostatos) y 56 cilindros vaginales. En el grupo arreglo simultáneo, la D2cc intestino estuvo en el rango de 53 a 1,153 cGy, media 324 cGy; en el grupo de cilindro vaginal, el rango fue de 36 a 549 cGy, media 224 cGy. Aplicando un modelo de regresión lineal múltiple se observó en el grupo arreglo simultáneo, 86.4 cGy más de dosis sobre el intestino delgado en comparación con el grupo de cilindro vaginal, con significancia estadística. **Conclusión:** La dosimetría en intestino muestra dosis mayores en arreglos simultáneos, pero se requieren estudios que evalúen la dosimetría obtenida con la toxicidad clínica aguda y tardía.

Palabras clave: Braquiterapia HDR. Cáncer cérvix. Braquiterapia 3-D basada en imagen. Parámetros dosis volumen.

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Introduction

Intracavitary brachytherapy associated with external beam radiotherapy is an essential component in the management of cervical cancer that produces high therapeutic control rates due to the release of high radiation doses at the primary cervical lesion¹. However, in some cases, the rectum, sigmoid and the bladder are irradiated with high doses due to their proximity to the cervical tumor, thus resulting in late complications in these at-risk organs².

For several decades, brachytherapy was based on two-dimensional (2D) orthogonal X-ray images, with the dose being prescribed to a virtual point called A, located at a fixed distance from the applicator, which results in a pear-shaped isodose; this technique is called conventional brachytherapy. Conventional brachytherapy prescribed dose never did adapt to the patient or tumor anatomy, which resulted in small over-treated tumors and large undertreated tumors, in addition to a higher percentage of doses received by organs at risk³.

The International Commission on Radiation Units and Measures (ICRU), in its report 38, describes how the determination of the points of dose absorbed by organs at risk bladder and rectum should be established for conventional brachytherapy⁴.

A modern focus on the planning of brachytherapy treatment is based on the acquisition of computed tomography images and 3D (three-dimensional) dose distribution, called 3D image-guided brachytherapy (IGBT). This allows ensuring better dose distribution at different volumes within the tumor, such as gross tumor volume (GTV) and clinical target volume (CTV), and in organs at risk¹.

In this regard, the new recommendations for the prescription and reporting of brachytherapy for cervical cancer (ICRU 89) were published in 2013, where the prescription and calculation of doses is changed from a point-based system (ICRU 38) to a volume-based system (GTV, CTV), which is what ICRU currently recommends for gynecologic IGBT applications⁵.

The GYN GEC-ESTRO working group recommendations for gynecologic 3D brachytherapy suggest the contouring of organs at risk bladder, rectum, sigmoid colon, vagina and, in some cases, small intestine; with a volumetric parameter called D2cc (dose in 2 cubic centimeters) being determined as the restriction value for said organs at risk, with the EQD2 (dose equivalent to 2 Gy) integral D2cc (external radiotherapy + brachytherapy) being 90 Gy for the bladder, and 70 Gy for the rectum and sigmoid⁶.

Regarding the small intestine, in his Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC) report, Kavanagh determines as restrictions for external radiotherapy, if bowel loops are delimited, 15 Gy in < 120 cc, and if the intestinal pouch is delimited, 45 Gy in < 195 cc; in the case of extracranial stereotactic radiotherapy, up to 12.5 Gy in < 30 cc per fraction is recommended, where the cumulative dose delivered to a single point should not exceed 30 Gy; but no recommendation is issued with regard to brachytherapy⁷.

In this same sense, it is the EMBRACE II study that mentions the prescription limits for integral dose (external radiotherapy + brachytherapy) for bowel D2cc in image-guided high dose rate brachytherapy; it recommends an EQD2 lower than 75 Gy (with EQD2 calculated with an alpha/beta of 3)⁸.

When the ICRU 38-determined rectum and bladder points are compared with the dose parameters in the dose-volume histogram established by GEC-ESTRO, the rectal point is correlated with dose-volume parameters, but the bladder point is unrelated to the maximum released dose or toxicity⁹, and no comparison parameters are established for the sigmoid or small intestine, given that these organs are not defined by ICRU 38 as being at risk.

Despite the rapid dose drop in relation to the distance of the brachytherapy applicator, normal adjacent structures may receive a significant radiation dose. In the case of the small intestine, this can occur when an intestinal loop is adjacent to the applicator, which is why, compared to 2D brachytherapy, IGBT has the advantage of being able to volumetrically identify the organ, and by determination of D2cc as dose tolerance, quantify the radiation dose it will receive. This is important, since when exceeding the dose threshold for this organ, there are more possibilities of generating acute and late toxicity in the patient. In this sense, Kibsgaard et al. report a cohort of 1,176 patients with stage IB-IVB cervical cancer treated with external radiotherapy to the pelvis at 45-50 Gy, associated with 5-6 cycles of cisplatin and high- or pulsed-dose IGBT; with a follow-up of 27 months, their purpose was to assess intestinal morbidity associated with a mean small intestine integral D2cc (external radiotherapy + brachytherapy) EQD2 of 57.4; 5-year risk of severe intestinal morbidity was found to be 5.9%, with mild to moderate bowel symptoms being the most common (28-33%), and most common symptom being diarrhea with flatulence¹⁰.

Most studies related to 3D gynecologic brachytherapy only recommend the contouring of organs at risk bladder, rectum, sigmoid colon and vagina and, similarly,

establish their dose restrictions, but without the doses received by the small intestine being clear and, consequently, the need to contour it as an organ at risk at each brachytherapy application. Therefore, the purpose of this study was to determine the doses received by the small intestine (D2cc) in the dose-volume histogram with the different gynecological IGBT applicators by means of computed tomography (CT).

Material and methods

Patient characteristics

A total of 39 patients, corresponding to 117 applications of intracavitary gynecologic 3D image-guided brachytherapy at a high dose rate carried out between December 2016 and September 2018, were included for this study. Out of them, 20 patients (61 applications) underwent the procedure by simultaneous arrangement (intrauterine tube [tandem] and one pair of ovoids), and 19 patients (56 applications) underwent the procedure by vaginal cylinder (2.5-, 3- and 3.5-cm diameter). Previously, each patient was assessed by a radiation oncology specialist, who determined the type of application.

Clinical stage IB-IVA cervical cancer was the diagnosis of 68.5% of the patients, while 31.5% of cases corresponded to operated endometrial cancer.

Overall mean age was 52.5 years. When the groups are divided into patients who were treated with simultaneous arrangement or vaginal cylinder, the parameters are the following:

- Simultaneous arrangement. Mean age: 59.2 years; 95% of patients received weekly cisplatin-based concomitant chemotherapy with a mean of 2.2 cycles; 100% of patients received a first phase of treatment by means of external radiotherapy to the pelvis, with a mean dose of 42.5 Gy.
- Vaginal cylinder. Mean age: 46.1 years; 45% of patients received sequential chemotherapy based on carboplatin/paclitaxel with a mean of 4.4 cycles; 95% of the patients received a first phase of treatment with external radiotherapy to the pelvis, with a mean dose of 48.7 Gy.

Description of the procedure

Brachytherapy was applied in the short-stay unit operating room under sedation for simultaneous arrangement and only with topical anesthesia for vaginal cylinder. Applicator insertion technique was carried out in accordance with the recommendations of the American Brachytherapy

Figure 1. CT axial section showing intrauterine catheter and contoured organs at risk: sigmoid in orange and intestine in blue.

Figure 2. Three-dimensional volumetric reconstruction of contoured organs at risk: rectum, brown; sigmoid colon, orange; bladder, yellow; intestine, blue.

Society^{11,12}. After insertion, images were obtained for treatment planning using a computed tomography (CT) scanner with 3 mm sections along the pelvis. Contouring of organs at risk rectum, sigmoid colon, bladder and small intestine was carried out. 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 up to 2 cm above the applicator; the small intestine was contoured from its appearance in the lower CT slice to up to 2 cm above the applicator (intrauterine tube or vaginal cylinder) (Figs. 1 and 2).

Ideally, the Radiation Therapy Oncology Group (RTOG) Contouring Guidelines for female pelvic normal tissue recommend using oral contrast medium 30 minutes prior to the simulation in order to more easily identify the intestinal loops¹³; but given that in our hospital this resource is not available, using contrast medium was not possible, and small intestine identification

in the CT images was therefore carried out based on two parameters:

1. Small intestine anatomical parameters. Small bowel loops generally have a central location and conniving valves (transverse folds) are therein identified as fine lines that surround the entire intestinal lumen¹⁴. The jejunum is found at the umbilical region, and tortuously runs from the upper left region to the lower right region of the abdomen¹⁵.
2. Colon anatomical parameters. Nelms refers that if there is no contrast to identify the small intestine, another way for doing it is by anatomical identification of the colon, where all the remaining loops will correspond to the small intestine¹⁶. Colonic loops are peripherally located and have haustra, which look as thick, incomplete lines¹⁴. The large intestine forms an almost complete arch or frame for the small intestine loops and can be easily distinguished from the small intestine by identifying its thick longitudinal muscle bands on its outer surface, called teniae coli or colon ribbons, as well as its sacculations on the wall between the teniae coli, called haustra¹⁵.

The prescription of the treatment dose was made to points A in the case of the simultaneous arrangements and to a 0.5-cm depth for the vaginal cylinders⁴ (Fig. 3).

The dose was calculated using the BrachyVision brachytherapy planning system, version 13.5.37 (Varian Medical Systems). The dosing schedules used were:

- For the simultaneous arrangement, 4 applications of 562 cGy twice weekly, for an EQD2 with alpha/beta of 10 of 29.3 Gy.
- In the case of the vaginal cylinders, two dosing schedules: without previous external radiotherapy, three 7-Gy applications twice a week for an EQD2 with alpha/beta of 10 of 29.8 Gy; and with previous external radiotherapy (generally 50 Gy/25 Fr. to the pelvis), the schedule used was three 500-cGy applications twice a week for an EQD2 with an alpha/beta of 10 of 18.8 Gy, with the dose being prescribed for a 0.5-cm depth of the vaginal mucosa in the case of the vaginal cylinders.

D2cc restrictions for small intestine per high dose rate EQD2 alpha/beta 3 brachytherapy fraction were: < 430 cGy for simultaneous arrangement and < 520 cGy for vaginal cylinder, in order to ensure an integral small intestine D2cc (external radiation therapy + brachytherapy) EQD2 alpha/beta 3 dose < 75 Gy.

To integrate total D2cc dose received by the small intestine, the technique recommended by GEC-ESTRO⁶ and the EMBRACE Protocol⁸ were used, where

Figure 3. Dose prescription to points A, with the classic pear-shaped distribution of the curve. Contoured organs at risk: rectum, brown; sigmoid, orange; bladder, yellow; intestine, blue.

it is assumed that the organ at risk in question receives external radiation therapy total dose prescribed at the initial plan plus the EQD2 alpha/beta 3 of the D2cc of each brachytherapy application.

Treatment was provided using the GammaMed Plus iX version 1.2 equipment (Varian Medical Systems).

Statistical analysis

Sociodemographic and clinical variables means and standard deviations and their p-values are shown for continuous variables, applying Mann-Whitney's U-test because there was no normality. In addition, dichotomous variables percentages and their p-values were calculated using the chi-square statistical test to find out if there were statistically significant differences according to the gynecological applicator. A multiple linear regression model was applied.

Results

Thirty patients were analyzed in this study, 20 of whom received applications with simultaneous arrangement and 19 with vaginal cylinder. According to the previously-described fractionation schemes, 117 applications of 3D high dose rate intracavitary gynecologic brachytherapy were carried out in these 39 patients using CT, out of which 61 insertions corresponded to simultaneous arrangement and 56 to vaginal cylinder. D2cc values for the small intestine were reported at each insertion, where for the group of simultaneous arrangement applicators, the values obtained for small intestine D2cc ranged from 53 to 1,153 cGy with a mean of 324 cGy, while in the group

Table 1. Values obtained for the mean and standard deviation, by applicator group

Group statistics					
	Applicator	Number of cases	Mean	Deviation	Average deviation error
INTD2CC	0 C	56	224.25	138.329	18.485
	1 F	61	324.41	162.414	20.795

INTD2CC: dose received in 2 cubic centimeters of small intestine; C: vaginal cylinder; F: Simultaneous

Table 2. Mann-Whitney's U-test results for sociodemographic and clinical variables. In addition, the chi-square test results for dichotomous variables are shown

Variable	Total	Simultaneous	Cylinder	p-value
	n = 39	n = 20	n = 19	
	Mean	Mean	Mean	
Age	52.54 (12.7)	59.2 (10.9)	46.1 (11.1)	< 0.001*
External radiotherapy dose	45.5 (13.4)	42.5 (18.3)	48.7 (2.3)	0.157*
Small intestine volume	99.5 (67.8)	83.1 (57.3)	116.8 (75)	0.127*
Chemotherapy cycles	3.3 (2.5)	2.2 (2.7)	4.4 (1.6)	< 0.001*
Diagnosis				
Cervical cancer	68.5	75	25	< 0.001†
Endometrial cancer	31.5	0	100	
Hysterectomy				
Yes, %	51.3	0	100	< 0.001†
No, %	48.7	100	0	
Chemotherapy				
Yes, %	68.4	95	45	< 0.001†
No, %	31.6	5	55	
External radiotherapy				
Yes, %	92.3	100	95	< 0.125†
No, %	7.7	0	5	

*Mann-Whitney's U-test was performed.

†Chi-square test was performed.

of vaginal cylinder type applicator, the values obtained ranged from 36 to 549 cGy, with a mean of 224 cGy. Table 1 shows the mean and standard deviation by applicator group.

Applying a multiple regression linear model, the patients who had a simultaneous arrangement applied were observed to have an average of 86.4 cGy higher dose to the small intestine in comparison with the patients in whom a vaginal cylinder was applied, which was adjusted for the dose variable, with the difference being statistically significant at 95%.

The results of the chi-square test show that there was a larger number of patients diagnosed with cervical cancer, and that most of them were treated with the

simultaneous applicator in comparison with those with endometrial cancer (75 vs. 0%; $p < 0.001$); in patients with endometrial cancer, only the vaginal cylinder-type applicator was used ($p < 0.001$); hysterectomized patients were entirely treated with vaginal cylinder ($p < 0.001$), and chemotherapy was used to a larger extent in patients with cervical cancer versus endometrial cancer (95 vs. 45%; $p < 0.001$).

Table 2 shows that, when Mann-Whitney's U-test was applied, demonstrating that previous external radiotherapy dose had statistically relevance was not possible, with the same being observed for small intestine contoured volume (external radiotherapy dose: $p = 0.157$; small intestine volume: $p = 0.127$).

Discussion

According to GYN GEC-ESTRO recommendations, dose prescription should be to high-risk CTV (HR CTV), defined as tumor gross extension at the time of brachytherapy insertion visualized by CT, including the entire cervix and tumor extracervical extension without adding a safety margin, with the dose having to cover at least 90% of this HR CTV volume, with this being called D90, aiming to achieve a total EQD2 dose (external radiotherapy + brachytherapy) delivered to this HR CTV of 80-90 Gy, depending on tumor clinical stage and risk factors¹⁷. In our study, the dose was not prescribed to the HR CTV but to ICRU 38-traditionally defined A points; this is due to the fact that the cases evaluated for this study were treated during the period of transition from using 2D to 3D brachytherapy technique in our hospital, with the purpose to make a safe transition in terms of results and dosimetric and clinical evaluations.

Gelover indicates that there are two different ways for integrating organs at risk D2cc from initial treatment with external radiotherapy and that from subsequent high dose rate brachytherapy. The first of them is the approach described by GEC-ESTRO and the EMBRACE protocol, where it is assumed that the organ at risk D2cc received the entire dose prescribed in the initial plan with external radiotherapy, and that only the D2cc that was obtained at each high dose rate brachytherapy application has to be added. The second method he describes involves obtaining the D2cc specific value of each organ at risk in external radiotherapy initial planning and adding it to the D2cc of each brachytherapy application. In his study, said author compared both methods in the rectum, sigmoid and bladder, and concluded that there is a D2cc underestimation ranging from 4.7 to 8.3% when the method of assuming that all the external radiotherapy prescribed dose was received is used, but that there is no significant difference when compared with the method of obtaining the D2cc of each external radiotherapy planning, to conclude that, due to this underestimation, obtaining the D2cc of each external radiation therapy plan is preferable¹⁸.

In our case, due to the fact that small intestine contouring is not ordinarily performed in the plans for external radiotherapy to the pelvis, using the D2cc integration method was decided, which assumes that the entire dose prescribed for external radiotherapy is received, to then add the D2cc values of each high dose rate brachytherapy application, and thus small

intestine final D2cc (external radiation therapy + brachytherapy integration) is obtained.

In this regard, the EMBRACE II study refers that the integral dose (external radiotherapy + brachytherapy) prescription limits for bowel D2cc should be an EQD2 lower than 75 Gy (calculating the EQD2 with an alpha/beta of 3, integrating 45 Gy/25 Fr. delivered by external radiotherapy), mentioning that this dose restriction is valid in the case of non-mobile intestinal loops, which results in that the highest volume of exposure is located in a similar part of the organ; exceeding this dose restriction can be associated with stenosis, fibrous rings and fistulae⁸.

In this same sense, Damato establishes 65 Gy as the limit for bowel D2cc (EQD2 with an alpha/beta of 3), alluding that, in the EMBRACE study, the prescription dose at HR CTV (high risk clinical target volume) D90 was 85 Gy (as external radiotherapy plus brachytherapy integral dose), while at his institution, this prescription was generally lower than 80 Gy¹⁹.

For our study, a dose limit for small intestine D2cc was established for each fraction according to the total sum (external radiotherapy 50 Gy/25 Fr. plus brachytherapy) with an EQD2 with alpha/beta of 3: < 430 cGy for simultaneous arrangement and < 520 cGy for vaginal cylinder, in order to ensure a small intestine D2cc integral dose (external radiation therapy + brachytherapy) with an EQD2 alpha/beta of 3 < 75 Gy. In this sense, [table 3](#) shows our results when the external radiotherapy dose plus the brachytherapy D2cc are integrated to represent final integral D2cc (EQD2 with an alpha/beta of 3) of the bowel, with only one patient exceeding the D2cc integration limit referred by EMBRACE II.

Our results show a mean small intestine volume of 83.1 cc for the simultaneous arrangement group, while for the vaginal cylinder group the mean was 116.8 cc; therefore, it could be inferred that the contoured small intestine volume would influence its D2cc values, but the statistical analysis showed that there is no significant correlation. Neither was there a correlation found for the reported small intestine D2cc in relation to previous external radiotherapy dose.

The benefit of contouring the small intestine that is not adjacent to the applicator as an organ at risk is controversial, which is why most institutions only contour the intestinal loops near the applicator¹⁹. In our study, contouring both the intestinal loops close to the applicator and those potentially susceptible to receive a moderate radiation dose (up to 2 cm from the applicator) was preferred.

Table 3. Integration of external radiotherapy and brachytherapy EQD2 dose

N°	Applicator	ERT Dose	INT D2CC BT a/b 3	EQD2 integral dose
1	S	50	17.6 Gy	67.6 Gy
2	C	50	1.6 Gy	51.6 Gy
3	C	50	4.3 Gy	54.3 Gy
4	C	0	3.4 Gy	3.4 Gy
5	C	50	4.4 Gy	54.4 Gy
6	C	50	20.6 Gy	70.6 Gy
7	C	50	4.8 Gy	54.8 Gy
8	C	50	2.8 Gy	52.8 Gy
9	S	50	8.4 Gy	58.4 Gy
10	S	50	18.1 Gy	68.1 Gy
11	C	50	2.9 Gy	52.9 Gy
12	S	45	48.2 Gy	93.2 Gy
13	S	50	8.5 Gy	58.5 Gy
14	S	50	6.8 Gy	56.8 Gy
15	S	50	9.8 Gy	59.8 Gy
16	C	50	1 Gy	51 Gy
17	S	45	11.9 Gy	56.9 Gy
18	S	50	19.8 Gy	69.8 Gy
19	C	50	10.8 Gy	60.8 Gy
20	C	50	2.4 Gy	52.4 Gy
21	C	50	5.9 Gy	55.9 Gy
22	C	50	5 Gy	55 Gy
23	C	50	8.7 Gy	58.7 Gy
24	C	50	4.5 Gy	54.5 Gy
25	S	50	6.1 Gy	56.1 Gy
26	S	45	7.8 Gy	52.8 Gy
27	S	50	19.4 Gy	69.4 Gy
28	C	0	19.1 Gy	19.1 Gy
29	S	50	22.3 Gy	72.3 Gy
30	C	50	7.3 Gy	57.3 Gy
31	S	50	4.5 Gy	54.5 Gy
32	S	50	23 Gy	73 Gy
33	S	45	12.6 Gy	57.6 Gy
34	S	45	10.3 Gy	55.3 Gy
35	C	50	19.3 Gy	69.3 Gy
36	C	0	13.3 Gy	13.3 Gy
37	S	50	3.9 Gy	53.9 Gy
38	S	50	8.9 Gy	58.9 Gy
39	S	50	3.2 Gy	53.2 Gy

EQD2: 2 Gy-equivalent dose; INT D2cc: dose in 2 cubic centimeters of intestine; Gy: Gray; a/b 3: alpha/beta of 3; BT: brachytherapy; ERT: external radiotherapy; S: simultaneous; C: cylinder.

Our results show that patients who had a simultaneous arrangement applied have an average of 86.4 cGy additional dose to the small intestine in comparison with those who had a vaginal cylinder applied, with the difference being statistically significant. This is related to observations described by Damato, who attributes this to a higher contribution of the radiation dose to the upper portion of the uterus by the intra-uterine tube¹⁹.

Finally, although the role of systematically contouring the small intestine as an organ at risk in image-guided brachytherapy has not yet been established, performing its contouring is considered useful, especially in cases where intestinal loops are visualized to be close to the applicator since, due to its proximity, they might receive higher radiation doses; it could also be considered when applications are performed with intrauterine tube (simultaneous arrangement) due to the radiation dose higher contribution at the upper portion of the uterus by the intrauterine tube, which could generate a higher radiation dose to the small intestine due to its proximity. It is also necessary having studies available that correlate the dosimetric values obtained when the small intestine is contoured with acute and late clinical toxicity in order to determine whether there is any clinical repercussion associated with the small intestine D2cc values obtained in gynecologic IGBT.

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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.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained informed consent from the patients and/or subjects referred to in the article.

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