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THE IMPACT OF VOLUMETRIC MODULATED ARC RADIOTHERAPY ON CLINICAL OUTCOMES OF PATIENTS WITH GYNECOLOGICAL MALIGNANCIES

UTICAJ PRIMENE VOLUMETRIJSKI MODULISANE LUČNE RADIOTERAPIJE NA KLINIČKI ISHOD KOD PACIJENTKINJA LEČENIH OD GINEKOLOŠKIH KARCINOMA

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Summary

Introduction. In locally advanced cancers of the cervix, endometrium and vulva, radiotherapy is the primary treatment modality. In recent years, new modern techniques of external radiation have been developed in radiation oncology, with the goal of dose escalation to the target volume, while sparing healthy tissues. The aim of this study is to determine the impact of volumetric modulated arc therapy on clinical outcomes of patients with gynecological malignancies. **Material and Methods.** Data were retrospectively collected from 60 patients treated for *International Federation of Gynecology and Obstetrics* stage I – III cervical, endometrial and vulvar cancers, using definitive (n = 35) or adjuvant (n = 25) radiotherapy/chemoradiotherapy. Thirty patients underwent three-dimensional conformal radiation therapy (definitive in 22 and adjuvant in 8) and the other 30 patients were treated with volumetric modulated arc therapy (definitive in 13 and adjuvant in 17). The following clinical outcome parameters were compared between the two groups: complete clinical response, disease free survival, progression free survival, and 4-year overall survival. **Results.** Progression free survival of patients treated with definitive radiotherapy/chemoradiotherapy using volumetric modulated arc therapy was 17.2 months, while in the group treated with three-dimensional conformal radiation therapy it was 7.9 months (p = 0.300). Four-year overall survival in patients who were treated with definitive radiotherapy/chemoradiotherapy using three-dimensional conformal radiation therapy was 50%, and 61.5% in the group treated with definitive volumetric modulated arc therapy (p = 0.200), while in patients treated using adjuvant radiotherapy/chemoradiotherapy it was 75% vs. 88.2%, respectively (p = 0.400). **Conclusion.** Although without statistical significance, volumetric modulated arc therapy showed better results with respect to progression free survival and 4-year overall survival in previously unoperated patients who underwent definitive radiotherapy/chemoradiotherapy.

Key words: Radiotherapy; Radiotherapy, Intensity-Modulated; Genital Neoplasms, Female; Survival Rate; Treatment Outcome

Sažetak

Uvod. Kod lokalno uznapredovalih karcinoma cerviksa, endometriuma i vulve, radioterapija predstavlja primarnu terapijsku metodu. Poslednjih godina došlo je do razvoja novih, savremenih tehnika spoljašnjeg zračenja čiji je cilj eskalacija doze na ciljni volumen uz što veću poštedu organa od rizika. Cilj ovog istraživanja je utvrđivanje uticaja primene napredne volumetrijski modulisanu lučnu radioterapijske tehnike na klinički ishod bolesnica lečenih od ginekoloških karcinoma. **Materijali i metode.** Retrospektivno su prikupljeni podaci od 60 pacijentkinja lečenih od karcinoma cerviksa, endometriuma ili vulve stadijuma po klasifikaciji Međunarodne federacije ginekologa i akušera, definitivnom (n = 35) ili adjuvantnom (n = 25) radioterapijom/hemioradioterapijom. Kod 30 pacijentkinja je sprovedena trodimenzionalna konformalna teleterapija (kod 22 definitivna i kod osam adjuvantna), a kod ostalih 30 volumetrijski modulisanu lučnu radioterapiju (kod 13 definitivna i kod 17 adjuvantna). Poredili smo sledeće kliničke ishode između dve navedene grupe: kompletan klinički odgovor, period preživljavanja bez bolesti, period do prve progresije bolesti i četvorogodišnje preživljavanje. **Rezultati.** Period preživljavanja do prve progresije bolesti je kod prethodno neoperisanih bolesnica lečenih volumenski modulisanom lučnom radioterapijskom tehnikom bio 17,2 meseca, dok je kod lečenih trodimenzionalnom konformalnom tehnikom bio 7,9 meseci (p = 0,300). Četvorogodišnje preživljavanje bilo je zastupljeno kod 50% lečenih definitivnom trodimenzionalnom konformalnom i 61,5% lečenih definitivnom volumetrijski modulisanom lučnom radioterapijskom tehnikom (p = 0,200) i kod 75% naspram 88,2% bolesnica lečenih adjuvantnom radioterapijom, respektivno (p = 0,400). **Zaključak.** Iako bez statističke značajnosti, pokazan je trend boljeg preživljavanja bez progresije bolesti kod prethodno neoperisanih pacijentkinja, kao i trend boljeg četvorogodišnjeg preživljavanja bolesnica kod kojih je primenjena volumetrijski modulisanu lučnu radioterapijsku tehniku. **Ključne reči:** radioterapija; volumetrijski modulisanu lučnu radioterapija; ginekološke neoplazme; preživljavanje; ishod lečenja

Introduction

According to the data published by the Global Cancer Observatory in 2020, cervical cancer was the fourth

most common malignancy in women (6.5% of all carcinomas) while endometrial cancer ranked sixth (4.5% of all carcinomas) [1]. Cervical cancer is the second most common cancer in women between the ages of

Abbreviations

CRT	– chemoradiotherapy
VMAT	– volumetric modulated arc therapy
IMRT	– intensity modulated radiation therapy
3DCRT	– three-dimensional conformal radiation therapy
EBRT	– external beam radiation therapy
CBCT	– cone beam computed tomography
FIGO	– International Federation of Gynecology and Obstetrics
MRI	– magnetic resonance imaging
CT	– computed tomography

15 and 44 [2]. According to the data published by the Institute of Public Health of Serbia “Dr. Milan Jovanović Batut”, the standardized incidence of cervical carcinoma in the territory of the Republic of Serbia in 2013 was 20.3, the incidence of endometrial carcinoma was 13.4 while the mortality rates were 12.7 and 7.1, respectively [3].

The treatment of patients with gynecological cancers varies and primarily depends on the local progression of the tumor and the stage of the disease. In locally advanced cancers of the cervix, endometrium and vulva, radiotherapy is the primary treatment modality, used alone or as chemoradiotherapy [4]. There are two types of radiation therapy used for gynecological malignancies: external beam radiation therapy (EBRT) (teletherapy) and intracavitary or interstitial radioisotope therapy (brachytherapy). In recent decades, three-dimensional conformal technique (3DCRT) of EBRT has gained precedence in the treatment of gynecological cancers. The main goal of conformal radiotherapy is to adjust and conform the external beam to the desired target volume (tumor) providing uniform distribution of the prescribed dose within the target volume, while at the same time minimizing the dose to the surrounding healthy tissues and organs [5, 6]. However, continual developments in radiation oncology have resulted in development of new, more precise techniques with the goal of further escalating the dose to the desired target volume and even greater sparing of healthy tissues. One of these new techniques is intensity modulated radiation therapy (IMRT). Many dosimetric studies have shown a significant reduction in the dose administered to organs at risk (small intestine, rectum and bladder) when IMRT is used, compared to 3DCRT [7]. Volumetric modulated arc therapy (VMAT) is a novel radiation therapy technique that derived from IMRT and was first described by Yu et al. in 1995 [8]. The VMAT technique allows continuous external beam shaping, as well as changes in the intensity of the beam, thus providing increased doses delivered to the target volume, while simultaneously reducing the treatment delivery time [9, 10].

The aim of this study is to examine the effects of VMAT on the clinical outcomes of patients with gynecological cancers using definitive and adjuvant radiation therapy.

Material and Methods

This retrospective study included 60 patients treated for gynecological cancers at the Oncology

Institute of Vojvodina in Sremska Kamenica, Republic of Serbia, between 2016 and 2018. At the moment of diagnosis, the patients were in stages I - III of the International Federation of Gynecology and Obstetrics (FIGO) classification. Patients with distant metastases or para-aortic lymph node spread were excluded from the study. The staging procedures and determination of local disease progression were based on pelvic and abdominal magnetic resonance imaging (MRI), computed tomography (CT) and chest X-ray. Treatment of these patients was conducted according to our institution's current protocols, which are based on National Comprehensive Cancer Network practice guidelines. Patients with cervical, endometrial and vulvar cancer were included in the study (**Table 1**). The treatment strategies were determined based on disease local progression, patients' age, and comorbidities. In 35 patients radiotherapy/chemoradiotherapy (RT/CRT) was the initial and definitive treatment, while the other 25 underwent primary surgical treatment, followed by adjuvant RT/CRT (**Table 2**). Most patients with cervical and endometrial cancer received brachytherapy following EBRT (**Table 2**). Based on the radiotherapy technique used, patients were divided into the following groups:

- Patients who underwent definitive RT/CRT – 22 treated with 3DCRT and 13 with VMAT (**Table 2**);
- Patients who underwent adjuvant RT/CRT – 8 treated with 3DCRT and 17 with VMAT (**Table 2**).

All patients received the same dose of 45 gray (Gy) in 25 fractions.

After completion of RT/CRT, all patients were regularly monitored at our institution by a radiation oncologist and a gynecologist. The monitoring included physical examination, analysis of blood samples, abdominal ultrasound and pelvic MRI which were done 4 months post treatment completion. Complete clinical response was based on the results of the first pelvic MRI. Further monitoring included the following parameters:

- Disease free survival – a measure of time after treatment during which no sign of cancer is found; also called relapse free survival.
- Progression free survival – a measure of time during and after treatment in which the disease is present, but there is no progression of the disease.
- Overall survival – percentage of patients in a study or treatment group who are still alive for a certain period of time from the date of diagnosis, most commonly stated as five-year survival; in this study it was stated as a four-year survival rate [11].

These parameters were observed separately for patients who received initial and definitive RT/CRT in comparison to those who received adjuvant RT/CRT following primary surgical treatment.

The Chi-square test was used for comparison of complete clinical response and 4-year overall survival and the Mann-Whitney test was used for comparison of disease free survival and progression free survival in patients treated with 3DCRT and VMAT. A $p < 0.05$ was considered to be a statistically significant difference.

Results

The mean patient age in the 3DCRT group was 57 years, while in the VMAT group it was 53 years. Patients were further divided into groups according to cancer localization, histopathological type of cancer and FIGO classification, as shown in **Table 1**. Squamous cell carcinoma of the cervix was the most prevalent type in both 3DCRT and VMAT groups. In regard to FIGO staging, patients in the

3DCRT group were predominantly in stage II, while in the VMAT group most were in stage I.

Of 60 patients, 35 were treated with definitive RT/CRT (**Table 2**). Adjuvant RT/CRT was performed in the remaining 25 patients. In total, 76.67% of patients in the 3DCRT group and 56.67% in the VMAT group underwent chemoradiotherapy (**Table 2**). Almost all of the 60 patients received brachytherapy following RT/CRT (**Table 2**).

Table 1. Mean age distribution according to cancer localization, histological type and FIGO classification

Tabela 1. Distribucija pacijentkinja prema prosečnoj starosti, lokalizaciji tumora, histološkom tipu tumora i FIGO klasifikaciji

		3D conformal/3D konformalna	VMAT/VMLT
Mean patient age at the time of diagnosis <i>Prosečna starost pacijentkinja u vreme postavljanja dijagonze (god.)</i>		57	53
Cancer localization <i>Lokalizacija tumora</i>	Cervix/Grlić materice	26 (86.67%)	20 (66.67%)
	Endometrium/Endometrium	3 (10%)	9 (30%)
	Vulva/Vulva	1 (3.33%)	1 (3.33%)
Histological type <i>Histološki tip tumora</i>	Planocellular/Planocelularni	23 (76.67%)	17 (56.67%)
	Adenocarcinoma/Adenokarcinom	5 (16.6%)	12 (40%)
	Adenosquamous/Adenoskvamozni	1 (3.33%)	1 (3.33%)
	Anaplastic/Anaplastični	1 (3.33%)	0
FIGO classification <i>FIGO klasifikacija</i>	I	10 (33.3%)	13 (43.3%)
	II	13 (43.3%)	12 (40%)
	III	7 (23.3%)	5 (16.6%)

Legend: 3D – three-dimensional; VMAT – volumetric modulated arc therapy; FIGO – International Federation of Gynecology and Obstetrics

Legenda: 3D – trodimenzionalan; VMLT – volumetrijski modulirana lučna terapija; FIGO – Međunarodna federacija ginekologije i akušerstva

Table 2. Distribution of patients according to treatment protocol

Tabela 2. Distribucija pacijentkinja prema primenjenim metodama lečenja

		3D conformal/3D konformalna	VMAT/VMLT
Primary surgery followed by RT/CRT <i>Operacija pre RT/HRT</i>	Yes/Da	8 (26.67%)	17 (56.67%)
	No/Ne	22 (73.33%)	13 (43.33%)
Chemoradiotherapy (Cisplatin IV series) <i>Hemioradioterapija (Cisplatin u IV serije)</i>	Yes/Da	23 (76.67%)	17 (56.67%)
	No/Ne	7 (23.33%)	13 (43.33%)
Brachytherapy following RT/CRT <i>Brahiterapija nakon RT/HRT</i>	Yes/Da	27 (90%)	24 (80%)
	No/Ne	3 (10%)	6 (20%)

Legend: 3D – three-dimensional; VMAT – volumetric modulated arc therapy; RT – Radiotherapy; CRT – chemoradiotherapy

Legenda: 3D – trodimenzionalan; VMLT – volumetrijski modulirana lučna terapija; RT – radioterapija; HRT – hemoradioterapija

Table 3. Comparison of treatment outcomes between 3D conformal and VMAT technique in patients who underwent definitive radiotherapy/chemoradiotherapy

Tabela 3. Poređenje kliničkih ishoda između pacijentkinja kod kojih je primenjena 3D konformalna i VMAT definitivna radioterapija/hemioradioterapija

Complete clinical response/Kompletan klinički odgovor	14 (63.6%)	8 (61.5%)	0.901
Disease free survival/Period bez prisustva bolesti	46.5 months/meseci	47.6 months/meseci	0.948
Progression free survival/Period do prve progresije bolesti	7.9 months/meseci	17.2 months/meseci	0.300
4-year overall survival/Četvorogodišnje preživljavanje	11 (50.0%)	8 (61.5%)	0.643

Legend: 3D – three-dimensional; VMAT – volumetric modulated arc therapy

Legenda: 3D – trodimenzionalan; VMLT – volumetrijski modulirana lučna terapija

Table 4. Comparison of treatment outcomes between 3D conformal and VMAT technique in patients who underwent adjuvant radiotherapy/chemoradiotherapy**Tabela 4.** Poređenje kliničkih ishoda između pacijentkinja kod kojih je primenjena 3D konformalna i VMAT adjuvantna radioterapija/hemioradioterapija

	3D conformal/3D konformalna	VMAT/VMLT	p/p
Complete clinical response <i>Kompletan klinički odgovor</i>	8 (100%)	15 (88.2%)	0.312
Disease free survival <i>Period bez prisustva bolesti</i>	53.2 months (meseći)	47.8 months (meseći)	0.184
Progression free survival <i>Period do prve progresije bolesti</i>	/	13.6 months (meseći)	/
4-year overall survival <i>Četvorogodišnje preživljavanje</i>	6 (75%)	15 (88.2%)	0.400

Legend; 3D – three-dimensional; VMAT – volumetric modulated arc therapy

Legenda; 3D – trodimenzionalan; VMLT – volumetrijski modulirana lučna terapija

In patients who underwent definitive RT/CRT, a complete clinical response was achieved in 14 (63.6%) patients who were treated with 3DCRT and in 8 (61.5%) patients treated with VMAT, thus showing no statistically significant difference ($p = 0.910$) (Table 3). In patients who were treated with adjuvant RT/CRT following surgery, a complete clinical response was achieved in all 8 (100%) patients who were treated with 3DCRT, and in 15 (88.2%) patients treated with VMAT (Table 4).

The average disease free survival in patients who were treated with definitive RT/CRT was 46.5 months in the 3DCRT group and 47.6 months in the

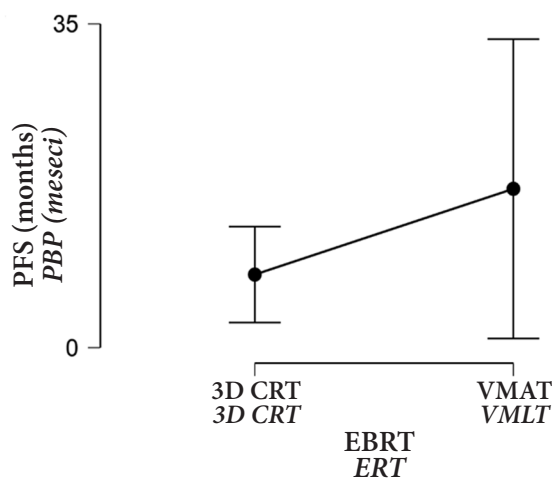
VMAT group, so there was no statistically significant difference between the two groups ($p = 0.316$) (Table 3). In patients who underwent adjuvant RT/CRT, the average disease free survival was 53.2 months in the 3DCRT group and 47.8 months in the VMAT group ($p = 0.184$) (Table 4).

The progression free survival in patients who were treated with definitive RT/CRT was 17.2 months in the VMAT group, almost double compared to 7.9 months in the 3DCRT group (Table 3, Graph 1). The VMAT group showed better 4-year overall survival as well, 65% compared to 50% in the 3DCRT group. Better 4-year overall survival was also reported in patients who underwent adjuvant RT/CRT when using VMAT technique (88.2%) compared to 3DCRT technique (75%) (Table 4). These differences were not statistically significant considering the sample size, but the reported results do show a trend of better survival in the VMAT group, which could potentially show a significant statistical difference in a bigger sample size.

Discussion

Although our study showed no statistically significant difference between clinical outcomes of patients treated with 3DCRT and VMAT, in absolute terms it is clear that progression free survival of patients treated with definitive RT/CRT in the VMAT group is twice longer than in the 3DCRT group (17 months versus 7.9 months) and this may be considered as a significant result in oncology patients. Furthermore, the 4-year overall survival was over 10% in patients treated with VMAT technique. While reviewing the literature, we have come across only a few studies that reported on clinical results of 3DCRT and VMAT techniques in the treatment in gynecological malignancies. The available studies on related topics usually examine the outcomes of IMRT, dosimetry and organs at risk of toxicity.

Droge et al. reported comparable clinical results among patients who were treated for cervical carcinoma (FIGO I - IVA) using 3DCRT ($n = 75$) and VMAT ($n = 30$) technique of RT/CRT [12]. Their study demonstrated no statistically significant dif-

**Graph 1.** Difference in progression free survival between 3D conformal and VMAT technique in patients who underwent definitive radiotherapy/chemoradiotherapy**Grafikon 1.** Razlika u periodu do prve progresije bolesti između 3D i VMAT tehnike kod pacijentkinja koje su primile definitivnu radioterapiju/hemioradioterapiju

Legend: EBRT – external beam radiotherapy (Teletherapy); PFS – progression free survival; 3DCRT – three-dimensional conformal radiotherapy; VMAT – volumetric modulated arc therapy

Legenda: ERT – eksterna radioterapija (Teleterapija); PBP – preživljavanje bez progresije; 3DCRT – trodimenzionalna konformna radioterapija; VMLT – volumetrijska modulirana lučna terapija

ference in survival rates between the two groups. Lan et al. observed 115 patients who were treated for cervical carcinoma (FIGO IA - IIIB) by radical hysterectomy, followed by either 3DCRT ($n = 89$) or IMRT ($n = 26$) technique, without brachytherapy [13]. The 2-year overall survival was 90.3% in the 3DCRT group, while in the IMRT group it was 91.6% ($p = 0.674$) and there was no statistically significant difference in the compared disease free survival either [13]. Comparable results can be seen in a study published by Tsuchida et al. [14]. They studied 73 patients diagnosed with locally advanced cervical carcinoma (parametrial tissue or pelvic lymph node involvement) who were treated using adjuvant radiation therapy. Out of 73 patients, 33 were treated with 3DCRT technique, and 40 using IMRT. This study showed no statistically significant difference in the 4-year overall survival (82% versus 78%, $p = 0.744$) or in the disease free survival. Cancer recurrence was recorded in 11 and 13 patients, respectively [14].

There is a concern that modern techniques, such as IMRT and VMAT, may increase locoregional recurrence by reducing the target volume, in order to protect organs at risk. However, previous studies have reported that the clinical outcomes did not deteriorate when using modern techniques compared to 3DCRT [15, 16].

A particularly difficult challenge in the treatment of gynecological malignancies and pelvic malignancies in general, is the interfractional target motion caused by variations in bladder and intestine volume compared to planning values, uterine peristalsis and motility. These can lead to reduced target volume coverage and consequent suboptimal radiation therapy. However, among modern techniques such as IMRT and VMAT, cone beam computed tomography (CBCT) is an effective image guided radiotherapy tool used daily to evaluate the position and coverage of target volume [5]. By using CBCT, we can generate volumetric CT images and perform target matching to the initial CT plan. If necessary, repositioning of patient is done in order to reduce

the possibility of error and to ensure precise delivery of treatment [5]. In 3DCRT, verification and target matching is performed by using kilovoltage orthogonal images which are compared with CT scans based on bony anatomy of the pelvis without any insight into the surrounding soft tissues. Consequently, it is expected that modern radiation therapy techniques will achieve better treatment results and thus better patient survival.

When reviewing the available literature on this topic, we have come across a few studies comparing IMRT and VMAT techniques in treatment of gynecological malignancies, most of them accenting dosimetry and organs at risk of toxicity. Cozzy et al. have noted that VMAT technique shows significant improvements in organs at risk and healthy tissue sparing with uncompromised target coverage compared to IMRT [17]. Knapp et al. reported similar results, noting greater sparing of organs at risk, while maintaining equal or even greater target coverage with VMAT, which has led to implementation of new clinical protocols in radiotherapy of gynecological carcinomas [18].

The limitations of our study include retrospective data collection and a small sample size; yet it is one of the few studies on this topic, which gives it significance. In our opinion, research on this topic should be continued in order to further examine the importance of modern radiotherapy techniques in the treatment of gynecological malignancies.

Conclusion

Our study showed that differences between the compared clinical outcomes among patients treated with three-dimensional conformal radiation therapy and volumetric modulated arc therapy technique were statistically insignificant. However, our results demonstrated a positive trend in progression free survival in patients who underwent definitive radiotherapy/chemoradiotherapy, as well as better 4-year overall survival with volumetric modulated arc therapy.

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