

ORIGINAL ARTICLE

## Vaginal packing volume impact on dose parameters during radiography and computed tomography based postoperative brachytherapy of cervical carcinoma

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### Summary

**Purpose:** To investigate the influence of the vaginal packing volume on the registered dose parameters evaluated by radiography (2D) and computed tomography (CT) (3D) based brachytherapy planning in cervical cancer patients treated with postoperative radiotherapy.

**Methods:** The postoperative radiotherapy was performed in 40 cervical cancer patients with increased risk for disease relapse. Both, radiography and CT based brachytherapy planning were done in all patients. Vaginal packing volume was evaluated by clinical target volume (CTV)<sub>uk</sub>, assessed on CT scans and analyzed according to the registered dose parameters: doses delivered to the organs at risk (OAR) and the defined CTV, using both planning methods.

**Results:** CTV<sub>uk</sub> volume had statistically significant influence on CTV coverage with the prescribed brachytherapy doses D<sub>90</sub> (p<0.01) and D<sub>100</sub> (p<0.01), revealing a CTV<sub>uk</sub> cut-off value of 25.6 cm<sup>3</sup>. Dividing the patients into two groups according to the cutoff value, we found a statistical

significance in the registered doses to the rectal wall and no significance in the bladder wall doses between the groups. Also, a statistically significant, negative correlation was found between CTV<sub>uk</sub> and following doses: R<sub>max</sub> (rho= -0.34, p<0.05), D<sub>0.1cc</sub> (rho= -0.76, p<0.01), D<sub>1cc</sub> (rho= -0.74, p<0.01) and D<sub>2cc</sub> (rho= -0.72, p<0.01), D<sub>90</sub> (rho= -0.80, p<0.01), D<sub>100</sub> (rho= -0.7, p<0.01).

**Conclusion:** If the brachytherapy vaginal packing is of a large volume (more than 25.6 cm<sup>3</sup>), an asymmetric deformation of the proximal part of the vaginal cavity might appear, leading to inappropriate dose coverage of the CTV part of the vaginal mucosa. Also, making a vaginal packing volume larger than 25.6 cm<sup>3</sup> made no further reduction in the bladder dose, but it made a statistically significant further reduction in the rectal doses.

**Key words:** brachytherapy, cervical cancer, postoperative radiotherapy, vaginal packing

### Introduction

According to the Serbian Cancer Registry for 2010 [1], cervical cancer is the fourth most common malignant disease in women, with 836 newly diagnosed cases, 341 deaths, incidence of 32.0/100,000 and mortality of 12.7/100,000 per year. These data poses Serbia to the very top of the list of European countries regarding cervical cancer incidence and mortality [2].

Early-stage cervical cancer is a disease with a high cure rate of up to 90%. Surgery is the main treatment method of early stages, but in the group of patients with increased risk of disease relapse, radiotherapy (alone or with concomitant chemotherapy) has an irreplaceable role in the post-operative treatment. A combination of different treatment modalities carries a risk of developing

post-therapy sequelae. In most cases these are temporal, but in some patients they may have a chronic character and they may progress over time and significantly reduce the patient quality of life, although a complete remission of disease is achieved.

Due to high doses that can be delivered to the surrounding tissues, brachytherapy (BRT) has an important role in developing high grade G3/4 late post-irradiation toxicity. According to the literature, the risk of developing severe late toxicity after postoperative radiotherapy is around 2-4% [3,4] and has been significantly reduced in the past few decades, mostly because of the implementation of CT/MRI-based (3D) brachytherapy planning instead of radiography-based (2D) planning. CT scanning in brachytherapy enables a precise delineation of the outer contours of all pelvic OAR, the visualization of the dose distribution and an estimation of the doses in small volumes of the OAR wall ( $0.1\text{cm}^3$ -  $D_{0.1\text{cc}}$ ,  $1\text{cm}^3$ -  $D_{1\text{cc}}$  and  $2\text{cm}^3$ -  $D_{2\text{cc}}$ ). It is proved that the dose registered in the most irradiated contiguous volume of  $2\text{cm}^3$  is the most important prognostic factor in developing high grade post-irradiation toxicity such as bladder-vagina and rectum-vagina fistulas [5,6].

In order to reduce doses to OAR, a gauze vaginal packing should be performed during every application. By placing it, the distance between the applicator system and the OAR (bladder and rectum) is enlarged. Due to a very steep dose decline with distance from the irradiation source, it significantly reduces the registered doses to these OAR. The application of an asymmetric and large vaginal packing volume may cause a deformation of the vaginal cavity, while dislocation of the vaginal walls from the applicator system are also present. As the vaginal postoperative cuff and the proximal vagina mucosa are CTV that need to be irradiated with a therapeutic dose, it is obvious that zones of an inappropriate dose coverage of CTV ("cold areas") can appear.

CT-based brachytherapy during the postoperative radiotherapy of cervical cancer definitely represents the most sophisticated approach. However, there are no many articles that address this clinically relevant issue.

## Methods

This research included 40 patients with cervical cancer, treated in 2014 with postoperative radiotherapy at the Institute for Oncology and Radiology of Serbia.

External beam radiotherapy (EBRT) dose was delivered with 40-45 Gy (depending on the operative nodal status) in 22-25 fractions, 1.8 Gy per day, 5 days

per week. EBRT was performed by either using two opposite pelvic fields, or, in most cases, with four box fields conformal CT planning. During EBRT, if risk factors were present, concomitant cisplatin chemotherapy was administered at a dose of  $40\text{ mg/m}^2$ , once a week during EBRT.

Brachytherapy was performed with high dose rate (HDR)  $\text{Ir}^{192}$  regimen, using Fletcher CT/MRI compatible applicator system, once a week in 3-4 applications, with a dose of 6 Gy per application, specified to 0.5 cm from the ovoid's surface. In order to reduce the registered doses to OAR, vaginal gauze packing towards the rectum and bladder was done during each application. For gauze-packing, a roll of gauze was soaked in sterile saline. Beginning at the proximal vagina, gauze was inserted with forceps, anteriorly and posteriorly to the applicator, until the vaginal introitus was reached.

Brachytherapy verification and planning was done for each patient in two ways: by two conventional orthogonal digital radiographies – frontal and lateral (x-ray based-2D planning), and a series of CT slices with the applicator system in place (CT based-3D planning). For the purpose of radiographic visualization, the bladder was marked with Folley catheter and 7 ml of diluted Ultravist iodine contrast in its balloon, while the rectum was marked with the catheter and 10 ml of Ultravist contrast with the same dilution. CT scanning was performed with a slice thickness of 2.5 mm, and both sets of images were imported to Oncentra planning system afterwards.

In order to assess the dose to the OAR during 2D planning, ICRU reference points for bladder ( $B_{\text{max}}$ ) and rectum ( $R_{\text{max}}$ ) were defined as recommended by the ICRU-38 report. For the purpose of 3D brachytherapy planning, the outer contours of OAR were delineated on each slice as follows: bladder through whole volume, rectum to the recto-sigmoid junction, sigmoid colon and small bowel to 2 cm cranial above the vaginal cuff. CTV was defined as the vaginal cuff and proximal vaginal wall in a length of 2 cm (Figure 1). In order to estimate the impact of the vaginal packing volume on registered dose parameters,  $\text{CTV}_{\text{uk}}$  was defined as the whole vaginal volume (including the volume of the vaginal packing) with the same length as CTV.

Brachytherapy planning was performed using Oncentra® planning system, and after dose volume histogram (DVH) calculation, maximal doses to the ICRU reference points and small volumes of the OAR wall ( $D_{0.1\text{cc}}$ ,  $D_{1\text{cc}}$  and  $D_{2\text{cc}}$ ) were obtained. Also, a dose delivered to CTV volume, presented as  $D_{100}/D_{90}$ , and defined as the minimal brachytherapy dose that covers 100% and 90% of the CTV volume, was analyzed (Figure 2).

## Statistics

For normal distribution data testing, the Kolmogorov-Smirnov and Shapiro-Wilk tests were used. Descriptive methods (frequencies, percent, mean, median, standard deviation /SD/range) were used to summarize the data. The statistical significance level was set at  $p < 0.05$ . For data testing, the Pearson test, Fisher exact test and Wilcoxon rank sum test were used. The

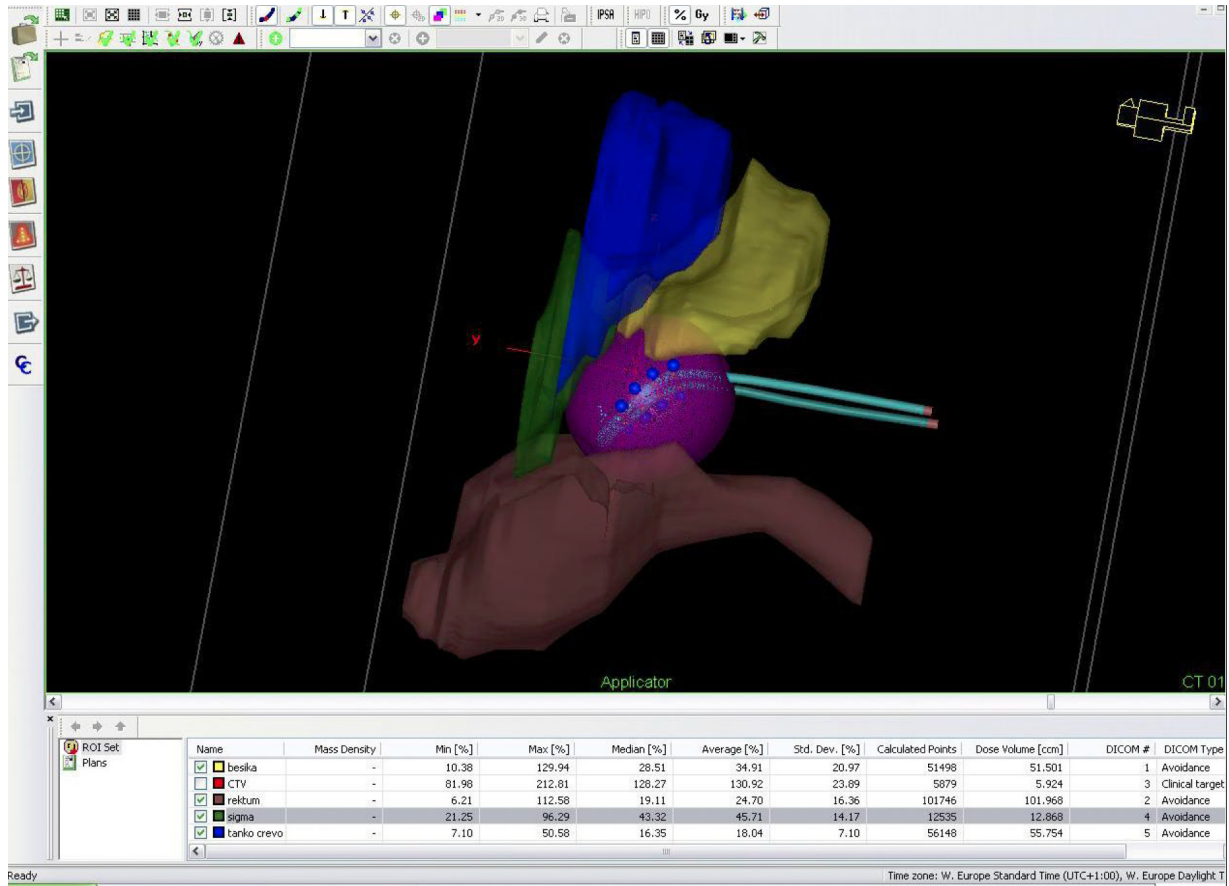


Figure 1. 3D view of the applicator system, dose distribution, bladder (yellow), rectum (brown), sigmoid colon (green) and small bowel (blue).

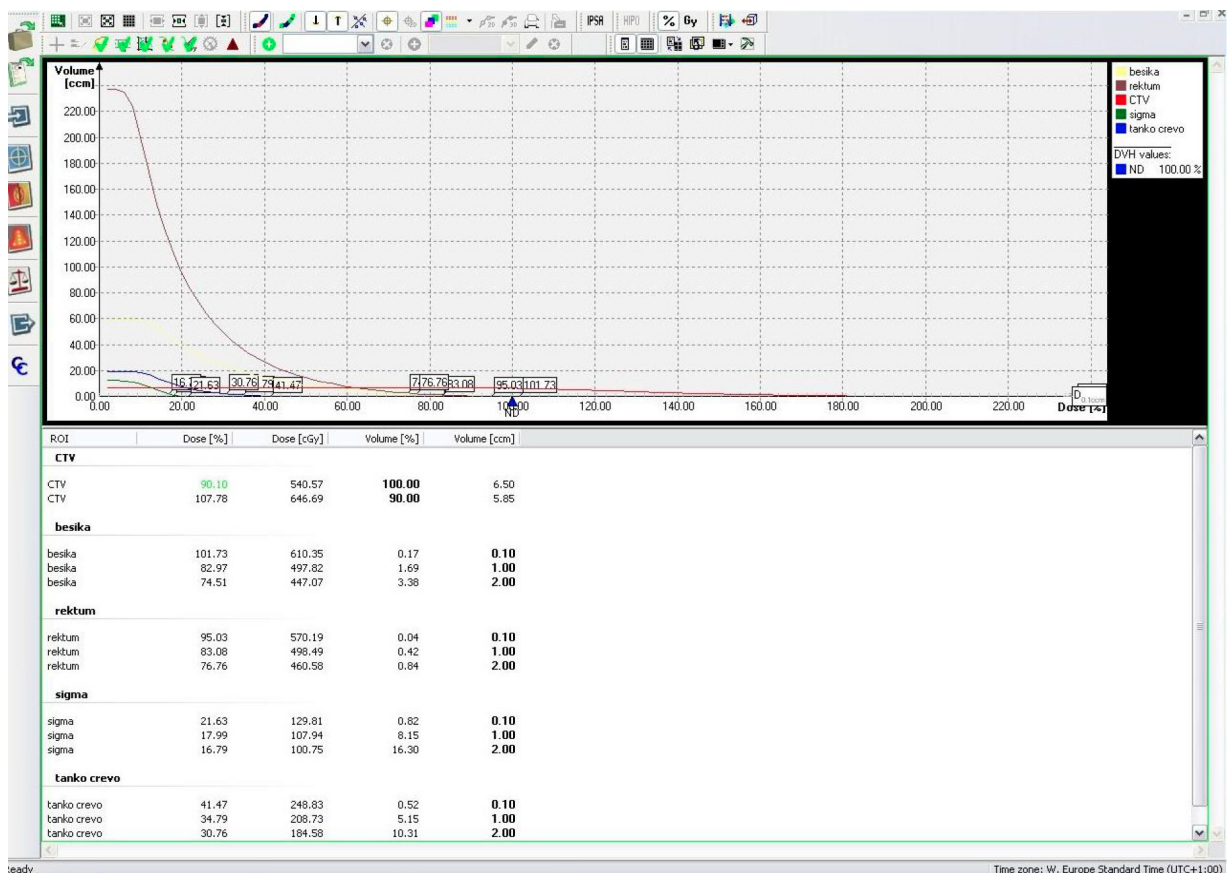


Figure 2. Brachytherapy plan DVH sheet.

Spearman's rank correlation was used for linear correlation investigation between  $CTV_{uk}$  and following doses:  $B_{max}$ ,  $R_{max}$ ,  $D_{0.1cc}$ ,  $D_{1cc}$ ,  $D_{2cc}$ ,  $D_{90}$ ,  $D_{100}$ . Receiver Operating Characteristics curve (ROC) methods were applied for investigation  $CTV_{uk}$  discriminative potential on  $D_{90}$  and  $D_{100}$  values (regarding recommended values) (AUC ROC-Area Under the ROC curve according DeLong's method; Likelihood ratio test for AUC ROC; the best cut-off value for  $CTV_{uk}$  was set as value with maximum sensitivity and specificity). The statistical analysis was done with the program R (version 3.3.2 (2016-10-31) -- "Sincere Pumpkin Patch"; Copyright (C) 2016 The R Foundation for Statistical Computing; Platform: x86\_64-w64-mingw32/x64 (64-bit); downloaded: January 21, 2017).

## Results

This study was conducted on 40 patients with mean age of  $48.68 \pm 8.99$  years, with three registered peaks of disease occurrence: 39, 44 and 62 years. In most of the patients disease was staged as FIGO Ib1 (65%), and squamous cell G2 histology was the most frequent finding (82.5%), with mean tumor size of  $29.2 \pm 13.3$ mm (Table 1). In 60% of the patients lymphovascular invasion was found and metastatic lymph node deposits were found in 22.5% of the patients. The mean number of lymph nodes removed was  $19.2 \pm 10.6$ .

$CTV_{uk}$  influence on  $D_{90}$  and  $D_{100}$  values observed during CT-based brachytherapy planning, directed our further analysis. ROC analysis confirmed the discriminative influence of  $CTV_{uk}$  on achieving the recommended  $D_{90}$  and  $D_{100}$  values, with best  $CTV_{uk}$  cut-off values  $24.07 \text{cm}^3$  for  $D_{100}$  and  $25.60 \text{cm}^3$  for  $D_{90}$  (Table 2; Figure 3).

According to the found  $CTV_{uk}$  cutoff values, the value of  $25.60 \text{cm}^3$  was used to divide

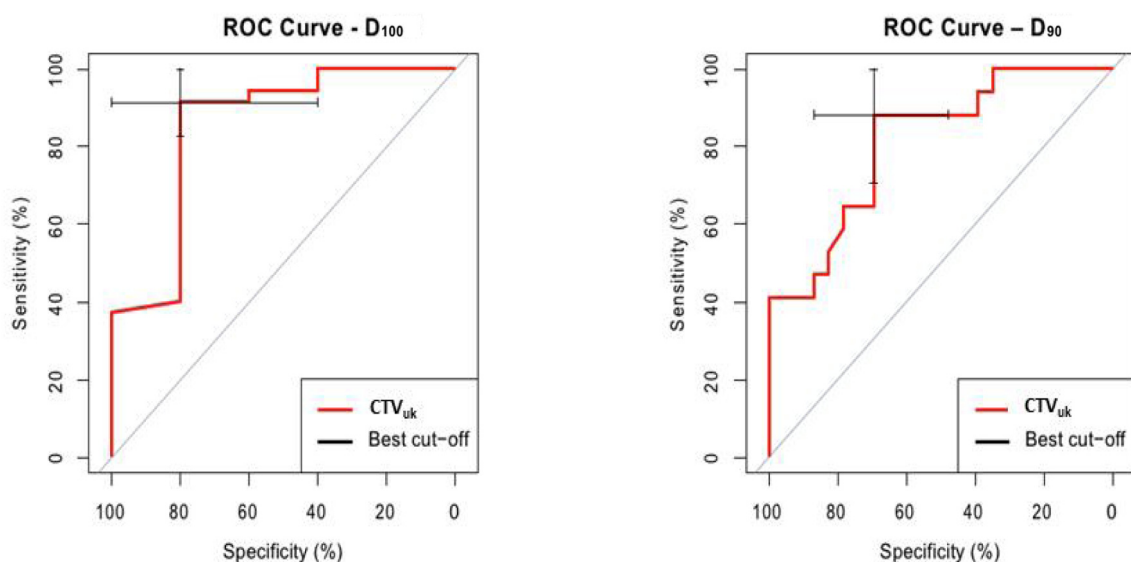
**Table 1.** Patient and disease characteristics

Characteristics	n (%)
Age (years), mean $\pm$ SD	48.68 $\pm$ 8.99
FIGO stage	
Ib1	26 (65.0)
Ib2	7 (17.5)
IIa	3 (7.5)
IIb	4 (10.0)
Histological type	
Squamous cell carcinoma	33 (82.5)
Adenocarcinoma	7 (17.5)
Histological grade	
G1	5 (12.5)
G2	29 (72.5)
G3	6 (15.0)

**Table 2.** Results of the ROC analysis for  $CTV_{uk}$  ( $\text{cm}^3$ ) and  $D_{100}$  /  $D_{90}$  doses (Gy)

$CTV_{uk}$	$D_{100} < 5.4 \text{Gy}$	$D_{90} < 6 \text{Gy}$
AUC ROC* (95%CI)	84.86 (61.4-100)	81.2 (67.9-94.6)
Likelihood ratio test**	p = 0.0016	p = 0.0002
ROC-cut-off value#	24.07	25.60
Sensitivity (95% CI)	91.4 (82.9-100.0)	88.2 (70.6-100.0)
Sensitivity (95% CI)	80.0 (40.0-100.0)	69.6 (47.8-87.0)

\*Area under the ROC curve (DeLong's method); \*\*Likelihood ratio test for AUC ROC; #Value ( $\text{cm}^3$ ) with maximum sensitivity and specificity



**Figure 3.** ROC curves of vaginal packing volume ( $CTV_{uk}$ ) for  $D_{100}$  and  $D_{90}$  doses. Graphical representation of  $CTV_{uk}$  cut-off values regarding their influence on  $D_{100}$  /  $D_{90}$  doses.

patients into two groups ( $CTV_{uk} \leq 25.60\text{cm}^3$  and  $CTV_{uk} > 25.60\text{cm}^3$ ), and the registered dose parameters between the groups were compared.

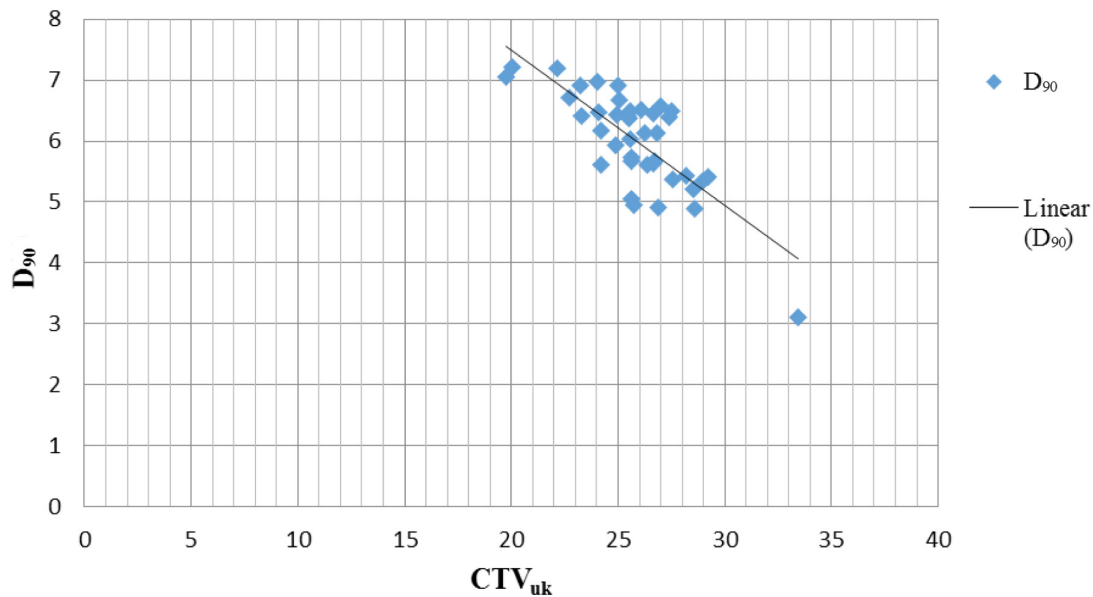
Regarding the registered doses to the bladder, there was not statistically significant difference between the groups (Wilcoxon Rank Sum Test), neither during 2D planning ( $B_{max}$ ), nor during 3D planning ( $D_{0.1cc}$ ,  $D_{1cc}$  and  $D_{2cc}$ ).

On the contrary, for the rectal wall doses, there was a highly statistical significance between the groups (Wilcoxon Rank Sum Test) for both brachytherapy planning methods (Table 3).

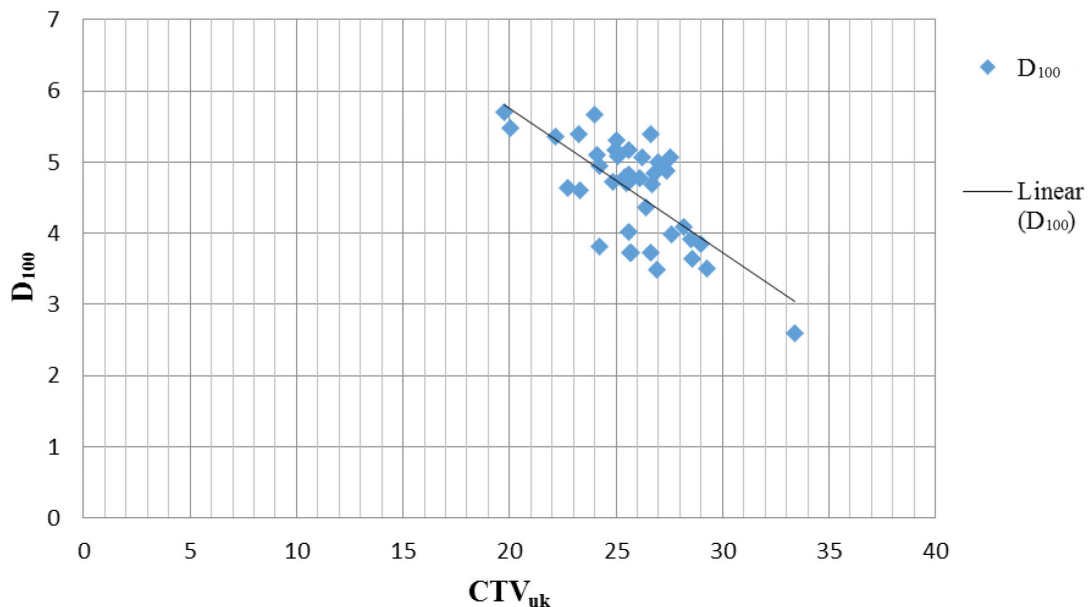
Analyzing the CTV coverage with the prescribed dose, according to  $D_{90}$  and  $D_{100}$  values, there was a highly statistical significance between

the groups ( $CTV_{uk} \leq 25.60\text{cm}^3$  and  $CTV_{uk} > 25.60\text{cm}^3$ ) (Wilcoxon rank sum test with continuity correction),  $6.56 \pm 0.44\text{Gy}$  vs  $5.58 \pm 0.78\text{Gy}$ ,  $p = 8.543 \cdot 10^{-05}$  for the  $D_{90}$ , and  $5.02 \pm 0.46\text{Gy}$  vs  $4.23 \pm 0.70\text{Gy}$ ,  $p = 0.0008$  for the  $D_{100}$ .

Analyzing the correlation between  $CTV_{uk}$  volume and the registered doses to OAR, (Spearman's rank correlation) a strong, negative, statistically significant correlation was found in rectal doses in both planning methods:  $R_{max}$  ( $\rho = -0.34$ ,  $p = 0.03$ ),  $D_{0.1cc}$  ( $\rho = -0.76$ ,  $p = 0$ ),  $D_{1cc}$  ( $\rho = -0.74$ ,  $p = 0$ ) and  $D_{2cc}$  ( $\rho = -0.72$ ,  $p = 0$ ). Also, a statistically significant strong negative correlation was found between  $CTV_{uk}$  and  $D_{90}$  dose ( $\rho = -0.80$ ,  $p = 0$ ),  $D_{100}$  dose ( $\rho = -0.7$ ,  $p = 0$ ) (Figures 4 and 5).



**Figure 4.** Strong negative correlation between  $CTV_{uk}$  ( $\text{cm}^3$ ) and  $D_{90}$  (Gy). Larger vaginal packing volume ( $CTV_{uk}$ ) reduced the minimal brachytherapy dose delivered to 90% of the vaginal cuff volume ( $D_{90}$ ).



**Figure 5.** Correlation between  $CTV_{uk}$  ( $\text{cm}^3$ ) and  $D_{100}$  (Gy). Negative correlation showed that larger vaginal packing volume ( $CTV_{uk}$ ) reduced the minimal brachytherapy dose delivered to 100% of the vaginal cuff volume ( $D_{100}$ ).

**Table 3.** Registered doses to the rectal wall (Gy), regarding CTV<sub>uk</sub> cutoff value groups

Parameter	CTV <sub>uk</sub> ≤ 25.60 cm <sup>3</sup>	CTV <sub>uk</sub> > 25.60 cm <sup>3</sup>	p value*
R <sub>max</sub> (Gy)			0.015
Mean (SD)	5.04 (1.33)	4.07 (0.87)	
Median (Range)	4.64 (2.94-8.38)	4.00 (2.86-5.82)	
D <sub>0.1cc</sub> (Gy)			6.380*10 <sup>-06</sup>
Mean (SD)	6.57 (0.75)	5.01 (0.89)	
Median (Range)	6.44 (5.67-8.34)	3.59 (5.1-6.91)	
D <sub>1cc</sub> (Gy)			1.200*10 <sup>-05</sup>
Mean (SD)	5.30 (0.53)	4.10 (0.72)	
Median (Range)	5.29 (4.44-6.32)	4.09 (2.89-5.48)	
D <sub>2cc</sub> (Gy)			1.959*10 <sup>-05</sup>
Mean (SD)	4.71 (0.47)	3.68 (0.64)	
Median (Range)	4.70 (3.76-5.54)	3.67 (2.61-4.80)	

\*Wilcoxon Rank Sum Test

## Discussion

The demographic characteristics of the treated patients are closely related to data presented in the Serbian Cancer Registry for 2010, with two peaks of disease occurrence at the age of 45-49 and 60-64 years. In this study, there is an apparent shift in the pathological findings, with reduction in squamous cell histology from 90 to 82.5% and an increase in adenocarcinoma histology from 5-10 to 17.5%. This trend is observed in many countries and is mostly explained by the increased frequency of HPV-18 type infection [7].

During the postoperative treatment of cervical cancer patients, brachytherapy is used as a boost to radiotherapy dose delivered with EBRT and allows the creation of dose escalation to the tumor bed (vaginal cuff), which is radio-biologically possible, since the tolerance dose of the proximal vagina is high [8,9]. In order to reduce doses to OAR and take advantage of the steep dose falloff around the brachytherapy source, a vaginal gauze packing is performed. In this way normal tissues are displaced from the high-dose gradients near the source. As verified on CT slices during brachytherapy planning, an extensive vaginal packing might produce a significant deformation of the vaginal cavity. Although OAR tissues are displaced and dose reduction to OAR is achieved, there is also a displacement of the vaginal mucosa from the therapeutic dose volume. Vaginal cuff and proximal 2 cm of vaginal mucosa are structures defined as CTV and should be irradiated with therapeutic dose, according to the expect recommendations [10-12].

Using ROC analysis, a significant influence of vaginal packing volume on achieving the

recommended D<sub>90</sub> and D<sub>100</sub> doses was shown (p=0.0002167 and p=0.001592, respectively), with high specificity and sensitivity as shown in Table 2. Also, a very distinct CTV<sub>uk</sub> cutoff value of around 25 cm<sup>3</sup> is indicated. After dividing the patients into two groups (regarding CTV<sub>uk</sub> cutoff value of 25.60cm<sup>3</sup>), a statistically significant difference between the groups was found for both dose values D<sub>90</sub> (p=8.543\*10<sup>-05</sup>) and D100 (p=0.0008), which means that zones of inappropriate CTV coverage of vaginal mucosa had appeared. Federico et al. [13] have found similar results, identifying a larger cutoff vaginal packing volume value of 60-70 cm<sup>3</sup> in their group of patients treated with radical radiotherapy.

A statistically significant strong negative correlation was found between CTV<sub>uk</sub> volume and doses D<sub>90</sub> (rho= -0.80, p=0), and D<sub>100</sub> (rho= -0.7, p=0), clearly showing that larger vaginal packing volume leads to a greater deformation of the vaginal cavity and significant displacement of the vaginal mucosa from the irradiation source. As D<sub>90</sub> dose is the most important dose parameter, it was necessary to redo the brachytherapy procedure for several patients in order to bring the D<sub>90</sub> dose to the recommended values.

The discrepancy between the registered ICRU reference point doses for bladder and rectum (B<sub>max</sub> and R<sub>max</sub>), and CT image-based dosimetry at small volumes of these OAR (D<sub>0.1cc</sub>, D<sub>1cc</sub> and D<sub>2cc</sub>), has been previously noted [14]. An image-based dosimetry has been shown to be more clinically relevant in terms of late post radiation toxicity [15].

Analyzing the doses registered to the OAR wall between the two groups of patients (CTV<sub>uk</sub> ≤ 25.60cm<sup>3</sup> vs CTV<sub>uk</sub> > 25.60cm<sup>3</sup>), no signifi-

cance was found for bladder dose, neither during radiography-based planning ( $B_{max}$ ,  $p=0.45$ ), nor during CT-based planning ( $D_{0.1cc}$ ,  $D_{1cc}$  and  $D_{2cc}$ ,  $p=0.54$ ,  $p=0.94$ ,  $p=0.98$ , respectively). This result shows that although the vaginal gauze packing is performed in order to reduce the bladder dose, an increase of its volume will not result in a further decrease of the bladder dose.

On the contrary, it was shown a highly statistical significance in the registered rectal wall doses between the two groups, for both brachytherapy planning methods, as shown in Table 3.

The observed differences in the vaginal packing volume influence on bladder and rectal doses can be explained by a very clear difference in the anatomic position and spatial relations of these OAR and the applicator system placed at the vaginal cuff.

The amount and quality of the vaginal gauze packing is very dependent on the experience and skill of the radiotherapist and often limited by the patient discomfort during the procedure. A problem of not enough tight packing, or an uneven distribution of the gauze can appear as a consequence. In order to perform the vaginal packing in a reproducible and volume controlled manner, vaginal balloon-packing system filled with diluted contrast has been developed and used in the past few years in radiotherapy centers. Rockey et al. [16] have found that the vaginal balloon-packing with filling 1:1 solution of saline and contrast enables an easy contouring for image-guided brachytherapy with minimal artefacts, but it showed no statistically significant benefit in sparing OAR,

compared to the gauze packing. Price et al. [17] have reported a decrease in  $D_{2cc}$  dose to bladder and rectal tissue by  $32.2\pm 4.5$  and  $11.0\pm 3.3$  respectively, a decreased dose to the ICRU bladder point for  $39\pm 4.9$ , and no significant change in ICRU rectal point dose. Other authors have found similar results [18,19]. The proved reduction in brachytherapy doses to OAR and the undisputed improvement in the patient comfort during application has led to permanent clinical implementation of this packing system.

## Conclusion

The results presented in this paper show that if the brachytherapy vaginal packing is of a large volume (more than  $25.6 \text{ cm}^3$ ), an asymmetric deformation of the proximal part of the vaginal cavity might appear, leading to an inappropriate dose coverage of the CTV part of the vaginal mucosa. Also, making a vaginal packing volume larger than  $25.6 \text{ cm}^3$  resulted in no further reduction in the bladder dose, but it made a statistically significant further reduction in the rectal doses.

In order to achieve lower doses to the OAR and to reduce the frequency and intensity of the late post-irradiation toxicity, the vaginal packing should be done, but with a controlled and a consistent volume in order to ensure the appropriate CTV coverage with a therapeutic dose.

## Conflict of interests

The authors declare no conflict of interests.

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