DOSIMETRIC EVALUATION STUDY ON CONVENTIONAL AND 3D CONFORMAL BRACHYTHERAPY TREATMENT OF CERVIX CANCER

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Abstract. The purpose of this study was to compare International Commission on Radiation Units and Measurements (ICRU, report 38) reference points, used in conventional brachytherapy planning, with Computed Tomography (CT)-based volumetric calculations of radiation doses for target volumes and organs at risk in biopsy-proven cervix carcinoma patients.

All patients underwent brachytherapy using CT-compatible applicators, followed by both conventional and CT scanning. The results confirm that point A radiation dose prescription overestimates target volume coverage, meanwhile for organs at risk the dose is underestimated. This suggests that brachytherapy needs to advance from a point-based (conventional) to a volume-based concept (3D conformal).

Key words: brachytherapy, 3D conformal, computer tomography, treatment planning, ICRU 38, organ at risk, dose, reference points.

1. INTRODUCTION

The most frequent types of lower female genital tract malignancies are cervix, vulva and vagina cancers. Epidemiological data suggest that cervical cancer is the most common gynecologic malignancy worldwide and the third most common cancer in women in the world [1].

In 2012, 266,000 deaths from cervical cancer were estimated worldwide, accounting for 7.5% of all female cancer deaths. Social and economic conditions proved to play an important role in cervix cancer mortality, being estimated that almost nine out of ten (87%) cervical cancer deaths occur in the less developed regions [2]. In Europe, bassed on estimated age-standardized rates per 100,000 women, Romania ranks as the country with the highest incidence and mortality rates from cervical cancer [3].

Concerning the histotype about 90% of cervical cancers are squamous cell carcinomas, adenocarcinoma and adenosquamous being less common sub types [4]. As for any cancer type, the treatment of patients with cervix cancer is determined by the stage and extent of the disease. Highest survival rates have been gained by adding radiotherapy in the curative management of cervical cancer [5]. Local tumor control has been associated with higher survival rates for cancer patients, therefore brachytherapy has become a treatment option for most cervix cancer stages in guidelines [6, 7].

Because it can be highly conformal adjusting dose to the target volume and to the sensitive structures, brachytherapy is usually associated as a boost to external beam radiotherapy (EBRT) of cervical cancer, especially for the treatment of locally advanced disease (stages IB2 to IVA)[5].

2. MATERIALS AND METHODS

PATIENT ENROLLMENT

A sample of thirty-two biopsy-proven cervix cancer patients treated between September 2013 and January 2016 were enrolled in this study based on the following criteria: biopsy-proven cervical cancer, stage IB1-IVB (according to International Federation of Gynecology and Obstetrics (FIGO) 2009 staging guidelines), preoperative radiotherapy and high dose rate (HDR) brachytherapy using Fletcher-Suit Delcos-Styple Applicator Set.

Tumor extension was assessed based upon clinical examination, laboratory testing (complete blood count, liver and renal function assessment), chest CT/X-ray and abdominopelvic CT/MRI (magnetic resonance imaging) scan. Assessment of the tumour extension included also description of tumour dimensions (width, height and thickness) as well as the possible involvement of parametria, vagina, bladder and rectum. The clinical examination has been documented by drawings used in the EMBRACE protocol [8].

All patients underwent pelvic EBRT with CT-based treatment planning to a total dose of 45 Gy to the tumor target volume and regional lymphnodes, using conventional fractionation schedule. For thirteen (40.62%) patients EBRT was administered using a seven or nine field intensity modulated radiotherapy (IMRT) technique, the other 19 (59.37%) patients being treated by a four field box technique. Nineteen patients (59.37%) underwent concurrent weekly cisplatin chemotherapy 40 mg/m^2, whilst for 7 patients (21.87%) concurrent q3w chemotherapy with paclitaxel and carboplatin was administered.

TREATMENT PROTOCOL

Following EBRT completion, patients underwent clinical and transvaginal ultrasound examinations in order to assess treatment response based on the initial EMBRACE protocol drawings. After that, tandem HDR brachytherapy was administered using CT-compatible applicator. Applicator curvature was selected according to uterus orientation, assessed at ultrasonography. Initially, before the applicator insertion, bladder and rectal catheters were inserted and cervical hysterometry was performed, using a straight hysterometer with graduated cursor, in order to select tandem length. All patients received HDR ^{192}Ir brachytherapy using a GammaMedplus iX remote afterloading system.

Following applicator and catheters positioning all patients underwent both X-ray and CT scanning. Lateral and anteroposterior X-ray images acquisition was done using Simulix orthogonal simulator. CT scanning machine used was a Somatom Sensation (Siemens, Germany). The images were generated at three-mm slice intervals from L5-S1 to two cm below the ischial tuberosities. The Foley bulb was filled with 7 ml of a solution containing 3 parts contrast agent and 7 parts saline. All patients were administered oral contrast before CT scanning. Also, for 28 patients (87.5%) intravenous contrast was administered initially.

CONTOURING

Gross tumor volume (GTV) could not be delineated on the CT images because tumor and normal cervical tissues have the same signal intensity. High risk (HR-CTV) and intermediate risk (IR-CTV) target volumes were contoured according to the EMBRACE protocol, adapting to the CT images the GEC-ESTRO recommendations [9, 10] for MRI. HR-CTV included the entire cervix and the residual macroscopic tumor extension at the end of EBRT. Uterine cervix was contoured from the cervical stopper inferiorly. The upper limit of the cervix was defined, based on current literature data [10] starting from the top of the endocervical applicator by adding another 2 slices with decreasing diameters to cover the conical cervical apex. IR-CTV included HR-CTV with a minimal margin of 10 mm in all directions. IR-CTV was modified by deletion of contour extending into bladder, rectum, sigmoid or bowel. The target volumes were edited according to initial tumor spread at diagnosis and around intact anatomical barriers (*e.g.* bone, fasciae etc.).

For all the organs at risk contours covered the outer wall. Rectum contour began at 2 cm above the anus, ending at the sigmoid flexure. From this level sigmoid was contoured to the anterior crossing of the sigmoid by the pubic symphysis and at this level bowel loops contouring continued on all CT slices. For the bladder volume, contouring started from the bladder top and ended at the beginning of the urethra.

TREATMENT PLANNING

For both conventional and 3D conformal planning we used BrachyVision v.11 software. In the workspace from this specific software, the Fletcher-Suit applicators were reconstructed on CT images using the virtual library provided by BrachyVision v.11, in accordance with the applicators that we have used for each patient. On planning images (Fig. 1) we determined A points (at 2 cm superior and lateral to the external cervical bone from the axis of flank), and also ICRU 38 reference points for rectum and bladder [11]. The rectum, point was at 5 mm from the posterior vaginal wall; for conventional planning, in addition to the ICRU 38 rectum point, additional points were added with 1 cm distance between each point, on the entire length of the rectal marker. All rectal points were evaluated in the 2D treatment planning report. The bladder ICRU 38 reference point was at the centre of the catheter balloon in anteroposterior view and at the lowest point in lateral view; for conventional planning we added three or four points on the perimeter of the bladder balloon that have been evaluated on final planning report. For sigmoid we chose the closest point to the applicators as a reference point.
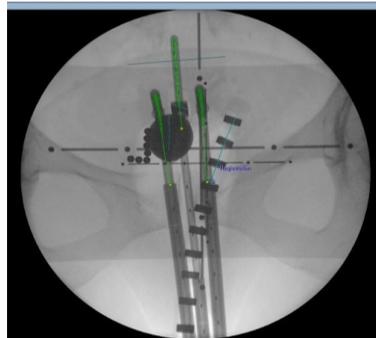
a)

b)

Fig. 1 – Conventional treatment planning, based on orthogonal radiographs:
a) anteroposterior view; b) lateral view.

Depending on the clinical indication, for each applicator we attributed a number of source positions and a dwell time so that we can obtain an appropriate dose distribution and recommended values for A points and ICRU 38 reference points. Figure 2 illustrates the isodose distribution on CT images.
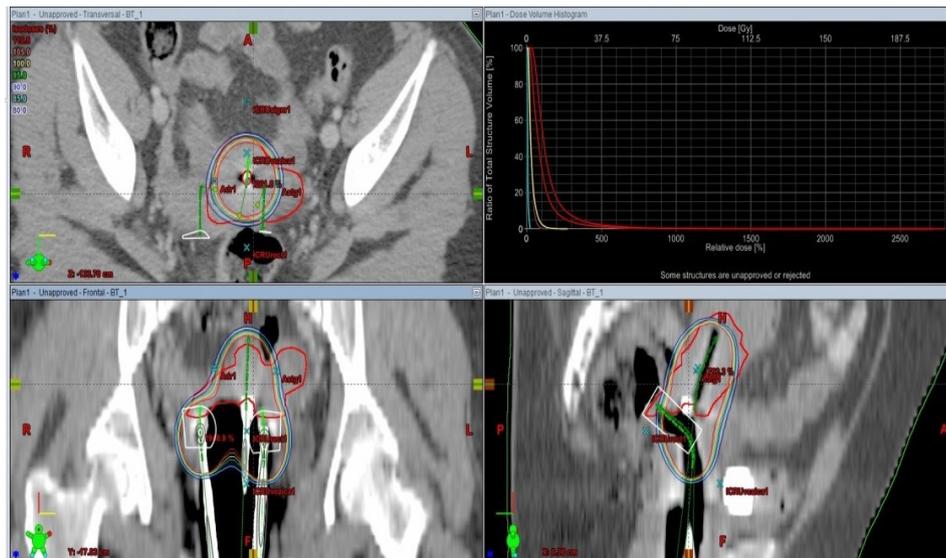

Fig. 2 – Isodoses distribution and dose volume histogram (DVH) in 3D conformal treatment planning, based on CT simulation.

Dose volume histogram (DVH) of bladder, rectum and sigmoid were then obtained. For the organs at risk $D_{0.1cc}$, D_{1cc}, D_{2cc}, D_{3cc} and D_{5cc} mean radiation doses were reported while for the CTV's D_{90}, D_{100}, V_{90}, V_{100}, V_{150} and V_{200} were evaluated.

3. RESULTS

As previously mentioned 32 patients with a median age of 50 years (range 25–74 years) were enrolled in this study, resulting in 61 brachytherapy plans which were used for comparison. Seventeen patients (53.1%) had stage III, 10 had stage II, 2 had stage IB and 3 had stage IVA. For 29 patients brachytherapy started during the last week of EBRT and the fractionation scheme was 7.5 Gy for two fractions performed approximately 1 week apart. Due to local EBRT toxicity for 3 patients only 1 application of brachytherapy could be performed. 2D and 3D treatment planning data were comparable in terms of point A and isodose distribution. For statistical analysis IBM-SPSS v 20.0 software package was used.

Prior to considering a comparison by significantly testing prescribed and received radiation doses in different points of the organs at risk, we have to assess if the values, for each variable that has been analyzed, come from certain, known or not, theoretical distributions. Applying the Kolmogorov-Smirnov and Anderson-Darling tests the results are showing that analized variables are coming from normal distribution.

Tables 1 and 2 prove that, regardless of the volume ($d = 0.1–5$) used in assessing the radiation doses received, this is significantly higher statistically than the standard radiation dose received by ICRU 38 standard points for each OAR (bladder and rectum). A statistically significant difference at less than 1 % ($p < 0.001$) alpha risk is based on the application of Student test (t) on one sample pairs defined by ICRU 38 points values combined sequentially with $D_{0.1cc}$, D_{1cc}, D_{2cc} etc.

Table 1

Comparison of volume and dose parameters for urinary bladder indicators
normalized to 7.5 Gy/fraction

Bladder Doses	ICRU [Gy]	B $D_{0.1cc}$ [Gy]	B D_{1cc} [Gy]	B D_{2cc} [Gy]	B D_{3cc} [Gy]	B D_{5cc} [Gy]
Mean	**3.93**	**11.11**	**8.78**	**<u>7.72</u>**	**7.10**	**6.36**
Standard Error	0.10	0.50	0.37	<u>**0.26**</u>	0.23	0.19
Median	4.05	10.20	8.32	<u>**7.53**</u>	6.97	6.30
Standard Deviation	0.80	3.94	2.93	<u>**2.01**</u>	1.77	1.52
Sample Variance	0.63	15.51	8.57	<u>**4.05**</u>	3.13	2.30
Minimum	2.52	5.20	4.45	<u>**3.80**</u>	2.90	2.50
Maximum	6.70	25.00	21.00	<u>**14.00**</u>	12.00	10.00
Sample volume ($n = \ldots$)	**61**	**61**	**61**	<u>**61**</u>	**61**	**61**
Conf. interval length (**P = 0.95**)	0.20	1.01	0.75	<u>**0.52**</u>	0.45	0.39
Lower 95(%)	**3.7**	**10.1**	**8.0**	<u>**7.2**</u>	**6.7**	**6.0**
Upper (95%)	**4.1**	**12.1**	**9.5**	<u>**8.2**</u>	**7.6**	**6.7**

The same result is obtained when using non-parametric Wilcoxon Rank Signed test for the median doses ($p < 0.001$) [12].

Table 2

Comparison of volume and dose parameters for rectal indicators normalized to 7.5 Gy/fraction

Rect Doses	ICRU [Gy]	R $D_{0.1cc}$ [Gy]	R D_{1cc} [Gy]	R D_{2cc} [Gy]	R D_{3cc} [Gy]	R D_{5cc} [Gy]
Mean	**3.88**	**6.45**	**5.31**	**4.80**	**4.45**	**4.00**
Standard Error	0.13	0.25	0.20	**0.17**	0.15	0.14
Median	3.90	6.16	5.21	**4.76**	4.44	4.02
Standard Deviation	1.04	1.94	1.54	**1.33**	1.20	1.07
Sample Variance	1.08	3.77	2.39	**1.78**	1.44	1.14
Minimum	1.59	2.05	1.70	**1.60**	1.51	1.37
Maximum	7.00	10.70	8.90	**7.90**	7.10	6.30
Sample volume ($n =...$)	61	61	61	**61**	61	61
Conf. interval length (**P = 0.95**)	0.27	0.50	0.40	**0.34**	0.31	0.27
Lower 95(%)	**3.61**	**5.95**	**4.92**	**4.46**	**4.15**	**3.73**
Upper (95%)	**4.01**	**6.70**	**5.51**	**4.97**	**4.61**	**4.14**

For sigmoid colon the following mean radiation doses were received: at ICRU reference point: 4.0 Gy, $D_{0.1cc}$ = 8.07 Gy, D_{1cc} = 6.23 Gy, D_{2cc} = 5.51 Gy, D_{3cc} = 5.02 Gy and D_{5cc} = 4.37 Gy. ICRU reference point dose maximum dose was 4.34 Gy, whilst in 3D treatment planning the radiation doses are as follows: $D_{0.1cc}$ = 9.02 Gy, D_{1cc} = 6.86 Gy, D_{2cc} = 6.03 Gy, D_{3cc} = 5.48 Gy and D_{5cc} = 4.76 Gy. A statistically significant variation between 2D and image guided brachytherapy can be seen for minimum radiation does received. So, at ICRU reference point the minimum dose was 4.00 Gy, as for the sigmoid volumes the results are: $D_{0.1cc}$ = 8.07 Gy, D_{1cc} = 6.23 Gy, D_{2cc} = 5.51 Gy, D_{3cc} = 5.02 Gy and D_{5cc} = 4.47 Gy.

Dose volume parameters for target volumes can be derived from cumulative dose volume histogram (DVH) analysis. DVHs for the CTV in intracavitary brachytherapy have a plateau, which indicates 100% dose coverage of the volume of interest. This plateau goes down smoothly indicating decreasing percentage of dose coverage with increasing dose (see Fig. 2, in the upper right quadrant). To describe the specific shape of DVH, dose coverage values can be defined, *e.g.* D_{100} and D_{90}, defining the minimum dose delivered to 100% and 90% of the volume of interest, respectively [13].

There are some specific considerations concerning dose-volume analysis of intracavitary brachytherapy. The minimum target dose D_{100} bears at least one practical limitation in accuracy as the reported dose value is extremely dependent on target delineation. Due to the steep dose gradient, small spikes in the contour cause large deviations in D_{100}. D_{90} is less sensitive to these influences and is therefore considered to be a more 'stable' parameter [13].

Although their clinical relevance has not been proven yet, D_{100} and D_{90} are both highly recommended for reporting: they can easily be calculated from a DVH and converted to biologically weighted EQD2 doses, which makes them suitable for correct plan comparison of all dose rate [14].

Table 3 shows that when comparing prescribed doses to the doses delivered to 90% and 100% of the tumor volume at diagnosis (IR_CTV) and after EBRT (HR_CTV) differences are large, statistically significant from a lower threshold of 1% ($p < 0.01$), no matter which (parametric or non-parametric) test was applied.

Table 3

Mean and median values of volume parameters between HR_CTV and IR_CTV obtained after formulating standardized computed tomography contours

Indicator	IR_CTV (100%)	HR_CTV (100%)	IR_CTV (90%)	HR_CTV (90%)
Mean	30.94%	54.41%	35.9%	61.4%
Median	29.06%	54.08%	33.3%	60%
Range	16.16–60%	11.16%–89.0%	18.6%–68.7%	32.5%–92%
Mean confidence interval at 95% level	+/–2.83p.p	+/–4.13p.p.	**+/–3.17p.p.**	+/–3.98p.p.

The volume of IR_CTV which receives 100% of dose varies between 16.16 and 60% with a 30.9 % mean showing how small the coverage with doses is. Even if high risk CTV which receives 100% of doses is larger than initial, in mean of 54.41% in broader band (11.2–89%) the coverage is still small as column 1 and 2 from Table 4 show it. The same conclusion is seen when CTV which receives 90% of dose is analyzed at diagnosis (IR_CTV) *versus* at brachytherapy (HR_CTV).

4. DISCUSSIONS

Although the GYN GEC-ESTRO recommends magnetic resonance (MRI) as imaging modality for 3D brachytherapy, previous publications [10, 15, 16] have shown that CT based brachytherapy is feasible. Therefore we have performed our study using CT, adapting the contours according to current literature data [17]. As previously mentioned GTV cannot be defined on CT due to similar signal intensity to the one of the normal cervical tissue. More than that, as previously mentioned in other studies [10], on CT images it is difficult to make a distinction between corpus and cervix uteri, which usually leads to overestimated cervix size. Insufficient tumor volume coverage is unacceptable, because previously published data [18, 19] clearly suggest that a lower brachytherapy is associated with lower progression free

survival and higher incidence o local relapse. Referring to the OARs, contouring was done according to previously published data that recommend whole organ contouring [20], although some studies suggest that for volumes smaller than 5cc OAR outer wall is accepted [21]. Referring to the 3D simulation scanning technology, current comparative dosimetrical studies [10, 22] proved that whether we use MRI, or CT, the $D_{0.1cc}$, D_{1cc} and D_{2cc} values are similar for each OAR.

Using reference point doses that have been defined by ICRU 38 report, we can correlate the normal tissue effects with radiation dose, but this correlation will be real if it relates to dose-volume relation. Introducing cross sectional image-based treatment planning for brachytherapy using CT, will provide a concret assessment of dosimetry aspects. 3D CT imaging asks for a dose prescription to a target volume; treatment planning phase aims to cover target as completely as possible. For this, it needs to optimize the plan, considering the dose prescription points, the dose normalisation point and the constraints for OAR. It is mandatory to perform planning phase for every session, in order to assess doses to the targets and as well as the normal tissues, even if fixed geometry applicators are used. Failure to perform dosimetry can result in exceeding the normal tissue tolerance of the organs at risk. 3D treatment planning can determine the bladder and rectal doses more accurately than conventional treatment planning. For correct assessment, should be considered a proper implementation of 3D conformal procedure, especially regarding time optimization between CT scan and treatment delivery, in order to avoid patient movements, which can seriously impact the treatment outcome.

At this time, GYN GEC ESTRO recommendations [14] for reporting OARs dose are for 0.1, 1 and 2cc. Previous studies [21, 22] suggest that $2 \, cm^3$ is most suitable volume to be associated with ICRU reference point for both rectum and bladder, therefore our study focused on comparing D_{2cc} values for rectum and bladder from 3D planning with ICRU reference points.

Current literature data [23] suggest that rectal toxicity is best correlated with D_{2cc} and D_{1cc}, but also that D_{5cc} is considered the minimal volume required for fistula formation [24, 25]. Although a few studies [26, 27] found no difference between D_{2cc} and ICRU 38 rectal points, most dosimetrical data [28, 29], including the ones from our study, confirm significantly higher doses for 3D planning compared with ICRU point doses.

For the urinary bladder, most published data [25, 28, 29, 30], also confirm a statistically significant higher dose for 3D brachytherapy planning for the D_{2cc} and maximum dose parameters, compared to ICRU 38 point. As presented in Table 4, our study's results are similar to those of currently published data [24], supporting the use of image guidance and 3D treatment planning for HDR brachytherapy of cervix cancer.

Table 4

Descriptive statistic of mean dose rapport in 3D *vs.* 2D plan

Ratio (Mean values)	Georgescu M.T. *et al.*	Chottaweesak P. *et al.* [24]
Bladder D_{2cc}/ICRU38	2.01 (+/–0.15)	1.56 (+/–0.45)
Rectum D_{2cc}/ICRU38	1.24 (+/– 0.06)	1.16 (+/–0.44)
Sample volume	*n* = 61	*n* = 16

Referring to sigmoid colon dosimetric results, few published literature data exist at this time [31]. Because in 2D brachytherapy the sigmoid cannot be visualized leading to the absence of an ICRU point for this organ, we defined it on 3D planning as the nearest point, of the sigmoid wall, to the brachytherapy applicator. Although our results are slightly different from the other studies, most probably due to organ contouring, the hypothesis that this organ should also be included in the OAR category due to its proximity to radiation sources in 3D planning, has been confirmed.
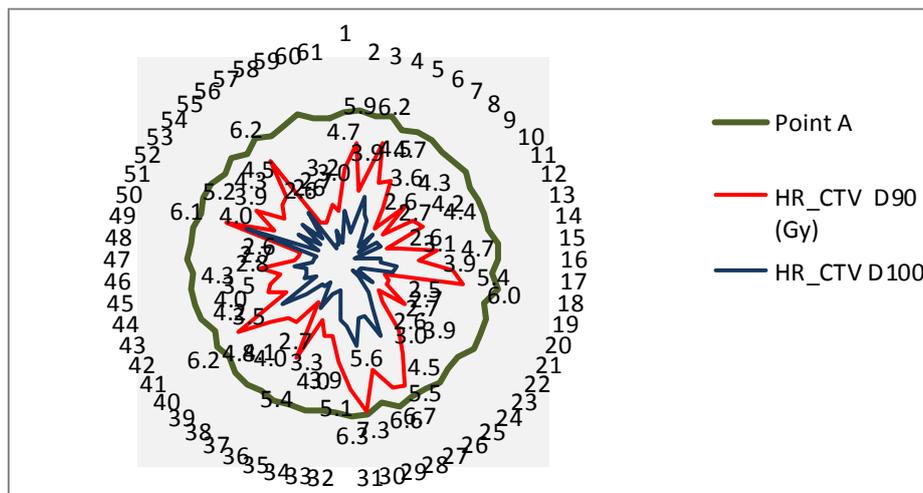

Fig. 3 – Dosimetric comparison between HR_CTV received and point A prescribed dose.

Dosimetric data analysis show that point A prescribed doses are much larger (higher) than the doses received by 90% and respective 100% of clinical target volumes (CTV's) in 3D brachytherapy. Figures 3 and 4 are suggestive enough for proving that this difference is statistically significant at threshold less than 1% in both type of statistical analysis parametric *vs.* non-parametric.
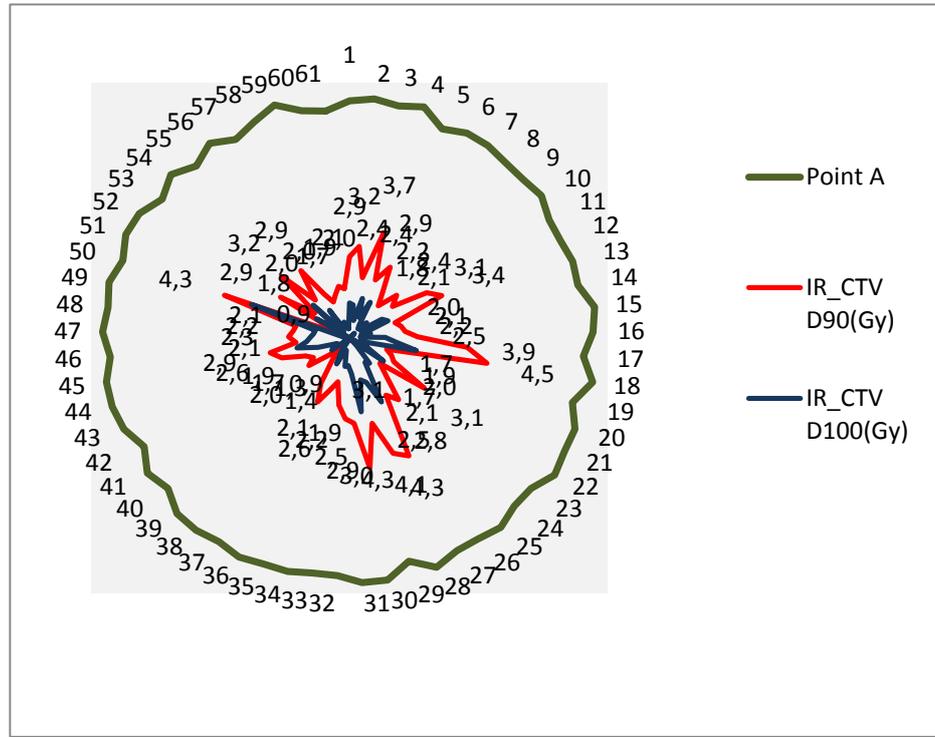
Fig. 4 – Dosimetric comparison between IR_CTV received and point A prescribed dose.

Factors like duration between orthogonal and CT simulation, the usage of intravenous contrast, CT slice size, accuracy of organ contour and applicator reconstruction might be the reason for dosimetric variations between currently published data [24, 32].

5. CONCLUSIONS

In terms of target coverage, our dosimetric study's results suggest that CT-guided brachytherapy planning is superior to conventional point A planning. Also, concerning avoidance of overdosed normal tissue volumes, we can conclude that, due to inaccurate estimates of the dose to the organs at risk, there is a low correlation between ICRU38 points and the late complications of brachytherapy; therefore volumetric treatment planning will correlate with some of the treatment's side effects, resulting in better evaluation and understanding of brachytherapy. 3D dose optimization should result in an adapted form of brachytherapy, according to individual clinical circumstances [10, 32]. Conformal brachytherapy, by the

introduction of modern imaging modalities, will obviously improve tumor control probability and morbidity, correlating them with the dose-volume parameters. Future directions to be evaluated shall be to determine how this additional information can be used so that risks would reduce without compromising cure.

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