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Dosimetric comparison of two-dimensional versus three-dimensional intracavitary brachytherapy in locally advanced cervical cancer

Дозиметриско упоређивање дво-димензионалне са тро-димензионалном интракавитарном брахитерапијом код локално узнапредовалог карцинома цервикса

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SUMMARY

Introduction/Objective The aim of this study was to dosimetric comparison of two-dimensional (2D) with three-dimensional (3D) planning for high-dose-rate intracavitary brachytherapy (HDR-BT) in locally advanced cervical cancer by dose evaluation in given International Commission on Radiation Units and Measurements (ICRU) reference points, as well as in target volume and organs at risk (OAR).

Methods 66 sessions of HDR-BT were performed in 22 patients, with 3D planning, but also virtual 2D plan for dosimetric comparison was made. 2D planning was performed on radiography obtained by C-arm in ICRU points, while 3D planning in volumes delineated on computer tomography.

Results The comparative analysis has indicated a significant mean dose difference of point "A" left (p=0.00014) and right (p=0.003), through higher doses in 2D and lower doses in 3D reconstructed points "A". According to the dose volume histograms 56.88% and 61.41% mean target volume received 100% and 90% of prescribed dose, respectively. 2D bladder analysis showed a mean dose of 3.487 Gy in ICRU point, while in 3D analysis a maximum mean dose of 8.804 Gy and mean dose of 4.716 Gy in 2ccm volume. 2D analysis showed rectal mean dose of 2.892 Gy in ICRU points, while 3D analysis maximum mean dose of 6.411 Gy and 3.947 Gy mean dose in 2ccm volume.

Conclusion 2D planning showed unreal higher doses in the ICRU points for the target and lower doses for the OAR.

Keywords: cervical cancer; intracavitary brachytherapy; organs at risk; target volume

САЖЕТАК

Увод/Циљ Циљ овог рада је био дозиметриско упоређивање дво-димензионалног (2Д) са тро-димензионалним (3Д) планирањем интракавитарне брахитерапије високе брзине дозе (ВБД-БТ) код локално узнапредовалог цервикалног карцинома са евалуацијом дозе у референтним тачкама датим од Интернационалне Комисије за радијационе јединице и мере (ИКРЈ), као и у циљном волумену и органима ризика.

Методе Код 22 болеснице са 3Д планирањем, реализоване су 66 сесије ХДР-БТ, али је урађено, ради компарације, и 2Д планирање на радиографији са *C-arm* апарата у ИКРЈ тачкама, а 3Д планирање на КТ у делинеираним волуменима.

Резултати Компаративна анализа је показала значајну разлику у дози у левој тачки "А" (p=0,00014) и десној (p=0,003), преко виших доза у 2Д и нижих доза у 3Д реконструисаним тачкама "А". Према дозно волуменским хистограмима просечно је 56,88% волумена примило 100% од преписане дозе, док је 61,41% волумена примило 90% преписане дозе. Анализа бешике као органа ризика, показала је да добија просечну дозу од 3,487 Gy у ИКРЈ тачки, а у 3Д анализи просечни максимум у тачки је био 8,804 Gy, у 2цм^3 волумена добија просечну дозу од 4,716 Gy. 2Д анализа ректума показала је да добија просечно 2,892 Gy у ИКРЈ тачки, док је у 3Д анализи максимална просечна доза у тачки била 6,411 Gy и 3,947 Gy просечне дозе у 2цм^3 волумена.

Закључак 2Д планирање је показало нереално високе дозе у ИКРЈ тачкама и ниже дозе у органима ризика.

Кључне речи: цервикални карцином; интракавитарна брахитерапија; органи ризика; циљни волумен

INTRODUCTION

Cervical cancer is the third most common malignant disease in women, with approximately 530,000 new cases and 275,000 lethal cases on global level in 2014 [1]. In spite of the well-developed screening program for early detection of cervical cancer, the locally advanced disease is still present and demands a specific therapeutic approach.

According to cervical cancer classification of the International Federation of Gynecology and Obstetrics (FIGO) [2], locally advanced cervical cancer means inoperable disease, treated with

external beam concurrent chemoradiotherapy followed by a high-dose-rate brachytherapy (HDR-BT). According to Datta [3], from 1999 till today this type of treatment has shown significant results in treating the advanced cervical cancer. The treatment has the highest curative effect if it is finished in a period of 8 weeks or 56 days [3].

HDR-BT is one of the most efficient radiotherapy techniques in the treatment of cervical cancer by which compensation of radiotherapy dose delivered by percutaneous radiotherapy is achieved [4]. This is due mainly to two factors. The first factor are anatomic conditions that allow insertion of intrauterine and intravaginal applicators, that is, injection of radioactive sources very close to or inside the tumor. The second factor is based on the principle of reducing the dose by the square of the distance, which means that the given high dose can be focused precisely in the tumor itself by quick dose decline in the surrounding normal structures.

In line with the current clinical practice in most of the centers when treating cervical cancer with HDR-BT, the dose is prescribed in reference points during conventional 2D treatment planning. These are empirical points and they do not always coincide with the specified dose. The ICRU report 38 points out the possibility that the specified high dose may not be realized in the tumor [5,6] and that precise data may not be obtained for the real dose at a certain distance from the tumor including the surrounding normal tissues and organs. In order to avoid this inconsistency, the conventional 2D planning treatment is most commonly replaced with 3D treatment planning. It enables radiation with precise dose distribution allowing supply of a controlled high-rate dose in the tumor, which results in better local control of the disease, as well as better control and dose distribution in the OAR hence reducing the adverse toxic events from radiotherapy [7].

Computerized 3D treatment planning by using computer tomography (CT) instead of 2D radiography shows precise localization of applicators, and the applicators relationship with the adjacent structures can be seen by the 3D anatomic model. At the same time, maintenance of applicators position has to be ensured since each shift can cause deviation from the prescribed dose [6,8].

3D brachytherapy treatment planning using image from CT simulation for cervical cancer has been available in our hospital since 2014. Both 2D and 3D planning were initially done to evaluate the dose between these two techniques, in terms of target coverage and doses to bladder and rectum.

METHODS

The study included 22 women with locally advanced inoperable cervical cancer, treated at the University Clinic of Radiotherapy and Oncology – Skopje in the period from November 2014 to September 2015. All patients underwent definitive treatment consisting of concurrent chemoradiation therapy and successive HDR-BT. Brachytherapy was realized according to 3D prepared plan. Additionally virtual 2D plan was made, according to the treatment protocol for 2D planning that we used before, for the purpose of dosimetric comparison of both planning techniques.

Treatment protocol

The treatment started by concurrent chemoradiation therapy. Chemotherapy consisted of administration of weekly bolus cisplatin 40mg/m^2, 5 times in total, followed by radiotherapy fraction 1-3 hours after its application. The external beam radiotherapy was conducted after previous CT scanning, followed by delineation of the target volume and OAR. Conformal "4-field box" technique was implemented on a LINAC with 15 MV photon energy. The total tumor dose was 50.4 Gy in 28 fractions, with daily dose of 1.8 Gy. After finishing the concurrent chemoradiation therapy, the treatment was continued with a HDR-BT in order to compensate the tumor dose, with additional 21 Gy in 3 fractions, once a week at a dose of 7 Gy per fraction.

Uterovaginal application technique

Foley's catheter was inserted, filled with 7ccm contrast and fixed against the bladder neck. CT compatible tandem-ring applicators were used for HDR-BT. After the applicators were inserted, they were stabilized, and rectum and bladder were set apart from the applicators with vaginal gauze packing. Only for 2D planning rectal marker was placed deeply in the rectum to visualize it. All patients underwent 3D – CT simulation and additionally virtual 2D - orthogonal simulation for each session.

When the application is done the patient is transferred to the CT simulator in order to make a 3D simulation. The main problem is the transport of patient from operating room to CT simulator and later back from the CT simulator to the operating room. During the transport there is a possibility of geometry change of the previously placed applicators. Because of that, applicator position during the irradiation will be different from the one present after the insertion by the radiation oncologist. We solved that problem with a construction of special tabletop. Tabletop consist of two parts: upper part of the table that ends at the patient's pelvis, on it patients are positioned as on gynecological table during the application, and the second lower (caudal) part which is joined with the upper part after the application is over. Patient's legs are stretched down and previously inserted applicators are fixated by using a clamping device which is firmly attached on the lower part of the tabletop. On upper and lower part of the tabletop there are handles so the patient can be lifted up and put on a transport cart. Patient is positioned on CT simulator and later returned to the operating room and/or brachytherapy bunker without fear of applicators displacement.

Virtual two-dimensional conventional planning (according to the 2D treatment protocol, which we used before)

The C-arm was used to generate orthogonal postero-anterior (PA) and latero-lateral radiography (LL) where reconstruction and treatment planning were defined. The prescribed dose was controlled in certain reference points for the target volume, along with monitoring the dose in the reference points for the OAR. As the critical structures are not fully visualized, the dose is prescribed in points. The ICRU reference point for the target volume in which dose of 7 Gy is prescribed, is point "A" (left

and right). The bladder reference point (ICRUb) on LL radiograph is projected on the posterior aspect of the balloon, the nearest point to the applicators, while on PA radiograph it is in the center of the balloon. Maximum allowed dose in the bladder reference point is 80% from the prescribed dose (5.6 Gy per fraction).

The reference point of the rectum (ICRUr) on LL radiograph is 5 mm behind the vaginal fornix or from the rectal marker whereas on PA radiograph it is on the inferior end of the tandem. Usually we used three points along the rectal marker that are nearest to the active length of the applicators. The maximum dose (rDmax) to rectum was the highest recorded dose at one of these three points.The maximum permitted dose in these reference points is 70% of the given dose (4.9 Gy per fraction).

Actual three-dimensional computer tomography-based planning

The applicators are CT compatible, thus 3D planning was carried out by CT simulator, where the region of interest was scanned after the application was realized. With delineation of structures of interest, the target volume (uterus) and the OAR (bladder, rectum) three-dimensional model was provided. In that way critical structures were clearly visualized in the reconstructed volume.

In both cases (for 2D and 3D planning), medical physicists calculated the dose with the special software Varian Brachyvision. HDR-BT was done in patients according to 3D designed plan with a Gamma Medplus apparatus, with a radioactive source Iridium 192. In outpatient setting three fractions of HDR-BT were given to each of the patients once a week.

Statistical analysis

All analyses were made with the SPSS for Windows 17.0 statistical program. Categorical variables are presented in absolute and relative numbers, and quantitative variables are presented with descriptive statistics (mean, ± SDi). To test the distribution of data Kolmogorov-Smirnov and Shapiro-Wilks test were used as well as the values of z score of the measure of asymmetry (skeweness) and of the measure of shape (kurtosis). Student's t-test was used to compare 2D and 3D treatment planning for target coverage and dose to OAR. A p-value <0.05 was considered statistically significant.

Table 1. Baseline characteristics.

	n (%)
Patient characteristics	
Gender: female	22 (100%)
Age (years)	51±11.3 (25–71)
Tumor characteristics	
Histology:	
squamous cell carcinoma	18 (81%)
mucoepidermoides carcinoma	3 (14%)
adenosquamous carcinoma	1 (5%)
Tumor cell differentiation:	
well differentiated	5 (22%)
moderately differentiated	11 (50%)
poorly differentiated	6 (28%)
Clinical stage:	
IIB	17 (77%)
IIIA	4 (18%)
IIIB	1 (5%)

RESULTS

In this study we have analyzed the data obtained from 22 patients with mean age of 51±11.3 years. Detailed characteristics of the patients and of the tumor are shown in table 1. According to the histopathology of malignant cells, the squamous cell carcinoma prevailed in 81% of patients. Moderate rate of malignant cells differentiation was observed in 50% of patients.

Concerning the clinical stage of the disease, the largest number of patients (77%) had stage IIB cancer.

Dosimetric analysis of all 66 brachytherapy applications and their comparison done with both ways of intracavitary brachytherapy planning was made. The mean values of the obtained doses per fraction in reference points that cover the target volume for both ways of planning are presented in table 2. Reconstruction of ICRU reference point "A" was made in 3D planning for the correct comparison of the data. The comparative analysis has indicated a statistically significant difference in

Table 2. Mean dose values for the target volume per reference points

	2D planning (Gy)	3D planning* (Gy)	2D planning vs. 3D planning
ICRU "A" - left	7.241±0.2 (6.632-7.818)	7.006±0.05 (6.925-7.143)	t=4.2 p=0.00014†
ICRU "A" - right	7.204±0.28 (6.676-7.961)	7.014±0.03 (6.953-7.120)	t=3.14 p=0.003†

2D: two-dimensional, 3D: three-dimensional,
ICRU: International Commission on Radiation Units and Measurements.
*(3D) reconstruction of ICRU reference point "A"
†t (Student's t-test) p<0.01

the mean dose of reference point "A" left (t=4.2; p=0.00014) and "A" right (t=3.14; p=0.003). 2D planning showed higher doses in reference points "A" compared to lower doses received in the reconstructed reference points "A" in 3D planning.

3D planning through dose-volume histogram showed isodose coverage of the target volume as a whole, and not only in a point. By its analysis it was found that V100 (volume that received 100% of the prescribed dose) had mean value of 56.88±19.5% and range of 18.573-99.163%, while V90 (volume that received 90% of the prescribed dose) had mean value of 61.41±19.7% and range of 21.133-99.606% (Figure 1).

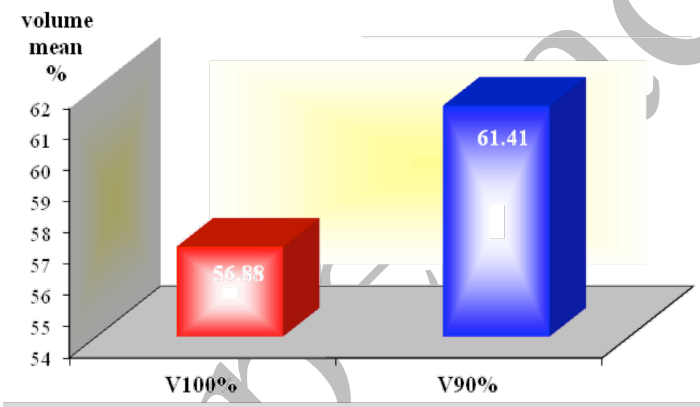

Figure 2. Percentage isodose coverage of target volume by analysis of V100 and V90.

Table 3 presents the obtained mean dose values in bladder as an OAR. Regarding the evidence and control of the dose in the bladder in 2D planning only one ICRU reference point (ICRUb) was used with obtained mean value of 3.487±1.9 Gy, which was within the tolerance limit of 80% of the prescribed dose. In 3D planning the obtained mean values were significantly higher both for the maximum dose (bDmax), which amounted to 8.804±4.9 Gy, as well as for the mean volume

Table 3. Mean dose values in bladder.

2D planning (Gy)	3D planning (Gy)	2D vs 3D
ICRUb	bDmax	
3.487±1.9	8.804±4.9	
(1.444–8.856)	(3.459–26.830)	t=4.7 p=0.00003
ICRUb	bD2ccm	
3.487±1.9	4.716 ±1.9	
(1.444–8.856)	(2.357–10.467)	t=2.2 p=0.035

2D: two-dimensional, 3D: three-dimensional, ICRUb: International Commission on Radiation Units and Measurements-bladder reference point, bDmax: bladder point with maximal dose, bD2ccm: dose in bladder volume of 2ccm. t - Student's t-test.

dose in 2 ccm (bD2ccm) of 4.716±1.9 Gy, but at the same time they were in the reference range. Statistically significant difference was obtained by comparing the ICRUb from 2D planning with bDmax (t=4.7 p=0.00003**) and bD2ccm (t=2.2 p=0.035*) from 3D planning.

Table 4 illustrates the obtained mean dose values in the rectum as the second analyzed OAR. In 2D planning three rectal reference points were used for dose evidence and control in the rectum. The obtained mean value (ICRUr) of 2.892±0.6 Gy was within tolerance limit. In 3D planning, significantly higher mean values were obtained both for the maximum dose (rDmax) that amounted to 6.411±1.8 Gy as well as for the dose in volume of 2 ccm (rD2ccm) with mean value of 3.947±0.8 Gy, ranging within tolerance limit. Statistically significant difference was obtained by comparing the ICRUr from 2D planning with rDmax (t=8.8 p<0.0001) and rD2ccm (t=4.8 p=0.00002) from 3D planning. Voluminously realized dose was obtained by analysis of dose-volume histogram in 3D planning.

Table 4. Mean dose values in the rectum.

2D planning (Gy)	3D planning (Gy)	2D vs 3D
ICRUr	rDmax	
2.892±0.6 (1.577-3.676)	6.411 Gy±1.8 (3.689-11.433)	t=8.8 p<0.0001
ICRUr	rD2ccm	
2.892±0.6 (1.577-3.676)	3.947 Gy±0.8 (2.391-5.247)	t=4.8 p=0.00002

2D: two-dimensional, 3D: three-dimensional, ICRUr: International Commission on Radiation Units and Measurements-rectum reference point, rDmax: rectum point with maximal dose, rD2ccm: dose in rectum volume of 2ccm. t: Student's y-test.

It can be clearly seen that unlike in 3D planning, significantly lower values for the absorbed dose in the OAR were obtained in 2D planning. But, that is due to the limited capabilities of 2D planning which gives information of the dose in a point, while the higher dose values in 3D planning are a result of the option for displaying the maximum dose and the absorbed volume dose.

DISCUSSION

As individualized treatment based on CT or nuclear magnetic resonance, 3D brachytherapy is more commonly used in the treatment of cervical cancer. The aim is to improve the dose control and its real presentation. 2D brachytherapy is a standard and routine treatment in our Institution. Traditionally, this has been done using plain film X-rays only, but this technique has its limitations. Our modest experience with 3D planning was aimed at improving the treatment of these patients. However, in the literature there are numerous studies reporting their results. Potter's study [4] presents the similarity in the dose of rectum in both ways of planning, but on the other hand, itpoints out the possibility for late rectal complication as an adverse effect. In addition, higher bladder toxicity is emphasized. Nevertheless, the recommendations of Gynaecological European Society for Therapeutic Radiology and Oncology (GYN GEC ESTRO) inform about certain tolerance by the OAR [9]. Ling et al. [10] studied the maximum doses of the bladder and rectum by using CT evaluation and they found out that bladder dose in 3D planning was almost two times higher than that in ICRU reference points during 2D planning. However, some studies present no statistically significant differences in the dose in the OAR between the two ways of planning. In the study of

Jamema et al. [11] there was no significant difference between the mean values in dose-volume histograms and ICRU reference points.

The variations in the dose are explained by several factors such as the possible difference during reconstruction of the points and applicators in planning since they should be carried out by the same medical physicist while very often difficulties appear due to presence of metal artifacts. Another factor is different techniques used in different centers when applying a rectal retractor (placed in the vagina) or marking the rectum with rectal marker (placed in the rectum). Certain centers position the reference points along the marker, while in other centers, such as ours, they are positioned in front of the marker, that is, in the rectal wall. The contours correctness in 3D delineating is important as well as the time for making the orthogonal radiographs for 2D and CT scanning for 3D planning (the best is up to 30 minutes).

Regarding the target volume a significant difference between 2D and 3D planning was observed in our study. While 2D planning the planner rotates slightly the applicators around the sagittal axes in order to get line projection of the ring applicator. That will cause different space position of points "A" between 2D and 3D planning. That results in dose difference with inherent uncertainty regarding image reconstructions in these two planning approaches. However, it has to be pointed out that 3D planning offers possibility for detailed monitoring of isodose coverage of the target volume through dose-volume histogram. A good isodose schedule secures better local control of the disease. In lack of opportunity for accurate visualization and setting a safety margin around the cervix, CT delineation encompasses target volume which covers the uterus entirely. This must be taken into consideration when analyzing isodose coverage of the target volume. In case of a large uterine volume it is logical to get a smaller 100% and 90% isodose coverage. Magnetic resonance imaging (MRI) is superior to CT and exceeds this limitation with the possibility of a clear visualization of the cervix and surrounding clinical target volume of high risk [7]. As it would be difficult to perform MRI-based brachytherapy for logistic reasons CT-based image planning is a reasonable substitute.

In addition, the specific radiobiologic characteristic of the HDR-BT has to be taken into consideration. The prescribed high dose (higher than the dose in EBRT) is well tolerated due to the volume-effect ratio (small volumes can tolerate high doses) showing the main difference between 2D and 3D dose reporting, that is, during 2D in point while during 3D in volume. With reference to the OAR (bladder and rectum) the comparison has shown significantly lower dose values in 2D and higher in 3D planning. The higher dose values that appear in 3D planning refer to the volume and are within the tolerance limits of OAR, but yet, it has to be taken into account as possibility for underlining the postirradiation adverse effects. Cumulative radiotherapy dose (from external radiotherapy and HDR-BT) in point "A" reaches biologically weighted up to 85 Gy_{EQD}^2, in our study 79.3 Gy_{EQD}^2 (α/β=10 Gy). OAR tolerance limit is confined to cumulative weighted dose in volume of 2ccm to 95 Gy_{EQD}^2 (α/β=3 Gy) for bladder and 65 Gy_{EQD}^2 (α/β=3 Gy) for rectum [4].

In the conclusions of majority of studies, 3D planning is recommended to be a more precise way of planning and provides easier overcoming of all previously presented errors. It is expected that therapeutic ratio analyzed through the adequate dose coverage of the target volume from one side and dose decline in OAR from the other side could be substantially enhanced if the radiation dose is prescribed according to 3D model of brachytherapy planning [4,12-16].

ICRU report 89 [7] provides latest comprehensive recommendations on prescribing, recording, and reporting brachytherapy focusing on volumetric imaging in cervix cancer brachytherapy. However, it is well recognized that the majority of advanced cervix cancer patients are and will be treated in developing countries with limited resources. Patients in these countries are ussualy treated with simple radiotherapy methods and with "minimal standard" for reporting the parameters.

CONCLUSION

This study demonstrated that 3D HDR brachytherapy planning using CT is an improved individual treatment method of planning compared to 2D HDR brachytherapy planning using orthogonal radiography. CT-based image planning allows more realistic, precise identification and dose optimization in the target volume and in the OAR. Each institution has to inspect its resources and number of patients in order to ensure the most sophisticated treatment of the patients. Further research and development of sophisticated brachytherapy techniques in locally advanced cervix cancer is of great importance having in mind the long survival of these patients.

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