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ORIGINAL ARTICLE

3D MRI-based evaluation of the 2D brachytherapy planning in patients with advanced cervical cancer: An analysis of the delivered dose

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Summary

Purpose: *To analyze the dose distribution achieved during 2D radiography-based brachytherapy (BRT) planning, by using a 3D MRI-based BRT replanning evaluation, in patients with advanced cervical carcinoma, treated with definitive concomitant chemoradiation (CCRT).*

Methods: *The curative CCRT was applied to 30 patients with advanced cervical carcinoma. For each patient, 2D radiography-based planning and a 3D MRI-based BRT replanning were performed. Applying the same source positions and dwell times in both planning methods, it was possible to use the MRI replanning to evaluate the dose distribution, maximum organs at risk (OAR) doses and target volume coverage, that was obtained during 2D BRT planning.*

Results: *A statistically significant difference for bladder and rectum maximum doses, between 2D planning (B_{max}, R_{max}) and 3D replanning ($D_{0.1ccm}$, D_{1ccm}, D_{2ccm}) was found, except between B_{max} and bladder D_{2ccm} dose (p=0.07), and R_{max} and rectal D_{2ccm} dose in the group of patients with symmetrical rectum position regarding the applicator system (p=0.47). MRI evaluation of the HR-CTV volume, according to the 2D planning achieved dose distribution, revealed total EQD2 HR-CTV doses: D_{90} (107.15±22.06 Gy) and D_{100} (80.66±14.58 Gy).*

Conclusion: *2D radiography-based BRT planning can provide a good estimation for the bladder and rectum 3D D_{2ccm} dose with a significant statistical difference for the doses in the smaller OAR volumes ($D_{0.1ccm}$, D_{1ccm}). Inability to visualize tumor tissue during 2D BRT planning provides no option in tailoring the dose distribution to the tumor volume and patient anatomy, leading to potential under/over-treatment in some patients.*

Key words: *brachytherapy, advanced cervical cancer, MRI*

Introduction

Like many other developing countries, Serbia has a big health challenge of cervical cancer high incidence (29.1/100.000) and high mortality (11.6/100.000), with 777 newly diagnosed patients and 311 deaths during 2015 (central Serbia data only) [1]. According to the latest European cancer data [2], Serbia is among the top five countries with an estimated incidence of 26 and mortality of 9.5 for 2018. Many of the patients are in advanced disease FIGO stages at the time of diagnosis.

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For over a decade, a standard option for primary curative treatment of advanced cervical cancer has been a concomitant cisplatin-based chemoradiation (CCRT). Different chemotherapeutic combinations were investigated due to the different patient biological characteristics and sensitivity of the tumor [3]. Radiotherapy consists of a combination of external beam radiotherapy (EBRT) and brachytherapy (BRT) [4-7]. In that setting, brachytherapy with its high contact doses near the irradiation source, has an irreplaceable treatment role as an EBRT dose boost. The total EBRT and BRT dose, EQD2 normalized to 2Gy per fraction, using LQ model with the α/β ratio of 10Gy for tumor tissue and 3Gy for normal tissues as recommended [8], reveals that volume covered with the BRT therapeutic dose receives more than 90Gy of EQD2 dose. This volume encompasses the cervical tumor, part of the upper uterus, proximal parametria, upper third of the vagina, and unfortunately parts of the surrounding organs at risk (OAR): bladder, rectum, sigmoid colon and bowel. Because of close anatomic relations in the pelvis, BRT has an important role in the development of late postirradiation toxicity. Sequels are mainly of a chronic character, refractory to therapy and can significantly reduce the quality of life although complete remission of the disease is achieved.

In the last decades, MRI imaging has found its place in BRT treatment, and image-guided brachytherapy (IGBRT) has become a standard treatment in some radiotherapy centers. The MRI IGBRT planning gives us precise information about dose distribution around the irradiation source, according to the visualization of the tumor tissue, tumor volume, and its changes during the course of treatment. Several target volumes (GTV, HR-CTV, IR-CTV) are defined and their coverage with the prescribed BRT dose is presented through D_{90} and D_{100} parameters. The adequate dose coverage of these volumes has a role in achieving local control and better disease-free survival [9-11]. Equally important, we can precisely visualizing the position of all of the OARs, and get the information of the level and the position of the maximum registered doses in the small volumes of their wall ($D_{0.1ccm}$, D_{1ccm}, D_{2ccm}), which closely corresponds with the development of late postirradiation toxicity afterwards [12,13]. GEC ESTRO working group has published recommendations [14] considering dose volume constraints that should be achieved during MRI-based gynecology BRT, regarding both the target volumes and the OAR tolerant doses.

IGBRT has its challenges in workflow and procedure organization, with a large time consumption and its dependence on technology availability. In radiotherapy centers with limited access to MRI machine and with a large number of brachy patients per day, the usual way of BRT planning is 2D - radiography based. There is no direct visualization of tumor or OARs, so it is not possible to precisely access the dose distribution to the tissues near the irradiation source. In that manner, it is of essential importance to know where exactly the BRT dose is delivered. In this paper, we used 3D MRI-based replanning, with the aim to analyze and evaluate the 2D radiography-based BRT plan and achieved dose distribution, doses registered to OARs, and target volume coverage with the prescribed dose.

Methods

This research included 30 patients with advanced cervical cancer FIGO stage, treated with definitive CCRT in the Institute of Oncology and Radiology of Serbia.

Every patient had an initial MRI pelvic exam prior to treatment for initial tumor volume assessment. All patients underwent curative EBRT with a dose of 45/46 Gy in 24/25 fractions, 1.8 - 1.91 Gy per day, 5 days per week delivered to the pelvic target volume. For all of the patients, EBRT was conducted using conformal planning and "box" 4 fields technique. During external beam radiation, concomitant cisplatin chemotherapy was administered with a dose of 40mg/m^2, once a week up to 5 cycles.

Brachytherapy was performed in HDR Ir^{192} regimen, using Fletcher MRI compatible applicator system (uterine probe and two vaginal ovoids), once a week in 4-5 applications, with a dose of 7 Gy per application, prescribed at point "A", starting after 15 EBRT fractions.

Brachytherapy verification and planning were performed for each patient at the time of the first and the fourth application done in two ways: radiography based - 2D planning, and MRI based - 3D replanning. The treatment was applied according to the 2D plan, while the 3D plan was used for dose-volume parameters assessment only. In order to analyze the delivered dose achieved by 2D planning, a 3D evaluation of the dose distribution was done, based on the same irradiation source positions and dwell times in both planning methods.

For the purpose of radiography 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 a radiopaque "wire" marker. MRI was performed on a 1.5T Siemens Magnetom Avanto Fit machine, using a surface pelvic coil (in order to increase the signal-to-noise ratio). During MRI, no additional markers for bladder and rectum were used. In order to displace the rectum and the bladder from the irradiation source, the vaginal packing was performed with cotton gauze. The gauze, soaked with the normal saline, gave the high signal intensity on the T2W images, with sufficient contrast to the surrounding tissues – vagina wall and lower parts of the cervix/tumor (Figure 1). For the purpose of MRI anatomic orientation and

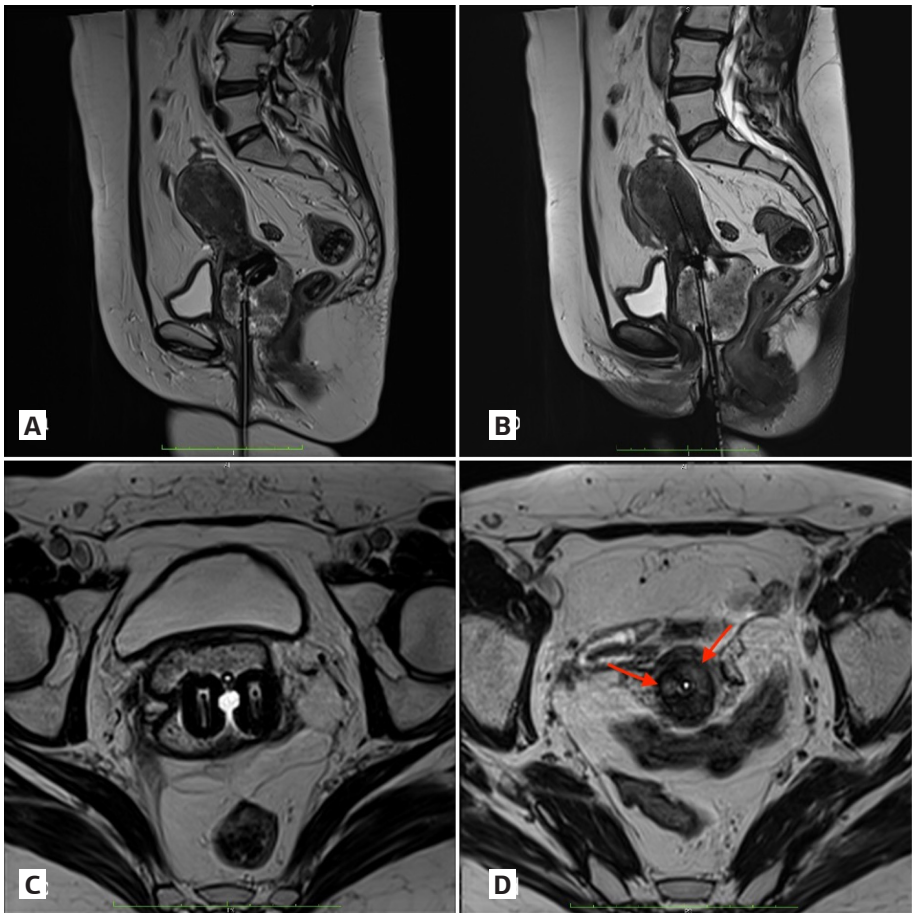

Figure 1. 1.5T T2W images in sagittal plain - visualization of the cotton gauze packing and its good delineation with the vagina wall and cervical tissue **(A,B)**. Axial plane 3D T2W TSE SPACE sequence used for delineation, with excellent visualization of the high-intensity signal tumor tissue (arrows) **(C,D)**.

imaging volume definition - sagittal T2W imaging was performed. A 3D T2W TSE with high sampling efficiency (SPACE) axial sequence was performed for OARs and target volumes delineation, and treatment planning - which gave us good image quality of the reconstructed planes. Both sets of images (radiography and MRI) were imported to the Oncentra® Brachy (Elekta) planning system.

Radiography reference points for bladder (B_{max}) and rectum (R_{max}) were defined as recommended by the ICRU-38 report and 2D planning doses to these OARs were obtained. In 3D brachytherapy planning, the outer contours of OAR were delineated on each axial MR slice as follows: bladder through the whole volume, rectum from anal-rectal junction (using the elevator ani muscle as the anatomic border between anal canal and rectum), to the rectosigmoid flexure, sigmoid colon, and bowels to 2cm above the top of the uterine probe. Also, target volumes (GTV, HR-CTV, IR-CTV) were delineated as described in the GEC ESTRO recommendations.

Oncentra® Brachy planning system was used for both planning methods. Maximal doses registered to the ICRU reference points and to the small volumes of the OAR wall ($D_{0.1ccm}$, D_{1ccm}, D_{2ccm}) were obtained. Target volume coverage presented as HR-CTV D_{100}/D_{90} doses, defined as the minimal brachytherapy dose that covers 100% and 90% of the HR-CTV volume respectively, was analyzed. In the end, the total EQD2 dose (EBRT + BRT), normalized to a daily fractioned dose of 2 Gy, using α/β ratio of 3 for normal tissue, and α/β ratio of 10 for tumor tissue, was calculated for OAR D_{2ccm} and HR-CTV D_{90} and D_{100}.

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, Wilcoxon rank sum test and Wilcoxon signed rank test were used. The Spearman's rank correlation was used for linear correlation investigation. The Receiver Operating Characteristics curve (ROC) methods were applied for investigation of initial tumor volume discriminative potential on D_{90} value (regarding recommended values) (AUC ROC-Area Under the ROC curve according to DeLong's method; Likelihood ratio test for AUC ROC; the best cut-off value for initial tumor volume was set as the 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

Definitive CCRT was performed in 30 cervical cancer patients, with a mean age of 51.5±12 years and two peaks of disease occurrence: 38 and 58 years. Most frequent FIGO stage was IIb (73.3%), with squamous cell G2 histology (93.3%) (Table 1).

With an average follow-up of 11 months, complete remission was achieved in 22 patients, local cervical relapse had 7 patients and one patient had a distant pulmonary relapse. MRI assessment of the initial tumor volume, and consequent tumor volumes at the 1st and the 4th BRT fraction are presented in Table 2.

Table 1. Characteristics of patients and disease

Characteristics	*n (%)*
Age (years), mean±SD	51.6 ± 12
FIGO stage	
IIb	22 (73.3)
IIIb	8 (26.7)
Histology	
Squamous cell carcinoma	28 (93.3)
Adenocarcinoma	2 (6.7)
Histological grade	
G1	5 (16.7)
G2	17 (56.7)
G3	8 (26.6)

Table 2. MRI assessment of the tumor volume (initial, at the time of the 1st and the 4th BRT fraction)

	Tumor volume (ccm)		
	mean±SD	*min*	*max*
Initial	49.9 ± 33.3	11.3	124.2
1st BRT	17.3 ± 19.2	1.7	78.4
4th BRT	7.0 ±10.9	0.8	58.5

Table 3. Difference between registered bladder and rectum doses, assessed during 2D radiography and 3D MRI based replanning, with correlation Rho values between doses

	Dose (Gy) mean±SD	*p value*	*Rho (p value)*
Bladder			
B_{max}	5.21 ± 1.64	-	-
$D_{0.1ccm}$	7.16 ± 1.55	2.27×10^{-9}	0.40 (0.00171)
D_{1ccm}	6.12 ± 1.23	2.532×10^{-5}	0.48 (1×10^{-4})
D_{2ccm}	5.63 ± 1.06	0.07	0.62 (0.0005)
Rectum			
R_{max}	3.65 ± 1.22	-	-
$D_{0.1ccm}$	5.76 ± 1.65	3.24×10^{-7}	0.53 (2×10^{-5})
D_{1ccm}	4.72 ± 1.26	1.18×10^{-7}	0.53 (1×10^{-5})
D_{2ccm}	4.24 ± 1.08	0.0001	0.56 (2×10^{-5})

The difference between the registered bladder and rectum doses, during 2D (B_{max}, R_{max}) and 3D planning ($D_{0.1ccm}$, D_{1ccm}, D_{2ccm}), presented with mean values, appropriate p values, and correlation rho values, are shown in Table 3. A statistically significant difference between 2D and 3D doses was found, except between B_{max} and bladder D_{2ccm} dose (p=0.07). Weak positive, a significant correlation was estimated for all doses, expressed the most between 2D and D_{2ccm} doses (bladder rho=0.56, $p=1\times10^{-5}$, rectum rho=0.56, $p=2\times10^{-5}$).

No correlation was found between the bladder volume and the registered bladder doses neither during 2D nor during 3D planning.

Dividing the patients in two groups, regarding the position of the rectum at the level of the vaginal ovoids, defined as symmetric or asymmetric position (Figure 2), a statically significant difference between 2D (R_{max}) and 3D ($D_{0.1ccm}$, D_{1ccm}, D_{2ccm}) rectal doses in both groups was found, except between R_{max} and D_{2ccm} dose in the symmetric rectum position group (p=0.47), with statistically significant positive correlation (rho=0.66, $p=3\times10^{-5}$).

Registered EQD2 D_{2ccm} sigmoid colon and bowel doses were as follows: 82.9±17.7 Gy and 82.6±15.9 Gy.

MRI evaluation of the HR-CTV volume, according to the 2D planning achieved dose distribution of 7 Gy prescribed to point "A", revealed

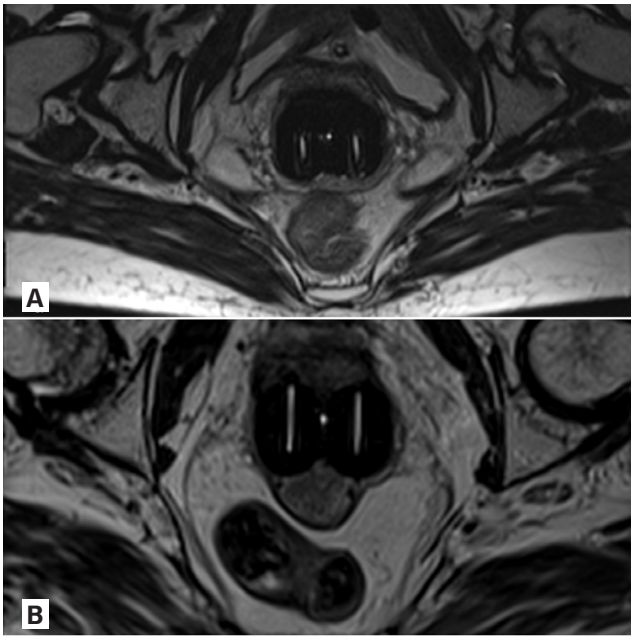

Figure 2. MRI presentation of the rectum position regarding the applicator system at the level of vaginal ovoids: symmetric **(A)**, asymmetric **(B)**.

the mean values of HR-CTV D_{90} (7.65±2.73 Gy, 109.29±39.19%) and D_{100} (5.08±2.02 Gy, 72.90±28.77%) for the 1st brachy fraction, and D_{90} (9.12±2.23 Gy, 130.41±32.27%) and D_{100} (6.26±1.96 Gy, 89.52±28.04%) for the 4th brachy fraction. The total EQD2 HR-CTV doses were: D_{90} (107.15±22.06 Gy), and D_{100} (80.66±14.58 Gy).

Testing the correlation between the initial tumor volume and the HR-CTV D_{90} dose at the time of the first brachytherapy showed a strong negative statistically significant correlation (rho= -0.77) (Figure 3).

Initial tumor volume influence on HR-CTV D_{90} dose directed our further analysis. Applying analysis of the ROC curve, we confirmed the discriminative influence of initial tumor volume on achieving recommended HR-CTV D_{90} dose (D_{90}≥100%), with best tumor volume cut-off value of 47.87ccm (Figure 4, Table 4). Dividing the patients into two groups regarding the cut-off initial tumor volume, we found a statistically significant difference for the total EQD2 doses, for both HR-CTV D_{90} and D_{100}, between the groups (Table 5), showing a lower total EQD2 dose delivered to the HR-CTV in the group of patients with initial tumor volume larger than 47.87ccm.

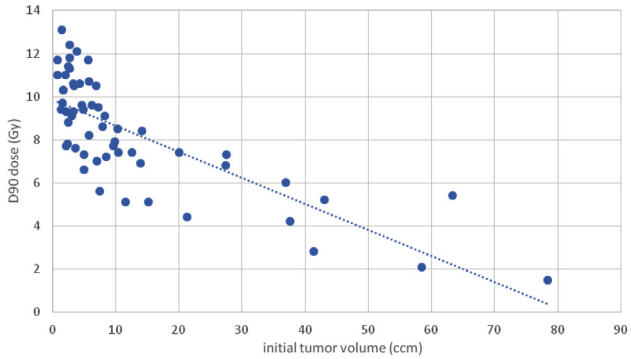

Figure 3. Correlation between initial tumor volume (ccm) and HR-CTV D_{90} dose (Gy) at the first brachy fraction.

Table 4. Results of the ROC analysis for initial tumor volume (ccm) and HR-CTV D90 dose (%)

Initial tumor volume	*D_{90}≥100%*
AUC ROC* (95%CI)	89.47% (72.55%-100%)
Likelihood ratio test**	$p=7.57*10^{-6}$
ROC-cut-off value#	47.87
Sensitivity (95% CI)	89.4% (73.6%-100.0%)
Specifity(95% CI)	90.9% (72.73%-100.0%)

*Area under the ROC curve (DeLong's method); **Likelihood ratio test for AUC ROC; #Value (ccm) with maximum sensitivity and specificity

Discussion

Intracavitary brachytherapy has an important role in overall treatment success and also postiradiation toxicity development. 3D MRI-based brachytherapy gives precise estimation of the target volume coverage and doses delivered to OARs. In this study, we showed our preliminary results in the implementation of 3D MRI-based cervical cancer brachytherapy, treatment technique and dose-volume parameters evaluation.

Patient demographic data in this research shows a close relation to the data presented in Serbia Cancer Registry for 2015, with two peaks of disease occurrence in the age of 38 and 58 years. High mortality in Serbia is mostly caused by poorly defined screening program, but new tendencies in the past few years bring hope that better epidemiological surveillance will be organized in the future [15].

As Shinya et al [16] showed, MRI DWI images provide an excellent possibility of precise initial tumor volume assessment, ranging in our study from 11.3ccm to 124.2ccm, with an average value of 50ccm. Big initial tumor volume is one of the

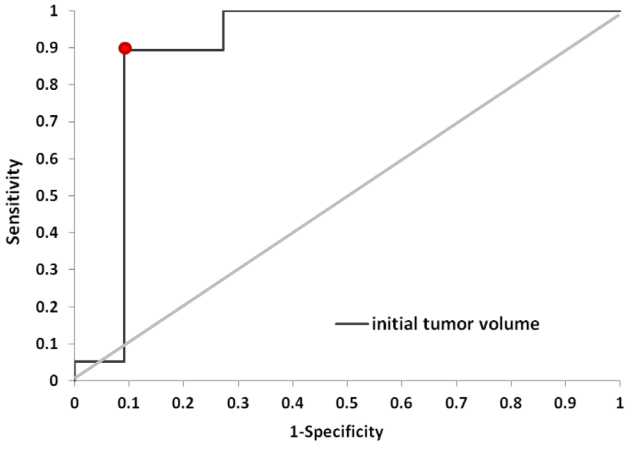

Figure 4. ROC curve initial tumor volume (ccm) for HR-CTV D_{90} dose (%).

Table 5. Difference between the EQD2 HR-CTV D_{90} and D_{100} doses (Gy), in two groups of patients regarding the initial tumor volume of 47.87ccm

	Initial tumor volume < 47.87ccm	*Initial tumor volume ≥ 47.87ccm*	*p value*
D_{90} EQD2 (Gy)	120.4 ± 14.6	87.33 ± 15.48	$6.93*10^{-7}$
D_{100} EQD2 (Gy)	88.55 ± 11.97	68.83 ± 9.19	0.0001

main reasons for the high mortality of cervical cancer in Serbia [17] and failure of radiotherapy.

Although the use of 2D BRT planning, in contrast to the 3D planning, doesn't allow adaptation of the prescribed dose to the individual patient anatomy or tumor volume, the follow-up in this study showed local control of 73%, local cervical relapse in 23% and distant relapse in 4% of the patients. Retro EMBRACE multicenter study [18] presented that MRI-guided BT leads to improvement in local disease control (87%), showing a clear benefit from MRI-based BRT planning. Improvements in overall survival and local control have been also proved in other studies [19, 20].

Assessment of the bladder dose-volume parameters showed no statistically significant difference only between 2D B_{max} and the 3D D_{2ccm} dose (p=0.07), with positive statistically significant correlation (rho=0.62, p=0.0005). For the rectal dose, no statistically significant difference between 2D R_{max} and 3D D_{2ccm} dose was found in the group of patients with the symmetric rectal position regarding the applicator system (p=0.47), also with positive statistically significant correlation (rho=0.66, $p=3\times10^{-5}$). In the case of asymmetric rectal position, R_{max} dose didn't adequately estimate the "real" D_{2ccm} rectal dose obtained by 3D planning. Volumetric doses in smaller volumes of the bladder and rectal wall ($D_{0.1ccm}$, D_{1ccm}) showed a statistically significant difference compared to ICRU 2D point doses. Tan et al [21] have found that mean bladder ICRU and D_{2ccm} dose were significantly different, while rectal ICRU dose was a good estimator for the D_{2ccm} dose. In their study Kirisits et al have shown a good correlation between the bladder and rectal ICRU point doses and the D_{2ccm} dose to this OAR [22]. Patil et al [23] showed a correlation between the ICRU point and D_{2ccm} bladder and rectum doses (correlation coefficients of 0.82 and 0.77 respectively), but further analysis of this data showed an error range which makes these findings unreliable for clinical use. Mazzeron et al [12] found that the position of the most exposed D_{2ccm} bladder volume is located 1.73±0.98cm cranially, 0.59±0.65cm backwardly, and 0.02±0.89cm to the right of the ICRU point, with significant correlation between Grade 2-4 urine incontinence and D_{2ccm} dose location in the lower part of the bladder wall. Goerg et al [13] showed a correlation between the rectoscopy finding of rectal ulceration, and the position and the value of the $D_{0.1ccm}$ dose, concluding that for clinical use, not only the dose value to the wall of this OAR is important, but also the position of the maximum dose.

Mean values of the doses registered to the sigmoid colon and bowel during MRI-based planning, transformed to total EQD2 dose (EBRT and BRT, normalized to the daily fraction of 2 Gy, with α/β ratio of 3 for normal tissues) were 82.9±17.7 Gy and 82.6±15.9 Gy, respectively. As recommended, the limit for the prescribed EQD2 D_{2ccm} dose to the sigmoid colon and bowel is less than 75 Gy. Doses in our study, higher than recommended, can be partially explained by the traditional fractionation regimen protocol - 5 fractions of 7 Gy, while in other centers, 4 fractions of 7 Gy are used as BRT boost after the completed EBRT treatment. Certainly, this indicates a need to change our current BRT protocol. Also, a plan optimization option should be used during 3D planning, particularly for smaller volume tumors, in order to reduce the dose delivered to the OAR [8].

Analyzing the HR-CTV coverage in our study, values for D_{90} (7.65±2.73 Gy, 109.29±39.19%, ranging from 1.5 Gy to 12.4 Gy) and D_{100} (5.08±2.02 Gy, 72.90±28.77%, ranging from 0.72 Gy to 8.9 Gy) for the 1st brachy fraction, and D_{90} (9.12±2.23 Gy, 130.41±32.27%, ranging from 2.1 Gy to 13.1 Gy) and D_{100} (6.26±1.96 Gy, 89.52±28.04%, ranging from 1.1 Gy to 9.5 Gy) for the 4th brachy fraction are revealed. The dose applied to the HR-CTV volume, presented as D_{90} and D_{100} doses, should be sufficient to cure the macroscopic disease. The minimum dose applied to the 100% of the HR-CTV volume (D_{100}) has one big clinical limitation: it is highly dependent on the accuracy of the HR-CTV delineation. Due to the brachytherapy steep dose gradient, small deviations during the delineation could cause large changes in D_{100} dose. Because of that, D_{90} dose as a less sensitive and more stable parameter is used for HR-CTV coverage reporting, with the recommended value of≥100%, according to the ordinated brachy dose [24].

The recommended values for EQD2 HR-CTV D_{90} dose are 85 Gy-95 Gy [25]. HR-CTV doses in our study, translated to total EQD2 dose (with α/β ratio of 10 for tumor tissue), showed values for D_{90} (107.15±22.06 Gy, ranging from 52.8 to 152.1Gy), and D_{100} (80.66±14.58 Gy, ranging from 48.2 to 113 Gy). Dividing the patients into two groups regarding the initial tumor volume cutoff value of 47.87ccm, as identified by the ROC analysis (Figure 4, Table 4), a statistically significant difference was found for HR-CTV total EQD2 D_{90} ($p=6.93\times10^{-7}$) and EQD2 D_{100} (p=0.0001) between groups, with a lower total EQD2 dose delivered to the HR-CTV in the group of patients with initial tumor volume larger than 47.87ccm.

In our study setting, according to our traditional treatment protocol, brachytherapy was performed simultaneously with EBRT once a week, starting after 15 EBRT fractions, with the regimen

of 4-5 fractions per 7 Gy, and no use of interstitial needles. Looking at the HR-CTV coverage, it becomes clear that 2D radiography-based BRT leads to potential undertreatment of large or asymmetric tumors, especially during the 1st brachy fraction. The results imply that, especially in the group of patients with initial tumor volume larger than 47.87ccm, brachytherapy should be used as a boost, after completed EBRT and maximum tumor reduction, to ensure better HR-CTV coverage at the time of first BRT fraction and overall. Also, an over-treatment of initially small volume tumors could occur. In these patients, plan optimization, achieved only by 3D planning, should be used to reduce the HR-CTV dose to the recommended values and to decrease the dose to the surrounding OARs at the same time.

Conclusion

The results in this study show that 2D radiography-based planning can offer a good estimation only for the bladder and rectum 3D D_{2ccm} dose, with a significant statistical difference for the doses in the smaller OAR volumes ($D_{0.1ccm}$, D_{1ccm}). The doses delivered to the sigmoid colon and the bowels can only be assessed through 3D planning. Different anatomic variations, such as asymmetric rectal position, will also provide an inadequate dose estimation during 2D planning, leading to a possible excess of the tolerated OAR doses, and increase in frequency and grade of the postirradiation toxicity.

Inability to visualize tumor tissue during 2D BRT planning provides no option in tailoring the dose distribution to the tumor volume and patient anatomy, leading to potential under/over-treatment in some patients. Only volumetric imaging, CT- or MRI-based, can obtain proper and precise information about therapeutic dose distribution, target volume coverage, and OAR doses.

Conflict of interests

The authors declare no conflict of interests.

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