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Three Dimensional Conformal versus Volumetric Arc Therapy in Gynecological Cancer: A Retrospective Study Evaluating Therapeutic Effect and Toxicity

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Rezumat

Radioterapia conformațională tridimensională versus radioterapia cu arc modulată volumetric în cancerul ginecologic: un studiu retrospectiv de evaluare a efectului terapeutic și a toxicității

Introducere: Progresele tehnologice din domeniul radioterapiei au consacrat tehnici moderne precum Volumetric Modulated Arc Therapy (VMAT) drept opțiunea terapeutică de referință pentru majoritatea afecțiunilor neoplazice. Cu toate acestea, din diverse motive care nu fac obiectul acestui articol, în prezent, accesul la aceste tehnici moderne rămâne limitat pentru o parte dintre pacienți, care continuă să fie tratați prin metoda convențională Three-Dimensional Conformal Radiation Therapy (3DCRT).
Metode: În acest studiu retrospectiv, am realizat o comparație între VMAT şi 3DCRT din perspectiva supraviețuirii globale la cinci ani (OS – overall survival), a supraviețuirii fără boală (DFS – disease-free survival) şi a profilului de toxicitate la paciente tratate pentru cancer endometrial şi cervical. În acest studiu retrospectiv, am realizat o comparație între VMAT şi 3DCRT din perspectiva supraviețuirii globale la cinci ani (OS – overall survival), a supraviețuirii fără boală (DFS – disease-free survival) şi a profilului de toxicitate la paciente tratate pentru cancer endometrial şi cervical. În acest studiu au fost incluse un total de 173 de paciente cu neoplazii ginecologice, tratate fie prin tehnica VMAT, fie prin 3DCRT: 73 de paciente (Grupul A) au primit tratament prin VMAT, iar 100 de paciente (Grupul B) au fost tratate prin tehnica 3DCRT. Principalele obiective ale studiului au fost: supraviețuirea fără boală (DFS), supraviețuirea globală (OS) şi toxicitatea tratamentului.

Rezultate: Rezultatele studiului au evidențiat o îmbunătățire semnificativă fără boală la 5 ani pentru pacientele din grupul A, în timp ce supraviețuirea globală nu a prezentat diferențe semnificative între cele două grupuri.
Concluzie: S-a observat o reducere a toxicității în grupul A comparativ cu grupul B, în special în ceea ce priveşte toxicitatea gastrointestinală.

Cuvinte cheie: Volumetric-Modulated Arc Therapy, Intensity-Modulated Radiation Therapy, Three-Dimensional Conformal Radiotherapy, cancer ginecologic

Abstract

Introduction: Technological advances in the field of radiation therapy have established modern techniques like Volumetric Modulated Arc Therapy (VMAT) as the radiation treatment of choice for nearly all malignancies. Unfortunately, due to many reasons that are not in the scope of this paper, even nowadays not all patients have access to these modern techniques and are managed with the "older" Three-Dimensional Conformal Radiation Therapy (3DCRT).
Methods: In this retrospective study, we performed a comparison of VMAT to 3DCRT by terms of five (5) year overall survival (OS), disease-free survival (DFS), and toxicity in patients treated for endometrial and cervical cancer. A total of 173 gynecological cancer patients treated with either VMAT or 3D-CRT technique were included in this study: 73 patients (Group A) were treated with VMAT, and 100 patients (Group B) were managed with 3D-CRT technique. The endpoints of this trial were: disease free survival (DFS), overall survival (OS), and toxicity of treatment. *Results:* Our results showed significant 5-year DFS advantage for the patients in group A, while OS had no significant difference between the two groups.
Conclusion: Reduced toxicity was demonstrated in group A compared to group B, regarding mostly gastrointestinal (GI) toxicity.

Keywords: volumetric-modulated arc therapy, intensity-modulated radiation therapy, three-dimensional conformal radiotherapy, gynecological cancer

Introduction

General Facts

Radiotherapy (RT) is a well-established treatment modality in the curative and adjuvant management of endometrial and cervical cancer. Despite the fact that RT is beneficial in eradicating cancer cells, damage to adjacent normal tissues is inevitable leading to acute and late toxicity. Intense concern and aim of radiation oncologists remain the minimization of toxicity without compromising therapeutic dose and resultant treatment outcome.

Modern treatment techniques such as Intensity Modulated Radiation Therapy (IMRT) and VMAT were developed in order to decrease radiation dose to the organs at risk (OAR) without compromising dose to the clinical tumor volume (CTV).

More specifically, VMAT is a complex arch-based treatment technique delivered from IMRT. It combines all together and simultaneously varying dose rate, gantry speed, and the shape of the multileaf collimator (MLC) aperture. VMAT is the evolution of fixed-field IMRT and intensity-modulated arch therapy (IMAT) delivery. The most dominant advantage of the VMAT technique is the enhanced efficiency of the treatment in terms of remarkable reduction of the monitor units (MUs), and the reduced delivery time (1-3). Many retrospective studies comparing IMRT and VMAT to 3D-CRT have shown remarkable reduction in the volume of small bowel, rectum, bladder, and bone marrow receiving dose of RT (4,5).

Gradually, due to the above-mentioned advantages, IMRT and VMAT techniques have become the standard of care across many centers worldwide for many malignancies and specifically gynecologic primaries such as endometrial or cervical cancer. Due to many reasons that are not in the scope of this paper, not all patients have access to these techniques and are still managed with 3DCRT. Many investigators have attempted to compare head-to-head VMAT to 3D-CRT by terms of toxicity and therapeutic results, but mature randomized data are lacking.

During delineation of volumes of interest according to guidelines, the CTV for endometrial and cervical cancer, should encompass gross tumor volume (GTV), cervix, uterus, parametria, vagina, and regional lymph nodes. More specifically, the regional pelvic lymph nodes that should be treated and included into CTV are: common iliac, internal and external iliac, presacral, and obturator nodes. As a consequence, a portion of gastrointestinal (GI) and genitourinary (GU) tracts are often included in the irradiated volume (6-10). In order to decrease the grade of toxicity and subsequent level of morbidity, while allowing therapeutic dose coverage of the target volume, there is always a concern to reduce dose to normal tissues and this is the exact therapeutic scope of radiotherapy that led to the adaptation of modern techniques of RT for gynecological malignancies (11,12).

Toxicity

Despite the fact that radiotherapy can be, in most cases, curative, treatment can cause serious acute and late morbidity, especially from GI system (12). Pelvic RT for cervical and endometrial carcinomas requires treatment of the pelvic lymph nodes which are mostly situated on the left and right side of the pelvis (13). Indeed, in patients after surgery, a larger proportion of small bowel might be exposed since the intestine fills the cavity of hysterectomy. Until mid 2020s, 3D-CRT was the treatment modality technique of choice for irradiation of patients. Applying anterior-posterior, and two lateral beams to treat the target volume (the so called "box technique"), the bowel, being in the center of the pelvis, was exposed to radiation dose. Employment, on the other hand, of IMRT and VMAT made it possible to shape and decrease radiation dose to normal tissues.

Materials and Methods

Institutional ethics approval was granted to conduct a retrospective study comparing VMAT and 3D-CRT for 173 patients, forming two groups of patients: group A treated with VMAT technique (73 patients) and group B managed with 3D-CRT technique (100 patients). Medical records of patients treated with pelvic RT were reviewed. Brachytherapy (BT) which represents an integral part of therapy in conjunction with external beam radiotherapy for gynecological malignancies was employed to either group of patients according to guidelines for each case. Combining BT (as a boost), with external beam radiation therapy (EBRT) either 3DCRT or VMAT, has been associated with improved survival compared to EBRT alone (14-17). The ethical committee approval number was 013225-24-0. Each patient was referred to our department after thorough tumor board evaluation (18).

Treatment Delivery

Treatment planning was performed on an Eclipse planning System and was delivered via a Varian accelerator with daily Cone-Beam Computed Tomography (CBCT) during RT for verification of the correct positioning of the patients and organs at risk. Regarding GI and GU system and according to guidelines, specific instructions were given and special care was taken to ensure almost empty rectum as well as full bladder during each daily treatment.

All patients had initially undergone computed tomography (CT) simulation. Patients were positioned supine using knee-feet stabilization devices. Scans were acquired with 3 mm slice thickness covering the region from L3 vertebra to the proximal half of the diaphysis of the femur. Volumes of interest were defined following the Radiation Therapy Oncology Group (RTOG) guidelines. GTV consisted of macroscopic disease combined with all visible positive lymph nodes according to diagnostic imaging modalities (Magnetic Resonance Imaging – MRI with or without Positron Emission Tomography – PET/ CT). Regional lymphatics, such as common, external, and internal iliac and obturator nodes, were delineated according to guidelines. Organs at risk were: small bowel, bladder, rectum and femurs. Delineation of CTV included the involved whole organ with 1 cm margin added around the GTV, or, in the case of adjuvant treatment, around the anatomic site of uterus, with a margin of 0.7 cm around vessels for regional lymph nodes. Additional margins from CTV to PTV were 0.5 cm. Planning was carried out using the VMAT protocol treatment planning system of the department, while 3D-CRT was delivered using the four-field box technique. All patients were treated on Varian Medical Systems (Clinac Dhx 6,16 MV).

Nearly all patients had ECOG performance status of 0 or 1. A large proportion of patients received postoperative RT and about half of the patients received concurrent chemotherapy. A

Table 1. VMAT (Group A) and 3D CRT (Group B) patients' characteristics.

	Characteristics Group A N=73	Number (percentage %)	Characteristics Group B N=100	Number (percentage %)
Age	≤ 60 years	28 (38.36%)	≤ 60 years	35 (35%)
	> 60 years	45 (61.64%)	> 60 years	65 (65%)
Primary	endometrial cancer	45 (61.64%)	endometrial cancer	58 (58%)
	cervical cancer	28 (38.36%)	cervical cancer	42 (42%)
Surgery	yes	50 (68.50%)	yes	70 (70%)
	no	23 (31.50%)	no	30 (30%)
Chemotherapy	yes	62 (84.93%)	yes	82 (82%)
	no	11 (15.07%)	no	18 (18%)

percentage of 95 of the patients received radiotherapy to the whole pelvis at a median dose of 50 Gy, while 5% of the patients received 46 Gy. Median treatment time was almost 1 month. All patients received brachytherapy boost with 3 sessions of 700 cGy in each session. Baseline characteristics of patients are shown in *Table 1*.

Follow-up

Patients were evaluated weekly, from the begging until the completion of treatment for acute toxicity monitoring. Consequently, patients were assessed after completion of treatment for late toxicity. Late toxicity, according to RTOG, is defined as toxicity devel-oped after 3 months of completion of RT. Patients were assessed every 2 to 3 months up to 12 months for late toxicity, OS, and DFS.

Statistical Analysis

The primary end point of this retrospective study was the 5-year OS and DFS of the patients treated with VMAT. Secondary end points were the comparison of either GI toxicity recorded and therapeutic results between two groups (A and B). According to the analysis from Minitab and from the logrank and Wilcoxon statistical test for both VMAT and 3D-CRT techniques, we set the p-value values of both of these tests lower than 0.05 in agreement to the rejection of the initial hypothesis that the distributions where they result from the categorization of the toxicity covariant to be identical but show that they differ from each other. Comparisons for categorical values were performed with Chi-Square test. The whole analysis was performed with R Project for Statistical Computing (www.r-project.org) and with the statistical package of MINITAB.

Results

Patients' treatment planning assessment revealed dosimetric differences between 3D-CRT and VMAT techniques regarding mean doses to PTVs and to OARs. Specifically, evaluation of 20, 30, and 45 Gy isodose lines showed that they were significantly smaller for the V-MAT plans. The dose constraints examined regarding the intestine were V30, V20, and V45 representing the volume of the organ receiving 30, 20, and 45 Gy, respectively. V30 was 47 (± 20%) for 3D-CRT technique versus 38 (± 16%) for VMAT, V20 was 65 (± 15%) versus 72 (± 14%), and, finally, V45, which represents the most important constraint, was 40 (± 10%) for 3D-CRT versus 20 (± 10%) for VMAT technique, all parameters with statistical significance in favor of VMAT ($p<0.001$).

As far as the femoral head is concerned, which is in some cases an underestimated organ at risk since women of some age suffer from bone metabolic disorders like osteoporosis which acts as a cofactor for radiation toxicity such as osteoradionecrosis, 3D-CRT was found superior to VMAT, even if we did not record any toxicity during follow-up in both treatment arms.

Finally, due to technical superiority of VMAT, treatment delivery time was significantly faster than 3D-CRT: 2.5 (± .04) minutes versus 4 (± 0.5) minutes ($p<0.001$) (*Table 2*).

Univariate and multivariate analysis was performed to determine the parameters that influence acute toxicity including concurrent administration of systemic therapy. Concurrent chemotherapy as well as cancer type, histology, RT dose, and RT modality did not show to influence significantly severe acute toxicity in univariate analysis. Cancer type and histology showed marginal significance in univariate analysis but not in multi-variate

Table 2. 3D-CRT (group B) vs VMAT (group A) dosimetric comparison.

	constraint	3D-CRT	VMAT	P value
PTV 95% reference dose coverage		98.91% ± 1.43%	98.92% ± 0.69%	0.950
Treatment delivery time (min)		4.0 ± 0,5	2.5 ± 0.04	<0.001
Bowel	V30	47% ±20%	38% ± 16%	<0.001
	V20	65% ± 15%	72% ± 14%	<0.001
	V45	40% ± 10%	20 ± 10%	<0.001
Left femoral head and neck	V30 < 50%	0%	7.5% ± 5%	0.011
Right femoral head and neck	V30 < 50%	0%	6.7% ± 4.3%	0.010

Abbreviations; min: minutes, V20: volume (of organ) receiving 20 Gy, V30: volume receiving 20 Gy, V450: volume receiving 20 Gy.

Table 3. Dosimetric differences between 3D-CRT and VMAT for incidence of acute toxicity re-garding primary and histology.

Factors	Univariate (p)	HR (95% CI)	Multivariate (p)	Univariate (p)	HR (95% CI)	Multivariate (p)
Cancer type	0.00		0.001	0.004		0.27
Uterine cervical		1.00 (referent)			1.00 (referent)	
Endometrial		0.02 (0.002–0.23)			0.24 (0.04–1.36)	
Histology	0.003		0.19	0.08	0.76	
Adenocarcinoma		1.00 (referent)			1.00 (referent)	
Squamous cell carcinoma		0.41 (0.13–1.30)			0.64 (1.93–2.10)	

analysis, as shown in *Table 3*.

Related to radiation induced morbidity, no grade 3 or grade 4 chronic toxicity developed in either group. However, there was a significant difference in grade 1 and 2 EORTC/RTOG toxicity profile in favor of group A by means of Pearson chi2 test p<0.001 (*Fig. 1*).

After a 5-year follow-up, DFS was inferior in the 3D-CRT group B, as shown in Kaplan Meier analysis in *Fig. 2* (p=0.012, log rank test). The 5-year DFS was 95.23% and 91.5%, for group A and B, respectively. However, OS showed no significant difference between group A and B (p=0.465, log rank test, *Fig. 3*). The 5-year OS was 86.1% and 84.3%, for group A and B, respectively.

Discussion

Radiation therapy, either in the radical or adjuvant setting, plays an important role in the management of cervical or endometrial cancer. Toxicity related to radiotherapy was, is, and will still be of major concern. Both IMRT and VMAT can delegate highly conformal radiation dose while constraining the dose to organs at risk (19-23). On the other hand, during 3D-CRT box-technique, the small

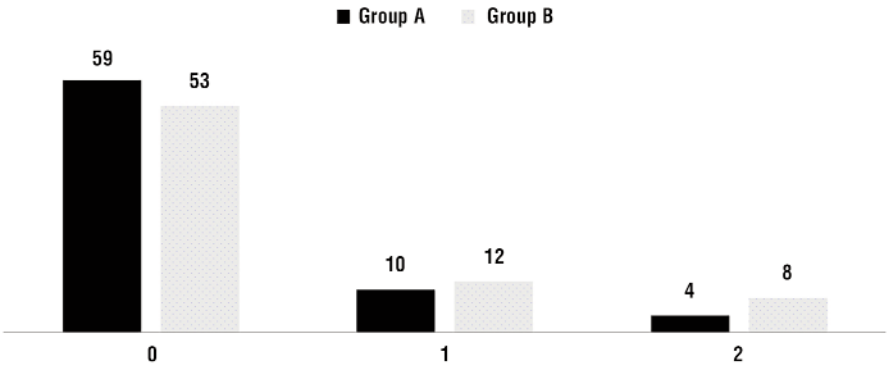

Figure 1. Late toxicity with VMAT and 3D-CRT (group A vs. group B).

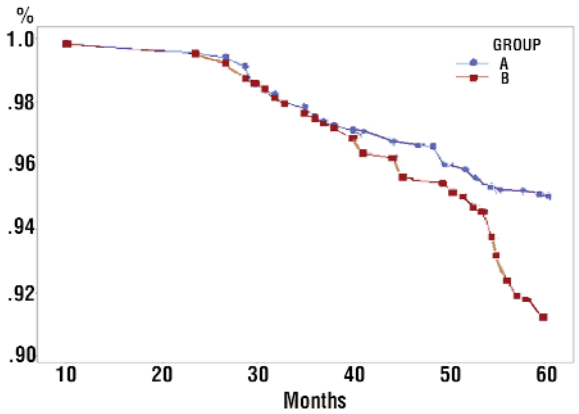

Figure 2. Survival plot for disease-free survival of patients treated with either VMAT or 3DCRT (group A vs. B, log rank test, p=0.012).

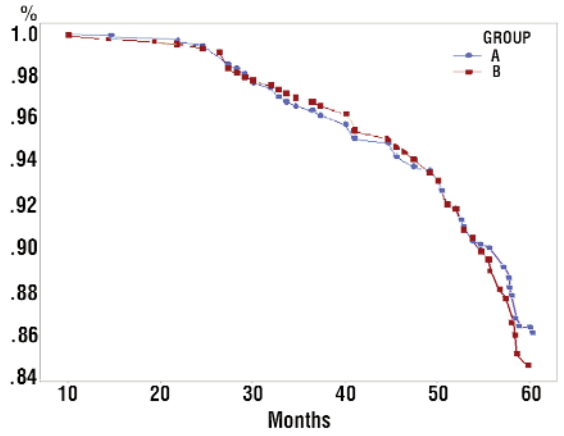

Figure 3. Survival plot for survival of patients treated with either VMAT or 3DCRT (group A vs. B, log rank test, p=0.465).

bowel is encompassed in the irradiated volume (24, 25). Relative data from dosimetry studies revealed that IMRT can achieve less radiation dose to organs at risk, and therefore reduced toxicity compared to 3D-CRT for patients with uterine carcinomas (26-45). Our study focused, apart from the therapeutic results, on patients' reported toxicity, which still remains an unsolved issue depending on objective and subjective factors.

For patients with endometrial carcinoma, adjuvant RT is generally indicated as landmark studies such as the Post Operative Radiation Therapy in Endometrial Cancer (PORTEC-1) trial which showed that RT decreased the 15-year locoregional recurrence rates to 5.8% from 15.5% ($p<0.001$) even without a statistically significant difference in the 15-year OS rates (52% vs. 60%, p=0.14). As expected, according to the conclusions of this trail, a special mention for the toxicity of treatment was made with the indication that EBRT should be avoided in low and intermediate-risk endometrial cancer, due to GI and GU toxicity. Similarly, the PORTEC-2 study, which compared BT to EBRT in the adjuvant postoperative setting, analyzed toxicity from EBRT. It is worth noting that both PORTEC-1 and PORTEC-2 trials included patients managed with 3D-CRT technique (25,46).

Our study showed that PTV coverage and homogeneity was more than satisfactory with VMAT, while median dose to bowel and treatment delivery time significantly improved with the VMAT plans. According to relative literature, limited data and dosimetry studies exist comparing directly and headtohead IMRT to VMAT for gynecological malignancies specifically. In general, VMAT demonstrates further reduction of dose to bladder, bowel, and rectum than IMRT, while coverage of PTV shows improved conformity and homogeneity (47-51). Cozzi et al. demonstrated that VMAT is more efficient for uterine malignancies than IMRT (11). Deng et al. concluded that there is no significant difference between OAR radiotherapy doses, but improved dose conformity, less MU and reduced delivery times with VMAT (52). Finally, Guy et al. also showed that VMAT resulted in reduced treatment delivery time and less MU while maintaining a conformity index similar to IMRT (53).

More data exist focusing on the role of IMRT for the postoperative and definitive treatment of cervical or endometrial carcinomas and its superiority over 3DCRT. Even nonrandomized data from several studies, either single or multi-institutional, demonstrate declined volumes of bladder, rectum, and bowel and a subsequent favorable toxicity profile (54-59). RTOG 1203 (TIME-C) remains the one and only published phase III trial of 3D-CRT versus IMRT for post-operative treatment and management of patients with early stage endometrial or cervical carcinomas (60). This randomized trial demonstrated a clear benefit of IMRT over standard 3DCRT by means of better therapeutic results end equivalent if no better toxicity profile regarding minimal toxicity. Despite the limitations on evaluation of toxicity, this study was performed to find out whether advanced radiotherapy techniques can influence the incidence of GI toxicity and if, as mentioned above, VMAT is not

applicable, 3D-CRT is still a viable radiation treatment option.

Conclusion

Therapeutic efficacy of VMAT by terms of 5-year OS and DFS of women with gynecological malignancies is excellent and the recorded Grade 1 and 2 toxicity was lower for VMAT technique compared to 3D-CRT. It is safe to conclude that due to the confirmed delivery efficiency, VMAT is the treatment of choice when compared to 3D-CRT for gynecological cancer, nevertheless, comprehensive 3DCRT Radiotherapy is a viable therapeutic option even in the modern era of VMAT.

Conflicts of Interests

The authors declare that they have no conflicts of interest.

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Ethics of Approval

The study was conducted in accordance with the Declaration of Helsinki, and approved by the Ethics and Research Committee of our institution (No. 013225-24-0).

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