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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

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

Violeta Klisarovska[1], Snezhana Smichkoska[2], Petar Chakalaroski[1], Valentina Krstevska[3], Nadica Dimitrovska[4], Zoran Stefanovski[4], Emilija Lazarova[2]

[1]University Clinic of Radiotherapy and Oncology, Department of Gynecologic Oncology and Brachytherapy, Skopje, Republic of Macedonia;
[2]University Clinic of Radiotherapy and Oncology, Department of Breast Cancer, Skopje, Republic of Macedonia;
[3]University Clinic of Radiotherapy and Oncology, Department of Head and Neck Cancer, Skopje, Republic of Macedonia;
[4]University Clinic of Radiotherapy and Oncology, Medical Faculty, Department of Medical Radiation Physics, Skopje, Republic of Macedonia

SUMMARY

Introduction The aim of this study was 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.

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

Results The comparative analysis 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 the prescribed dose, respectively. 2D bladder analysis showed a mean dose of 3.487 Gy in ICRU points, while in 3D analysis a maximum mean dose of 8.804 Gy and a mean dose of 4.716 Gy in 2 cm^3 volume. 2D analysis showed a rectal mean dose of 2.892 Gy in ICRU points, while 3D analysis showed maximum mean dose of 6.411 Gy and 3.947 Gy mean dose in 2 cm^3 volume.

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

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

INTRODUCTION

Cervical cancer is the third most common malignant disease in women, with approximately 530,000 new cases and 275,000 lethal cases on the 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, locally advanced cervical cancer means inoperable disease, treated with external beam concurrent chemoradiotherapy followed by a high-dose-rate brachytherapy (HDR-BT) [2]. According to Datta and Agrawal [3], from 1999 to date this type of treatment has shown significant results in treating advanced cervical cancer. The treatment has the highest curative effect if it is finished in a period of eight 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 medical 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 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 [5, 6]. In order to avoid this inconsistency, the conventional 2D planning treatment is most commonly replaced with 3D treatment planning.

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Correspondence to:
Violeta KLISAROVSKA
University Clinic of Radiotherapy and Oncology
17 Mother Theresa Str.
Skopje 1000
Republic of Macedonia
vikiklisarovska@yahoo.com

It enables radiation with precise dose distribution allowing a 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 organs at risk (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 40 mg/m^2, five times in total, followed by radiotherapy fraction one to three hours after its application. The external beam radiotherapy was conducted after previous CT scanning, followed by delineation of the target volume and OAR. Conformal "four-field box" technique was implemented on a linear accelerator with 15 MV photon energy. The total tumor dose was 50.4 Gy in 28 fractions, with a 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 three fractions, once a week at a dose of 7 Gy per fraction.

Uterovaginal application technique

A Foley catheter was inserted, filled with 7 cm^3 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 the rectum and bladder were set apart from the applicators with vaginal gauze packing. Only for 2D planning, a rectal marker was placed deeply in the rectum to visualize it. All the patients underwent a 3D-CT simulation and additionally a 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 the patient from the operating room to the 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 this, applicator position during the irradiation will be different from the one present after the insertion by the radiation oncologist. We solved this problem with a construction of a special tabletop. The tabletop consists of two parts: the upper part of the table that ends at the patient's pelvis – during the application, patients are positioned on it as on a gynecological table; the second, lower (caudal) part, is joined with the upper part after the application is over. The patient's legs are stretched down and previously inserted applicators are fixated by a clamping device firmly attached to the lower part of the tabletop. There are handles on both the upper and the lower part of the tabletop so the patient can be lifted and put on a transport cart. The patient is positioned on the CT simulator and later returned to the operating room and/or brachytherapy bunker without any fear of applicator displacement.

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

The C-arm was used to generate orthogonal posteroanterior and laterolateral radiographs 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 the dose of 7 Gy is prescribed is point A (left and right). The bladder reference point (ICRUb) on the laterolateral radiograph is projected on the posterior aspect of the balloon, the nearest point to the applicators, while on the posteroanterior radiograph it is in the center of the balloon. The maximum allowed dose in the bladder reference point is 80% of the prescribed dose (5.6 Gy per fraction).

The reference point of the rectum (ICRUr) on the laterolateral radiograph is 5 mm behind the vaginal fornix or from the rectal marker, whereas on the posteroanterior radiograph it is on the inferior end of the tandem. We usually used three points along the rectal marker that are nearest to the active length of the applicators. The maximum dose (rDmax) to the 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 3D CT-based planning

The applicators are CT compatible, thus 3D planning was carried out by a CT simulator, where the region of interest was scanned after the application was realized. With delineation of structures of interest, the target volume (the uterus) and the OAR (the bladder, the rectum) 3D model

was provided. In this way, critical structures were clearly visualized in the reconstructed volume.

In both cases (for 2D and 3D planning), medical physicists calculated the dose by using specialized BrachyVision™ software (Varian Medical Systems, Palo Alto, CA, USA). HDR-BT was done in patients according to 3D designed plan with a Gamma Medplus apparatus (Varian Medical Systems), with iridium 192 as the radioactive source. In an outpatient setting, three fractions of HDR-BT were given to each patient once a week.

Statistical analysis

All analyses were made with the SPSS Statistics for Windows, Version 17.0 (SPSS Inc., Chicago, IL, USA) 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–Wilk tests were used, as well as the values of z-score as the measure of asymmetry (skewness) and of the 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.

RESULTS

In this study we have analyzed the data obtained from 22 patients with the mean age of 51 ± 11.3 years. Detailed characteristics of the patients and of tumors are shown in Table 1.

Table 1. Baseline characteristics

Characteristics	n (%)
Patient characteristics	
Sex: female	22 (100)
Mean age (years) ± SD, (range)	51 ± 11.3 (25–71)
Tumor histological characteristics	
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)

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

Reference point	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

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 was made for all 66 brachytherapy applications and the comparison of both ways of intracavitary brachytherapy planning was done. 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 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 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 a mean value of 56.88 ± 19.5% and a range of 18.573–99.163%, while V90 (volume that received 90% of the prescribed dose) had a mean value of 61.41 ± 19.7% and a range of 21.133–99.606% (Figure 1).

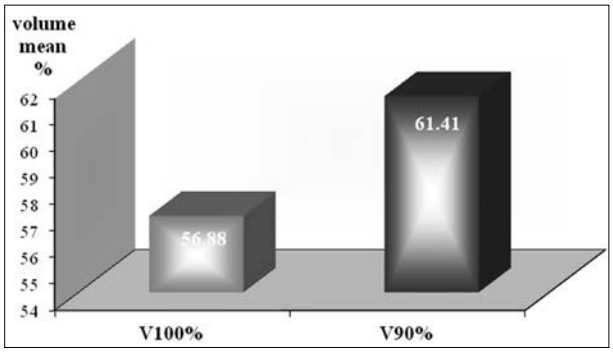

Figure 1. Percentage isodose coverage of target volume by analysis of V100 and V90 (volumes that received 90% and 100% of the prescribed dose, respectively)

Table 3 presents the obtained mean dose values in the 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 the 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, and for the mean volume dose in 2 cm^3 ($bD2cm^3$) of 4.716 ± 1.9 Gy, but at the same time they were in the reference range. A statistically significant difference was obtained by comparing the ICRUb from 2D planning with bDmax (t = 4.7; p = 0.00003**) and $bD2cm^3$ (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

Table 3. Mean dose values in the 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	bD2cm^3	
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 the maximal dose; bD2cm^3 – dose in the bladder volume of 2 cm^3; t – Student's t-test;
*p < 0.05
**p < 0.01

Table 4. Mean dose values in the rectum

2D planning (Gy)	3D planning (Gy)	2D vs. 3D
ICRUr	rDmax	
2.892 ± 0.6	6.411 Gy ± 1.8	
(1.577–3.676)	(3.689–11.433)	t = 8.8; p < 0.0001
ICRUr	rD2cm^3	
2.892 ± 0.6	3.947 Gy ± 0.8	
(1.577–3.676)	(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; rD2cm^3 – dose in the rectum volume of 2 cm^3; t – Student's test p < 0.01

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 the tolerance limit. In 3D planning, significantly higher mean values were obtained for both the maximum dose (rDmax), which amounted to 6.411 ± 1.8 Gy and the dose in volume of 2 cm^3 (rD2cm^3) with a mean value of 3.947 ± 0.8 Gy, ranging within the tolerance limit. A statistically significant difference was obtained by comparing the ICRUr from 2D planning with rDmax (t = 8.8; p < 0.0001) and rD2cm^3 (t = 4.8; p = 0.00002) from 3D planning. Voluminously realized dose was obtained by analyzing the dose-volume histogram in 3D planning.

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. However, this is due to the limited capabilities of 2D planning, which gives information on 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. A study by Potter et al. [9] presents the similarity in the dose of the rectum in both ways of planning, but, on the other hand, it points out the possibility for late rectal complication as an adverse effect. In addition, higher bladder toxicity is emphasized. Nevertheless, the recommendations of the Gynaecological European Society for Therapeutic Radiology and Oncology inform about certain tolerance by the OAR [10]. Ling et al. [11] studied the maximum doses of the bladder and the 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 by Jamema et al. [12] 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 difficulties very often appear due to the 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 contour 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 time is up to 30 minutes).

Regarding the target volume, a significant difference between 2D and 3D planning was observed in our study. During 2D planning, the planner rotates slightly the applicators around the sagittal axes in order to get line projection of the ring applicator. This causes a different space position of points A between 2D and 3D planning, which 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 a 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, specific radiobiological characteristics of the HDR-BT has to be taken into consideration. The prescribed high dose (higher than the dose in external

beam radiation therapy) 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 – during 2D in point and during 3D in volume. With reference to the OAR (the bladder and the 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 it has to be taken into account as a possibility for underlining the postirradiation adverse effects. Cumulative radiotherapy dose biologically weighted (from external radiotherapy and HDR-BT) in point A reaches 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 2 cm^3 to 95 Gy_{EQD}^2 (α/β = 3 Gy) for the bladder and 65 Gy_{EQD}^2 (α/β = 3 Gy) for the rectum [4].

In the conclusions of the majority of studies, 3D planning is recommended as 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 on one side and dose decline in OAR on the other side could be substantially enhanced if the radiation dose is prescribed according to 3D model of brachytherapy planning [4, 13–17].

ICRU Report 89 [7] provides the 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 in developing countries are and will be treated with limited resources. Patients in these countries are usually treated with simple radiotherapy methods and with the "minimal standard" for reporting the parameters.

CONCLUSION

This study demonstrated that 3D HDR-BP planning using CT is an improved individual treatment method of planning compared to 2D HDR-BP 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 the number of patients in order to ensure the most sophisticated treatment of patients. Further research and development of sophisticated brachytherapy techniques in locally advanced cervix cancer is of great importance having in mind long survival of these patients.

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Дозиметријско упоређивање дводимензионалне са тродимензионалном интракавитарном брахитерапијом код локално узнапредовалог карцинома цервикса

Виолета Клисаровска[1], Снежана Смичкоска[2], Петар Чакаларoски[1], Валентина Крстевска[3], Надица Димитровска[4], Зоран Стефановски[4], Емилија Лазарова[2]

[1]Универзитетска клиника за радиотерапију и онкологију, Одељење гинеколошке онкологије и брахитерапије, Скопље, Република Македонија;
[2]Универзитетска клиника за радиотерапију и онкологију, Одељење за малигне болести дојке, Скопље, Република Македонија;
[3]Универзитетска клиника за радиотерапију и онкологију, Одељење за малигне болести главе и врата, Скопље, Република Македонија;
[4]Универзитетска клиника за радиотерапију и онкологију, Медицински факултет, Одељење медицинске радијационе физике, Скопље, Република Македонија

САЖЕТАК

Увод/Циљ Циљ овог рада је био дозиметријско упоређивање дводимензионалног (2Д) са тродимензионалним (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 ВБТ-БТ, али је урађено, ради поређења, и 2Д планирање на радиографији са *C-arm* апаратом у ИКРЈ тачкама, а 3Д планирање на компјутерској томографији у делинеираним волуменима.

Резултати Компаративна анализа је показала значајну разлику у дози у левој тачки А ($p = 0,00014$) и у десној ($p = 0,003$), преко виших доза у 2Д и нижих доза у 3Д реконструисаним тачкама А. Према дозноволуменским 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, у 3Д анализи просечни максимум у тачки је био 8,804 *Gy*, а у 2 cm^3 волумена добија просечну дозу од 4,716 *Gy*. 2Д анализа ректума показала је да ректум 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 2 cm^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