ORIGINAL ARTICLES
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UDC: 615.849::618.1-006
DOI: https://doi.org/10.2298/VSP210520077P

The transition from conformal to advanced radiotherapy techniques in the treatment planning of gynecological cancer patients

Prelaz sa konformalne na napredne radioterapijske tehnike u planiranju lečenja obolelih od ginekoloških karcinoma

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Abstract

Background/Aim. The transition from standard to highly conformal radiation therapy techniques requires the implementation of complex advanced dosimetry. The aim of the study was to compare dosimetric parameters of the three-dimensional conformal radiotherapy (3DCRT) and volumetric modulated arc therapy (VMAT) plan, as well as complications after treatment in relation to dosimetric parameters in gynecological cancer patients. **Methods.** A total of 49 gynecological cancer patients were included in the study. All patients were planned for 3DCRT, but due to unacceptable doses to organs at risk (OARs), treatment plans for intensity modulated radiation therapy (IMRT), or VMAT, were generated for 21 patients. The patients were prescribed 50.4 Gy/28 fractions (4 patients) and 45 Gy/25 fractions (45 patients). The coverage of planning target volume (PTV) and doses to OARs were recorded. PTV margins were evaluated for both techniques according to the Van Herk formula. **Results.** ICRU 83 criteria were fulfilled in all 3DCRT/VMAT/IMRT plans providing optimal coverage of PTV. Doses to OARs, on average, the V45Gy in the small bowel in IMRT/VMAT plans was four times smaller than the same in 3DCRT plans. The V45 Gy of small bowels was, on average, 49.4 cm^3 in IMRT/VMAT plans, while in 3DCRT plans, it was 211.6 cm^3. In the case of the femoral head, a significant reduction in V30Gy (10.8% vs. 33.1%) and mean dose in the case of IMRT/VMAT plans was recorded (30.4 Gy in 3DCRT vs. 23.6 Gy). Rectum was planned with a significantly lower dose in terms of V30Gy (79.5% vs. 95.2%) in IMRT/VMAT plans. The bladder was better spared in VMAT plans in terms of V40Gy (51% vs. 91%), but the maximum dose was higher in VMAT plans than in 3DCRT (50.1 Gy to 48.1 Gy on average). For all OARs, there was a statistically significant difference registered at $p < 0.05$. Toxicities recorded in VMAT and 3DCRT patients included mainly radiation-induced cystitis and enteritis. Patients treated with 3DCRT generally had longer recovery time. The homogeneity index was 0.11 for VMAT plans and 0.09 for 3DCRT plans. **Conclusions.** Analysis of dosimetric parameters revealed significant differences in normal tissue doses for the same 3DCRT and VMAT patients, which confirmed the necessity for the implementation of advanced techniques for as many patients as possible.

Key words:
genital neoplasms, female; radiotherapy; radiotherapy, conformal; radiotherapy planning, computer-assisted; treatment outcome.

Apstrakt

Uvod/Cilj. Prelaz sa standardnih na visokokonformalne radioterapijske tehnike zahteva implementaciju kompleksne dozimetrije. Cilj rada bio je da se uporede dozimetrijski parametri trodimenzionog konformalnog plana (3DCRT) i lučnog zapreminski modulisanog plana zračenja (VMAT), kao i komplikacije nakon tretmana i veza sa dozimetrijskim parametrima kod bolesnica sa ginekološkim malignitetima. **Metode.** Ukupno 49 bolesnica sa ginekološkim malignitetima su bile uključene u studiju. Sve bolesnice su bile planirane za 3DCRT terapiju, ali zbog neprihvatljivih doza na organe pod rizikom (OPR), generisani su i isporučeni terapijski planovi u tehnici VMAT/radioterapija sa podesivim intenzitetom zračenja (IMRT) za 21 bolesnicu. Bolesnicama je propisana apsorbovana doza 50,4 Gy/28 frakcija (4 bolesnice) i 45 Gy/25 frakcija (45 bolesnica). Praćene su pokrivenosti planiranog ciljnog volumena (PCV) i doze na OPR. Margine PCV evaluirane su u obe tehnike prema formuli Van Herka. **Rezultati.** Kriterijumi ICRU 83 bili su ispunjeni u svim 3DCRT/VMAT/IMRT planovima i pokazali su optimalnu pokrivenost PCV. Doze od V45Gy

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na tankim crevima u IMRT/VMAT planovima bile su skoro četiri puta manje zapremine nego one u 3DCRT planovima (srednja vrednost zapremine obuhvaćene 45 Gy izodozom u IMRT/VMAT planu bila je 49,4 cm^3, dok je u 3DCRT planu iznosila 211,6 cm^3. U slučaju glave femura zabeleženo je značajno smanjenje doze V30Gy (10,8% vs. 33,1% kod 3DCRT) i smanjenje srednje doze u slučaju IMRT/VMAT planova (30,4 Gy vs. 23,6 Gy u 3DCRT). Rektum je u IMRT/VMAT planovima primio značajno manju dozu V30Gy (79,5% vs. 95,2% u 3DCRT). Bešika je bila bolje sačuvana u VMAT planu V40Gy (51% vs. 91% kod 3DCRT), ali su maksimalne doze veće kod VMAT planova nego kod 3DCRT (50,1 Gy Gy vs. 48,1). Za sve OPR registrovana je statistički značajna razlika ($p < 0,05$) između dve tehnike. Toksičnosti koje su praćene i kod 3DCRT i kod VMAT bolesnica bile su uglavnom, radijacioni cistitis i enteritis. Bolesnice lečene 3DCRT oporavljale su se duže od posledica zračenja. Indeks homogenosti bio je 0,11 za VMAT i 0,09 za 3DCRT planove. **Zaključak.** Analiza dozimetrijskih parametara otkrila je značajne razlike između doza na zdrava tkiva u 3DCRT i VMAT planovima, što potvrđuje neophodnost implementacije naprednijih tehnika zračenja za što veći broj radikalno lečenih bolesnika.

Ključne reči:
polni organi, ženski, neoplazme; radioterapija; radioterapija, konformalna; radioterapija, kompjutersko planiranje; lečenje, ishod.

Introduction

Cervical and uterine cancers are global public health care problems since they are the fourth most frequent cancers in females worldwide, after breast, colorectal, and lung cancer. Cervical cancer represents nearly 7% of all female cancers globally. Its incidence in developed and developing countries is not equal and varies from 2 to 75 per 100,000 women, while the mortality in developed and developing countries varies largely [1]. The average age at diagnosis worldwide is 53, and the average age at death from cervical cancer is 59. It is ranked highly as one of the top three cancers affecting women younger than 45.

The situation in the Republic of Serbia is somewhat similar for *cervix uteri*, but another cancer contributes to the cancer burden – *corpus uteri*. The Republic of Serbia had over 7 million inhabitants in 2017 [2, 3], of which 51.3% were women. Epidemiological data [2, 4] show that 5.8% of all new yearly cancers were *cervix uteri*, and 7% of all new cases were *corpus uteri*, and still increasing. Serbia is the third highest ranked country in Europe in the incidence of cervical and uterine cancer, after Moldavia and Bulgaria. Most newly diagnosed patients are 45–49 years old.

Treatment modalities of cervical or corporal cancer are multidisciplinary and include surgery, chemotherapy, and radiotherapy (RT). The main problem in RT treatment of any site is how to appropriately cover the planning target volume (PTV) with as high a dose as possible and at the same time minimally irradiate organs at risk (OARs), which are very often in the nearest vicinity of the PTV. Sometimes even PTV and close OARs overlap, and it is impossible to deliver the prescribed dose to PTV without delivering a significant dose to the OARs.

During the last 20 years in the developed world, intensity-modulated radiotherapy (IMRT) has become a standard RT treatment. In Serbia, due to a long-lasting economic crisis, RT patients were offered 2.5 dimensional (D) and 3D conformal radiotherapy (CRT) plans.

The concept of advanced techniques in RT is actually very old and consists of standard static fields, where the movement of a gantry is added and is synchronized with the movement of a multileaf collimator (MLC), as well as a controlled dose rate. Powerful com puters handle these complex movements, and the machine delivers highly conformal dose distribution to a patient. In recent years, not only has a huge investment of the Serbian government in RT improved access to RT services but also enabled the implementation of highly conformal techniques in RT, thus improving the overall outcome of patient treatment. The Oncology Institute of Vojvodina introduced advanced techniques into clinical practice in 2016 after cumbersome verification of advanced treatment modalities.

The paper deals with two different RT approaches to the treatment of cervical and uterine cancer, 3DCRT, as standard, and advanced treatment modality IMRT and volumetric modulated arc therapy (VMAT) as newly implemented one.

Methods

A total of 49 randomly selected patients from the treatment planning logbook included in the study were irradiated between January 2016 and December 2019. The patients were identified from the hospital registry together with their clinical and treatment data. Treatment planning data were taken from the treatment planning system.

All patients were initially planned for the 3DCRT technique. Due to heavy dose load to the small bowels, a subset of 21 patients was re-planned for VMAT or IMRT and treated, whilst another subset (the remaining 28 patients) was treated with 3DCRT according to the treatment plan. For the subset treated with VMAT/IMRT, a comparative analysis of their clinically applied VMAT and initially planned 3DCRT treatment parameters was presented in this work. For this subset of 21 VMAT/IMRT patients, daily imaging was performed, and after completing all treatments, clinical target volume (CTV) to PTV margins coming from interfraction motions recorded in the record and verify system were evaluated according to the Van Herk formula [5]. Additionally, these margins were also evaluated for a subset of 28 3DCRT treated patients, according to the same protocol.

All patients (both subsets) were followed-up in the following time frame: during the treatment or immediately

after treatment, one month after the treatment, and 6 months after the treatment (after the 6th month, patients were followed-up by their oncologists). The complications were collected from the hospital registry system [noted during their treatment and control examinations according to the Radiation Therapy Oncology Group (RTOG) toxicity grading system], evaluated and compared.

The Radiotherapy Clinic, Oncology Institute of Vojvodina, is equipped with two Versa HD linear accelerators (manufactured by Elekta, Crawley, UK). The 3DCRT treatment plans were generated by collapsed cone algorithm, while VMAT and IMRT plans were generated by the Monte Carlo calculation engine, both in the Monaco treatment planning system (Elekta, Crawley, UK).

The beams were verified according to the end-to-end dosimetry audit for 3DCRT and VMAT/IMRT [5], as recommended by the International Atomic Energy Agency. The beams are regularly calibrated and verified biannually in thermos-luminescence dosimeter (TLD) postal dose audits.

For 3DCRT plans, treatment strategy basically includes box technique with segments field-in-field, while VMAT plan includes one or two arc techniques or static IMRT 7 field techniques.

The dose was prescribed to the PTV according to the adopted clinical protocols of the Clinic and included a prescription of 45 Gy/25 daily fractions or 50.4 Gy/28 daily fractions. The treatment plans were evaluated based on the dose volume histograms and the International Commission of Radiation Units and Measurements (ICRU) recommendations 62 and 83. The dosimetric parameters were evaluated according to RTOG1203, which was designed to compare late toxicities in pelvic cervical and endometrial treatments with standard box and IMRT [6].

The toxicities between the two groups (3DCRT and VMAT/IMRT) were statistically compared using Fisher's exact test.

Results

Patient demographics

At the time of prescription and treatment in the selected group of patients, the distribution of the age of all women was as follows: there were no patients younger than 39 or older than 73. The mean age of the patients was 55.

The distribution of diagnosis was as follows: the group treated with 3DCRT – 68% of patients had a diagnosis of *cervix uteri* cancer (C53 according to International Classification of Diseases and Related Health Problems − ICD 10), while 32% had *corpus uteri* cancer (C54). The staging was evaluated according to the International Federation of Gynecology and Obstetrics – FIGO classification, where 46% of patients were FIGO I, 46% FIGO II, 7% FIGO III, and none in FIGO IV. In IMRT/VMAT group – 57% of patients had a diagnosis of *cervix uteri* cancer (C53), while 43% had *corpus uteri* cancer (C54). Staging: 38% of patients were FIGO I, 38% were FIGO II, 19% were FIGO III, and 5% were FIGO IV.

The patients in 3DCRT irradiated group were also treated with neoadjuvant chemotherapy (total of 4 patients) and concurrent cisplatin chemotherapy (18 patients). The comorbidities were detected for 16 patients out of 28 [*hypertensio arterialis* (10), diabetes mellitus (7), arrhythmia (3), and renal insufficiency (2)]. The patients in VMAT/IMRT irradiated group were also treated with neoadjuvant chemotherapy (4 patients) and concurrent cisplatin chemotherapy (11 patients). The comorbidities were detected for 14 patients out of 21 [*hypertensio arterialis* (9), arrhythmia (1), asthma bronchiale (1), epilepsy (1), varicose veins (1), and ulcerative colitis (1)].

Brachytherapy modality was used as combined therapy with external beam RT in all patients included in the study.

Radiotherapy treatment

According to the institutional protocol, all patients were advised to fill in the bladder and empty bowels and rectum before computed tomography (CT) scanning and every treatment. CT scanning was done on a 3 mm slice distance (CT simulator model Definition As Open, manufacturer Siemens, Germany). Patients were scanned in the supine position, with immobilizing cushions for knees and feet.

All patients were treated according to clinically adopted radiotherapy protocols, their staging, and the type of illness.

CTV included primary tumor, cervix, entire uterus, parametrial and paravaginal tissue, and proximal vagina. If there was minimal or no vaginal tumor extension, the upper half of the vagina was included. In patients with involvement of the upper vagina, the proximal two-thirds were included in CTV and the whole vagina if there was more vaginal involvement. Moreover, CTV included regional lymph nodes as common iliac, external and internal iliac, presacral, and nodes close to the medial edge of the obturator muscle. An additional margin of up to 1 cm was added to CTV to represent PTV.

OAR delineation was performed for the small bowels cavity, femoral heads, bladder, and rectum.

Treatment planning was performed as a four-field box for 3DCRT with a 15 MV beam, 2 arcs for VMAT, or 7 fields for IMRT treatment with a 10 MV beam. The calculation was done with a 3 mm grid size resolution. Since the 3DCRT, as well as VMAT/IMRT treatment plans, were made for the subset of patients treated with VMAT/IMRT, the PTV dosimetric evaluation was performed through the evaluation of ICRU83 parameters of both plans [7]: the doses (DS) to 50%, 95%, 98% and 2% of the considered volume (DS50%, DS95%, DS98% and DS2%, respectively) and homogeneity index (Table 1).

The conformity index was not compared as it is proven to be much better for highly conformal treatments such as VMAT/IMRT than for 3DCRT.

Table 1

PTV 95% reference coverage, D50%, D98%, D2%, and HI according to ICRU83 and data obtained from the dosimetric evaluation of 3DCRT and VMAT/IMRT plans of same patients

Variable	ICRU 83	3DCRT plans	VMAT/IMRT plans
PTV 95% reference coverage	> 95% D	97.0 ± 1.03	98.3 ± 1.3
DS50%	100–102% D	101.3 ± 0.6	101.2 ± 0.8
DS98%	< 95% D	95.04 ± 1.3	94.6 ± 1.5
DS2%	< 107% D	104.6 ± 0.7	105.9 ± 0.9
HI	Ideally 0	0.09 ± 0.017	0.11 ± 0.012

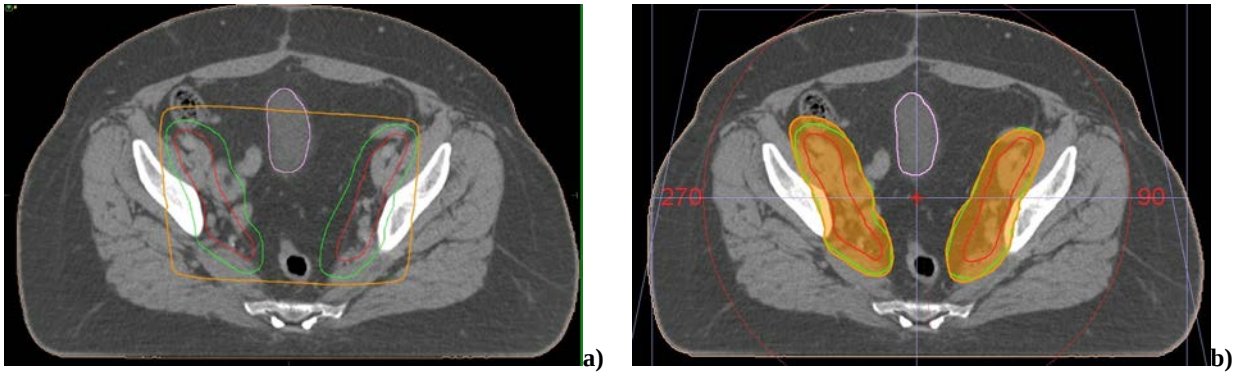
Values are expressed as mean ± standard deviation, minimum–maximum, or < of percentage dose (DS). ICRU – International Commission of Radiation Units and Measurements; 3DCRT – three-dimensional conformal radiotherapy; PTV – planning target volume; VMAT – volumetric modulated arc therapy; IMRT – intensity modulated radiation therapy; HI – homogeneity index.

Table 2

Organ at risk constraints according to RTOG1203 and data obtained from the dosimetric evaluation of 3DCRT and VMAT/IMRT plans of the same subset of patients

Organ at risk	RTOG 1203	3DCRT plans	VMAT/IMRT plans
Small bowel (the average volume of small bowel in the subset 492 cm^3)	Less than 30% of volume receives 40 Gy V40 < 30% V45 cm^3 < 195 cm^3	V40 = 304.2 ± 176 cm^3 (61.8 %) V45 = 211.6 ±143 cm^3	V40 = 140.8 ± 70 cm^3 (28 %) V45 = 49.4 ± 32 cm^3
Rectum	Less than 80% of the volume receives 40 Gy V40 < 80%	V30 = 95.2 ± 6.1 %	V30 = 79.5 ±12.3 %
Bladder	Less than 35% of the volume receives 45 Gy V45 < 35%	V45 = 65.5 ± 28.8 %	V45=27.0 ±12.3%
Femoral heads	Less than 50% of the volume receives 30 Gy V30 < 50%	L: V30 = 33.1 ± 22.2 % R: V30 = 30.6 ± 21.0 %	L: V30 = 10.8 ± 8.7% R: V30 = 9.7 ± 7.5%

Values are expressed as mean ± standard deviation.
RTOG – Radiation Therapy Oncology Group; 3DCRT – three-dimensional conformal radiotherapy; VMAT – volumetric modulated arc therapy; IMRT – intensity modulated radiation therapy.



a) b)

Fig. 1 – A 95% isodose distribution in: a) typical three-dimensional conformal radiotherapy (3DCRT) treatment plan; b) typical volumetric modulated arc therapy (VMAT)/ intensity modulated radiation therapy (IMRT) plan.

Organs at risk dosimetry evaluation

For the first subset of patients, planned both for 3DCRT and VMAT/IMRT and irradiated by VMAT, significantly lowered doses were registered in VMAT/IMRT treatment plans (Table 2).

Typical dose distributions are shown in Figure 1: a) in the same patient 3DCRT technique, and b) in VMAT/IMRT technique.

Clinical examination and follow-up comparison of the small bowel and bladder complications in two techniques – standard 3DCRT group vs. VMAT/IMRT group

All patients are followed-up during RT treatment delivery, one month after the last fraction and six months after the treatment. The parameters followed-up were radiation-induced cystitis and enteritis, both graded, and

other effects such as fistula or small bowel obstruction. The early effects on OARs were analyzed, and dose-volume dependence was determined for small bowels.

Table 3 shows acute effects in two examined groups treated with 3DCRT and VMAT/IMRT techniques.

It appeared that toxicity rates were significantly higher for the 3DCRT group at 1 and 6 months after treatment ($p < 0.05$), while it was the opposite during and immediately after treatment for the VMAT/IMRT group. The toxicities recorded within the VMAT/IMRT group after 1 month and after 6 months of follow-up were not statistically significant at $p < 0.05$, as well as for the group 3DCRT, but between groups, there is statistical significance recorded in toxicities.

Table 3

Acute effects (complications) of radiation treatment

Time of complication occurrence	No complications registered in the group		Radiation-induced cystitis		Radiation-induced enteritis		Small bowel obstruction	
	3DCRT subset (28 pts)	VMAT/IMRT subset (21 pts)	3DCRT subset	VMAT/IMRT subset	3DCRT subset	VMAT/IMRT subset	3DCRT subset	VMAT/IMRT subset
During or immediately after treatment	46.4	47.6	7.1 (GII)	23.8 (4.8 GIII, 9.6 GII, 9.6 GI)	25.0 (20 GII, 5 GIII)	19.0 (14.3 GI, 4.7 GII)	-	-
1 month after the last fraction	71.4	57	10.7 (7 GII, 3 GI)	14.3 (GI)	10.7 (GI)	9.5 (GI)	1 patient	-
6 months after treatment	75	61.9	17.8 (3.6 GIII, 3.6 GII, 10.6 GI)	9.5 (GI)	7.1 (GI)	6.3 (GI)	1 patient	-

Note: 3DCRT subset included 28 patients; VMAT/IMRT subset included 21 patients.
G – toxicity grading according to the Radiation Therapy Oncology Group (RTOG); 3DCRT – three-dimensional conformal radiotherapy; VMAT – volumetric modulated arc therapy; IMRT – intensity modulated radiation therapy.

Table 4

Average shifts during daily imaging in VMAT/IMRT and 3DCRT patients

Parameter	3DCRT	VMAT/IMRT
x (cm)	0.35 ± 0.22	0.32 ± 0.17
y (cm)	0.38 ± 0.22	0.37 ± 0.20
z (cm)	0.27 ± 0.22	0.30 ± 0.22
Calculated margins (cm)	x = 0.82; y = 0.78; z = 0.74	x = 0.75; y = 0.64; z = 0.75

Values are expressed as mean ± standard deviation.
3DCRT – three-dimensional conformal radiotherapy; VMAT – volumetric modulated arc therapy; IMRT – intensity modulated radiation therapy.

According to the daily shifts recorded in the RV system, which originated from daily kV-kV pairs or cone-beam CT (CBCT) imaging, for both groups of patients (3DCRT and VMAT), the PTV margins were calculated and evaluated according to the Van Herk formula [5] and instructions. The imaging was performed in the first three fractions and then weekly. The tolerance limit was 5 mm.

The results obtained are shown in Table 4.

Discussion

This study compared dosimetric parameters for the target and OARs in 3DCRT and VMAT/IMRT techniques in gynecological patients treated at our Institute between 2016 and 2019. It was found that the coverage and homogeneity of the PTV were similar for VMAT and 3DCRT treatment plans, which complies with literature data [6, 8–11].

VMAT/IMRT is not only a highly conformal treatment technique but also enables much better sparing of OARs, neighboring to the clinical targets. Target coverage in both VMAT/IMRT and 3DCRT was practically very similar, but this was not the case with OARs, where doses for small bowel, rectum, bladder, and femoral heads were significantly higher for 3DCRT plans than in VMAT/IMRT, and the doses also carried an accompanying risk of acute and later effect.

Parallel analysis of dose-volume histograms for two different techniques in the same subset of patients revealed that the V45Gy in the small bowel in IMRT/VMAT plans was four times smaller than the same of 3DCRT plans (49.4 cm^3 in IMRT/VMAT plans vs. 211.6 cm^3). In the case of the femoral head, a significant reduction in V30Gy (10.8 % vs. 33.1%) and mean dose in the case of IMRT/VMAT plans was recorded (30.4 Gy in 3DCRT vs. 23.6 Gy). Rectum was planned with a significantly smaller dose in terms of V30Gy (79.5% vs. 95.2%) in IMRT/VMAT plans. The bladder was better spared in VMAT plans in terms of V40Gy (51% vs. 91%), but the maximum dose was higher in VMAT plans than in 3DCRT (50.1 Gy to 48.1 Gy on average). For all OARs, a statistically significant difference was registered at $p < 0.05$.

The RTOG1203 trial, whose dosimetric limits were used in this work, concluded that pelvic IMRT/VMAT is associated with significantly fewer toxicities than standard RT from the patient perspective, which was confirmed here. Other literature data show that the use of advanced techniques instead of four field boxes (3DCRT) significantly reduces the grade of acute toxicity, as demonstrated in our work.

Acute effects were similar in both groups. Since doses for the OARs were smaller in VMAT/IMRT group, patients recovered faster than in the 3DCRT group, which correlates to data found in literature [9]. It is also important to mention that there were no GIII toxicities in VMAT/IMRT group during follow-up, which were fairly often seen in 3DCRT patients.

In 2010, Quantitative Analysis of Normal Tissue Effects in Clinic [8] summarized the dose-volume relationship for many OARs, but the data for small bowel were very limited, providing one high dose parameter for the dose-volume constraint. During many years of clinical experience, we have noticed that this Quantitative Analysis of Normal Tissue Effects (QUANTEC) 2010 parameter V45 < 195 cm^3 was not sufficient to predict toxicity to small bowels, so other parameters were used, in accordance with literature data [6, 9]. Literature data found a positive correlation between late effects of the small bowel and small bowel volume parameters in cases of cervical radiotherapy. But these parameters were different between the studies, review of the literature showed some studies recommended a V40 < 340 cm^3, while others recommended a V15 < 275 cm^3 [6, 9].

As for the small bowel and radiation-induced enteritis, in VMAT/IMRT patients, the small bowel reactions hardly went over GI (RTOG Toxicity Grade I), while most patients in 3DCRT had GIII and GII and recovered slower than the patients in the VMAT/ IMRT group. In recent years, we have seen that the recovery of 3DCRT patients can prolong from one to even more years, as proven in literature [11].

We noticed that radiation-induced cystitis appeared later in the subset of patients treated with 3DCRT and increased in terms of grade and number of cases as time passed up to 6 months after treatment (and later) than in VMAT/IMRT treated patients where cystitis appeared in lower grade during or after treatment and already at the first or second follow-up examination; it was not registered anymore. This could be explained by the accumulated volume/dose relationship to the bladder and the response of its epithelium to it [10].

Toxicities between two groups (3DCRT and VMAT/IMRT) were statistically compared using Fisher's exact test. The test showed that toxicity rates were significantly higher for the 3DCRT group 1 month and 6 months after the treatment ($p < 0.05$), while it was the opposite during and immediately after the treatment for the VMAT/IMRT group. That can be explained by higher stages of illness in VMAT/IMRT group, which contributed to the acute effects recorded in this group.

The margins of CTV to PTV are dependent on at least two factors: the position of the target inside the patient's body and its relationship to other organs, and the position of a patient in relation to the radiation beam. The size of the margin of CTV-PTV is a compromise between the risk of underdosing of CTV and also the risk of toxicity to healthy tissue around the CTV.

The margin is calculated by a widely used Van Herk's formula [5], based on the probability distribution of the cumulative dose over a range of patients.

Our data show that, currently, margins for CTV to PTV in VMAT/IMRT patients must remain the same as in 3DCRT (1 cm) due to daily setup movements. In future months, there will be a need to re-evaluate margins and correct them to smaller ones according to the improvements achieved in clinical practice in VMAT/IMRT cases. The reduction of margins will further decrease the dose burden on OARs, but it must be proven clinically acceptable.

Conclusion

The study showed that QUANTEC data used for 3DCRT is not detailed enough to support advanced treatments in the pelvic area, in this particular case-gynecological treatments. Clinical follow-up showed the origin of problems, which can be solved by the implementation of additional dose-volume parameters during treatment planning, thus creating the desired dose-volume histogram for a particular organ and, therefore, predicting the possible complication probability and rates. We clinically implemented multiple dose-volume parameters of all associated OARs, including small bowels, based on QUANTEC 2010, RTOG 1203, and other studies of pelvic IMRT/VMAT treatments.

In summary, we can conclude that VMAT/IMRT is a better treatment modality for gynecological malignancies in comparison to 3DCRT, significantly dosimetrically superior. Both techniques provide optimal coverage of the target volume, but OARs can be better spared in the advanced modality and, therefore, complications minimized, which complies with literature data. This advanced treatment modality should be an option for all radically treated patients.

The margins for CTV-PTV must be re-evaluated regularly to decrease the potential dose of OARs during advanced RT treatments.

REFERENCES

1. *Arbyn M, Weiderpass E, Bruni L, de Sanjosé S, Saraiya M,* et al, Estimates of incidence and mortality of cervical cancer in 2018: a worldwide analysis, Lancet Glob Health 2020; 8(2): e191–e203.
2. *Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A.* Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018; 68(6): 394–424.
3. Women and men in Republic of Serbia Belgrade, Serbia: Republički zavod za statistiku 2017. Available from: https://publikacije.stat.gov.rs/G2017/Pdf/G20176008.pdf
4. Cancer registry. Belgrade: Institute of Public Health of Serbia "Dr. Milan Jovanovic Batut"; 2015. Available from: http://www.batut.org.rs/download/publikacije/Incidencija%20i%20mortalitet%20od%20raka%202015.pdf (Serbian)
5. IAEA Human Health Reports No. 16. Introduction of Image Guided Radiotherapy into Clinical Practice. Vienna: International Atomic Energy Agency; 2019. Available from: https://www-pub.iaea.org/MTCD/Publications/PDF/P1827_web.pdf
6. *Klopp A, Yeung A, Deshmukh S, Gil KM, Wenzel L, Westin S,* et al. RTOG 1203: A Randomized Phase III Study of Standard vs. IMRT Pelvic Radiation for Post-Operative Treatment of Endometrial and Cervical Cancer (Time-C). Philadelphia, PA: NRG Oncology; 2015
7. International Commission on Radiation Units and Measurements. ICRU Report 83. Prescribing, Recording, and Reporting Photon-Beam Intensity-Modulated Radiation Therapy (IMRT). J Int Comm Rad Units 2010; 10(1): 1–2.
8. *Bentzen SM, Constine LS, Deasy JO, Eisbruch A, Jackson A, Marks LB,* et al. Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC): an introduction to the scientific issues. Int J Radiat Oncol Biol Phys 2010; 76(3 Suppl): S3–9.
9. *Jadon R, Higgins E, Hanna L, Evans M, Coles B, Staffurth J.* A systematic review of dose-volume predictors and constraints for late bowel toxicity following pelvic radiotherapy. Radiat Oncol 2019; 14(1): 57.
10. *Stacey R, Green JT.* Radiation-induced small bowel disease: latest developments and clinical guidance. Ther Adv Chronic Dis 2014; 5(1): 15–29.
11. *Greven KM, Paunesku T.* Radiation complications of the pelvis. Cancer Treat Res 2006; 128: 125–53.

Received on May 20, 2021
Revised on June 19, 2021
Accepted on August 4, 2021
Online First August 2021