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Acute toxicities of three-dimensional conformal radiotherapy in the treatment of gynecological cancer, and retrospective dosimetric comparison of three dimensional conformal radiotherapy and invers intensity-modulated radiotherapy

Jinekolojik kanserlerde retrospektif üç boyutlu konformal radyoterapi ve yoğunluk ayarlı radyoterapinin dozimetrik karşılaştırılması ve üç boyutlu konformal radyoterapinin akut yan etkileri

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Abstract

Aim: The study was designed to compare the critical organ and bone marrow doses with three-dimensional conformal radiotherapy plans and intensity-modulated radiotherapy re-treatment plans and to evaluate acute toxicities of three-dimensional conformal radiotherapy for gynecological cancer.

Methods: Twenty-eight patients who underwent conformal radiotherapy (3D-CRT) were evaluated retrospectively and were re- planned according to IMRT technique. The critical organ and bone marrow doses of patients were compared dosimetrically. Evaluation of early side effects was performed using RTOG toxicity scale and European Organization for Research and Treatment of Cancer (EORTC) QLQ30 side effect evaluation questionnaire.

Results: The assessment of early toxicity revealed Grade 1 lower gastrointestinal (GIS) toxicity in 16 (57.1%) patients, grade 1 upper GIS toxicity in 9 (32.1%) patients, grade 1 hematological toxicity in one (3.6%) patients, grade 1 genitourinary toxicity in 15 (53.6%), grade 1 skin toxicity in (50%) 14 patients . One patient (3.6%) had grade 2 upper GIS toxicity, 11 patients (39.3%) had grade 2-3 hematological toxicity. Bone marrow V20 ($p<0.001$), V95 (%) of bone marrow ($p<0.001$), urinary bladder V40 ($p<0.001$), urinary bladder mean dose ($p<0.001$), rectum V40 ($p<0.001$), rectum mean dose ($p<0.001$), small bowel V40 ($p<0.001$) were received lower doses in the IMRT planning arm than the conformal planning arm.

Conclusion: 3D-CRT is a safe treatment with acceptable low toxicity levels in gynecological cancer patients, and it does not adversely affect quality of life. IMRT reduce dose to the bone marrow and the normal tissues as compared to 3D-CRT.

Keywords: Gynecological cancer, Acute toxicities, Quality of life, Conformal radiotherapy, Intensity modulated radiotherapy

Öz

Amaç: Jinekolojik kanserlerde retrospektif üç boyutlu konformal radyoterapi tedavisine ait akut yan etkileri değerlendirmek ve yoğunluk ayarlı radyoterapinin ve üç boyutlu konformal radyoterapinin kemik iliği ve riskli organların dozimetrik olarak karşılaştırmak amaçlanmıştır.

Yöntemler: Üç boyutlu konformal radyoterapi ile tedavisi tamamlanmış 28 hasta retrospektif olarak değerlendirildi ve hastalar IMRT tekniğine göre yeniden planlandı. Olguların kemik iliği ve kritik organ dozları dozimetrik olarak karşılaştırıldı. Olgularda yan etki değerlendirmesi RTOG toksisite skalası ve yaşam kalitesi Avrupa Kanser Araştırma ve Tedavi Merkezi (EORTC) QLQ30 anketi uygulanarak değerlendirildi.

Bulgular: Akut yan etkiler değerlendirildiğinde grad 1 alt gastrointestinal (GIS) yan etki 16 (% 57,1) olguda, grad 1 üst GIS yan etki 9 (%32,1) olguda, grad 1 hematolojik yan etki 1 (% 3,6) olguda, grad 1 cilt yan etki 14 (% 50) olguda görüldü. Grad 2 üst GIS yan etki 1 (% 3,6) olguda, grad 2-3 hematolojik yan etki 11 (% 39,3) olguda görüldü. Kemik iliği V20 ($p<0,001$), kemik iliği V95 (%) ($p<0,001$) mesane V40 ($p<0,001$), mesane ortalama doz ($p<0,001$), rektum V40 ($p<0,001$), rektum ortalama doz ($p<0,001$), ince barsak V40 ($p<0,001$) yoğunluk ayarlı radyoterapi ile konformal radyoterapiden daha düşük doz aldı.

Sonuç: IMRT reduce dose to the bone marrow and the normal tissues as compared to 3D-CRT. Üç boyutlu radyoterapi jinekolojik kanserlerde düşük yan etki seviyesiyle kabul edilebilir güvenilir bir tedavidir ve yaşam kalitesini olumsuz etkilemez. Yoğunluk ayarlı radyoterapi kemik iliği ve riskli organ dozlarını konformal radyoterapiye göre daha iyi kısıtlar.

Anahtar kelimeler: Jinekolojik kanser, Akut yan etkiler, Yaşam kalitesi, Konformal radyoterapi, Yoğunluk ayarlı radyoterapi

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Introduction

Endometrial cancer is the most common gynecological cancer in the USA and Europe [1,2]. Endometrial cancer is the most common gynecological cancer in developed countries. The number of newly diagnosed cases in Europe was nearly 100,000 in 2012. More than 90% of cases of endometrial cancer occur in women >50 years of age, with a median age at diagnosis of 63 years. Four percent of women with endometrial cancer are younger than 40 years old [3,4]. The majority of endometrial cancers are diagnosed early (80% in stage I), with 5-year survival rates of over 95%. However, 5-year survival rates are much lower if there is regional spread or distant disease 68% and 17%, respectively) [5]. Cervical cancer is the third most common cancer in women. More than 85% of the global burden occurs in developing countries, where it accounts for 13% of all female cancers [6].

The hematopoietic stem cells of the bone marrow are very sensitive to radiation [7]. It is shown that increased dose to the bone marrow and increased volume of the marrow in the field of radiation can proportionately increase the risk of acute hematological toxicities [8]. Addition of chemotherapy along with radiation reduces the tolerance of marrow and increases the acute hematological toxicities. Intensity modulated radiotherapy (IMRT) can give conformal dose distributions while sparing the normal tissues. Hence, it is recommended that sparing bone marrow using IMRT in patients receiving concurrent chemotherapy can reduce the hematological toxicities [9]. The aim of the study was to compare three-dimensional conformal radiotherapy plans and intensity-modulated radiotherapy re-treatment plans in our patients for the normal tissues and to evaluate the treatment-related side effects and the change in quality of life in patients treated with 3D-CRT (three-dimensional conformal radiotherapy) for cervical and endometrial cancer. We created the 3D-CRT plans and IMRT re-treatment plans for our patients who had previously received 3D-CRT, and performed their comparisons dosimetrically.

Materials and methods

Twenty-eight patients who underwent conformal radiotherapy (3D-CRT) were evaluated retrospectively and were re- planned according to IMRT technique by the Department of Radiation Oncology at the University of Pamukkale. Critical organs and bone marrow doses of 28 patients with cervical and endometrial cancer were compared dosimetrically. Evaluation of early side effects was performed using RTOG toxicity scale and European Organization for Research and Treatment of Cancer (EORTC) QLQ30 side effect evaluation questionnaire in patients with cervical and endometrial cancer who had undergone curative pelvic radiotherapy with three-dimensional conformal radiotherapy (3D-CRT) technique.

Details of radiotherapy

All patients underwent aquaplast immobilization in the supine position and contrast-enhanced computed tomography (CT) scan for simulation following a uniform water protocol. Axial CT sections of slice thickness 3-5 mm were taken. The organs at risk (OAR) (urinary bladder, rectum, small bowel, head of femur, and bone marrow) and target volumes were delineated on commercial treatment planning system, Prowess version 4.71. The OARs and the target volumes were delineated based on standard Radiation Therapy Oncology Group guidelines [10,11]. Figure 1 shows the contours of CTV and organs at risk (OARs) in pelvic region on a transverse plane of a typical patient.

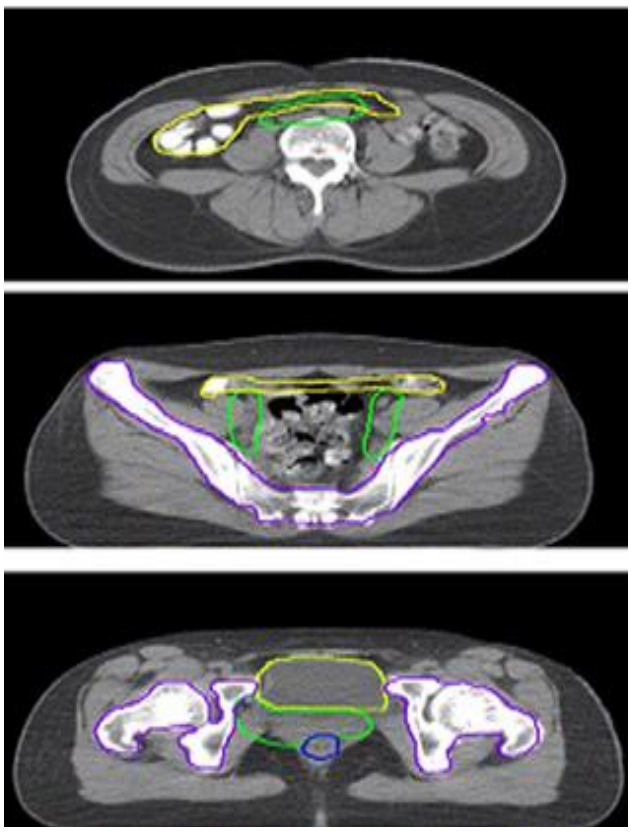

Figure 1: The contour of CTV and organs at risk, including CTV (green), small bowel (yellow), rectum (blue), bladder (yellowish green), pelvic bone marrow (violet)

IMRT plans were made to examine the patient planning system's ability to better cover the target volume and to provide less normal tissue toxicity with IMRT planning. To ensure homogeneity of the comparison, IMRT plans were reconstructed with critical structures and critical normal tissue dose limits for the same target volumes based on volumes of 45 Gy in all patients treated. A 7-field IMRT technique with 6 MV photon energy was used in the IMRT treatment plans. With both technique target organ and critical organ doses were evaluated with DVH. During the planning comparison, in the cases planned using both techniques, V40, rectum mean dose and rectum maximum dose for the rectum; V40 bladder, bladder mean dose and bladder maximum dose for the bladder; V20 and V40 for the small bowel; V40 for the femoral head; V10 and V20 for the bone marrow; V95, V75, V70, V60, V50 and V40 percent doses for the total bone marrow PTV were measured. For dose comparison of 3D-CRT and IMRT, small intestine, urinary bladder, rectum, bone marrow from L4 vertebra to below the trochanter minor, and femoral head were contoured as the organs at risk. 3D conformal therapy plans and inverse intensity-modulated radiotherapy (IMRT) plans were made to ensure that the defined desirable (prescription) dose covered 95% of the PTV.

Chemotherapy

Concurrent weekly 40 mg/m² cisplatin (median 3 weeks cisplatin) was administered to 7 patients.

Statistical analysis

The analysis was made using the SPSS software package. Continuous variables were given as mean ± standard deviation, and categorical variables were given as number (percentage). Mann-Whitney U test, independent samples t- test and Chi-square analysis were used to compare independent groups. Paired samples t-test and Wilcoxon paired two-sample tests were used to compare dependent groups. Pearson correlation analysis and multiple regression analysis were used to examine inter-variable relationships. P <0.05 was considered statistically significant.

Results

Twenty-eight patients were enrolled in this study. Their ages ranged from 34 to 73, with a median age of 60. Among these patients, 23 (82%) were postmenopausal and 5 (18%) were premenopausal. Seventeen patients (61%) had operable and 11 (39%) had inoperable gynecologic tumors. Of the inoperable patients, seven were diagnosed based on cervical biopsy and diagnosed with inoperable cervical cancer after examination and investigation. Two were diagnosed based on Probe / Curatage + cervical biopsy due to systemic diseases and were diagnosed with inoperable cervical cancer, and 2 were diagnosed with inoperable endometrial cancer. Of the patients with operable cancer, 16 were diagnosed with endometrial cancer and 1 with operable cervical cancer. The general characteristics of gynecological cancer patients treated with conformal radiotherapy are given in Table 1.

Table 1: General characteristics of gynecological cancer patients treated with conformal radiotherapy

	Result
Age (Median)	60 years old
General characteristics	Number
Pre-menopausal	5
Post-menopausal	23
Operable uterine tumor	16
Inoperable uterine tumor	2
Operable cervical tumor	1
Inoperable cervical tumor	9
External radiotherapy	19
External radiotherapy and brachytherapy	9
Concomitant Chemotherapy	
Yes	7
No	21
Adjuvant Chemotherapy	
Yes	11
No	17
Lymphovascular invasion	
Yes	7
No	8
Lymph node involvement	
None	20
1-3	1
More than 3	7
Systemic disease	
Yes	16
No	12

External radiotherapy was applied to the patients (range: 45 Gy to 65 Gy; median dose 50.4 Gy). The doses of external radiotherapy were 45 Gy in 13 patients (46.4%), 50.4 Gy in 7 patients (25%), 54 Gy in 1 patient, 59.4 Gy in 3 patients, 46.8 Gy in 1 patient, 61.2 Gy in 1 patient, 45 Gy (45 Gy for first treatment) in 1 patient (due to re- irradiation therapy) and 65 Gy in 1 patient. Intracavitary brachytherapy of median 18 Gy (13-28) was applied to the patients in whom brachytherapy indication was found subsequently, with median 3 fractions (2-4) at another center. Concurrent weekly 40 mg/m² cisplatin (median 3 weeks cisplatin) was administered to 7 patients (25%).

When the side effects and quality of life were assessed, grade 1 lower gastrointestinal (GIS) toxicity was seen in 16 / 28 patients (57.1%). Nine of the patients (32.1%) had grade 1 and 1 (3.6%) had grade 2 upper GIS toxicity. Grade 1 genitourinary (GUS) toxicity was seen in 15 of the patients (53.6%), while 14 of the patients had grade 1 skin toxicity. Hematological toxicity was observed in 12 of the patients (42.8%) of whom 1 (3.6%) had grade 1 and 11 (39.3%) had grade 2-3 hematologic toxicity. Grade 3 hematologic toxicity was seen in 2 patients who received external radiotherapy of 61.2 Gy and 65 Gy. Early toxicities due to conformal radiotherapy in our patients are given in Table 2.

Table 2: Early toxicities of gynecological cancer patients treated with conformal radiotherapy

Early toxicities	Number
Lower GIS	
Grade 0	12
Grade 1	16
Grade 2-3-4	0
Upper GIS	
Grade 0	8
Grade 1	9
Grade 2	1
Grade 3-4	0
GUS toxicity	
Grade 0	13
Grade 1	15
Grade 2-3-4	0
Skin toxicity	
Grade 0	14
Grade 1	14
Grade 2-3-4	0
Hematological	
Grade 0	16
Grade 1	1
Grade 2-3	11
Grade 4	0

In the assessment of quality of life, the results were "good" in all patients except 2 (7.1%) who had "moderate" well-being. The quality of life of patients who received conformal therapy has shown that "mental well-being," "social life," "metabolic status," "general condition assessment" and "physical well-being" of patients in conformal therapy were not adversely affected. The assessment of quality of life is given in Table 3.

Table 3: Quality of life of gynecological cancer patients treated with conformal radiotherapy

	Number of patients
Physical well being	
Good	26
Moderate	2
Poor	0
Mental well being	
Good	28
Moderate-Poor	0
Social well being	
Good	28
Moderate-Poor	0
Metabolic status	
Good	28
Moderate-Poor	0
General condition	
Good	28
Moderate-Poor	0

The total bone marrow V10, V20 values were reduced statistically significant in the IMRT arm (p<0.001). When the planning methods were compared, the bladder V40 values and the bladder mean dose values were found to be lower and statistically significant (p<0.001). When the planning methods were compared, the rectum V40 values and the rectum mean dose values were lower in the IMRT arm, and this difference was statistically significant (p<0.001). The bladder max dose and rectum max dose values were higher in the IMRT arm than in the conformal planning arm, but no statistical significance was found

(p>0.05). The small bowel V40 values were lower in the IMRT arm than the conformal planning arm (p=0.01). When the doses received by 95%, 75%, 70%, 60%, 50% and V 40% of the total bone marrow were compared, it was found that only the 95% values received a lower dose in the IMRT arm than the conformal planning arm (p<0.001). The dosimetric comparison of 3D-CRT and IMRT plans for bone marrow and OAR in patients with gynecological cancer is given in Table 4.

Table 4: Dosimetric comparison of 3D-CRT and IMRT plans for bone marrow and OAR in patients with gynecological cancer

p value	IMRT < 3D-CRT	IMRT > 3D-CRT	IMRT = 3D-CRT
BM V10 (p<0.001)	12	10	6
BM V20 (p<0.001)	28	0	0
BL V40 (p<0.001)	26	1	1
BL MEAN (p<0.001)	28	0	0
BL MAX (p> 0.05)	0	28	0
REC V40 (p<0.001)	28	0	0
REC MEAN (p<0.001)	28	0	0
REC MAX (p>0.05)	28	0	0
SB V40 (p<0.001)	13	6	9
BM V 95 % (p<0.001)	28	0	0
BM V 75 % (p<0.001)	28	0	0
BM V 70 % (p<0.001)	28	0	0
BM V 60 % (p<0.001)	28	0	0
BM V 50 % (p<0.001)	16	12	0
BM V 40 % (p<0.001)	15	12	1

Abbreviations: BM V95 % (Volume) :Radiotherapy dose received by 95% of total bone marrow (BM); Bone Marrow (BM) V10: Volume % of the total pelvic bone that received 10 Gy; Bladder (BL) V40: Volume % of the bladder that received 40 Gy; Rectum (REC) V40: Volume % of the rectum that received 40 Gy; Small bowel (SB) V40: Volume % of the small intestine that received 40 Gy; Bladder mean dose: The average dose received by the bladder; Bladder max dose: The maximum dose received by the bladder; The organs at risk (OAR)

Discussion

In a study conducted by Yamazaki et al. [12] to compare 3D-CRT with 2D conventional therapy in cervical cancer patients in a post-operative setting, it was demonstrated that grade 2-3 small intestine complications were reduced from 17.5% to 2.9% with 3D-CRT. In a study by Mundt et al. [13] acute toxicity was evaluated in 40 patients with gynecologic tumors to whom IMRT planning was applied. Acute toxicities in 35 previously treated conventional pelvic radiotherapy patients were analyzed. IMRT planning resulted in excellent PTV coverage, with considerable sparing of normal tissues. Grade 2 acute GIS toxicity was less common in patients with IMRT (60 vs. 91%, p = 0.00) than in patients with conventional RT. In a study by Liu et al. [14], who published their clinical therapy experiences with 3D-CRT and IMRT in 50 patients with recurrent and metastatic disease, nine patients developed grade 3 leukopenia. No patient developed grade 3 or greater acute gastrointestinal toxicity or GUS toxicity. In a study by Lim et al., 7 patients developed Grade 2 proctitis, 1 patient had Grade 3 proctitis requiring surgical intervention, and 1 patient had Grade 3 intestinal obstruction treated with conventionally fractionated 60 Gy. Grade 2 hematuria was observed in 3 patients. In a study by Brixey et al. [9], grade 2 hematological toxicity was 31.2% in the IMRT arm and 60% in the conventional therapy arm in women with gynecologic tumors (p=0.08). In our study, no grade 3 GIS toxicity was observed. We also found similar grade 1 and 2 GIS toxicities to those found by other investigators in the literature. Sixteen of our patients (57.1%) had grade 1 GIS toxicity, and no serious toxicity of grades 2-3-4 was observed. As for upper GIS toxicity, 9 patients (32.1%) had grade 1 and 1 (3.6%) had grade 2 toxicity, and none had grade 3-4 toxicity. Fifteen of our patients (53.1%) had grade 1 GUS toxicity. None of our patients had grades 2-3-4 toxicity. One patient had grade 1, 9 (32.1%) had grade 2 and 2 (7.2%) had grade 3 hematological toxicity.

The PORTEC–2 study, which was one of the largest studies known in the literature relating to gynecologic tumors, examined 5-year quality of life in patients who underwent post-operative radiotherapy for endometrial cancer. This study investigated the changes in quality of life as assessed by EORTC QLQ-C30 in patients who received brachytherapy and external radiotherapy. Patients who received EBRT showed reduced social well-being compared to the normal population [15]. When we assessed the quality of life in our patients who received 3D-CRT, we observed that the results were “good” in all patients except 2 (7.1%) who had “moderate” well-being. No statistical cause was found in those with moderate physical well-being. The quality of life results obtained for conformal therapy demonstrated that “mental well-being”, “social life”, “metabolic status”, “general condition assessment” and “physical well-being” of patients in conformal therapy were not adversely affected. Physical well-being changes were seen in very few patients, and none was changed to “poor”.

Heron et al. [16] compared 3D-CRT and IMRT therapies dosimetrically in gynecologic tumors. They found that the small intestine, rectum and bladder doses that received 30 Gy were lower by 52%, 66% and 36%, respectively, in the IMRT arm. In a study by Avinash et al. [17], 11 consecutive patients treated with IMRT and 12 patients treated with 3D-CRT to the whole pelvis, along with concurrent chemotherapy, were selected. V10 Gy, V20 Gy, V95%, and mean of bone marrow were recorded. The dose to the bone marrow V20 Gy was 206.78 ± 57.10 cc (75%) and 251.70 ± 40.45 cc (91%) for IMRT and 3D-CRT, respectively (p=0.04), and V95% was 23.30 ± 8.34% and 46.76 ± 6.71% for IMRT and 3D-CRT, respectively (p<0.001). The grade of toxicities each week did not show a difference in either arm. However, the total count and Neutrophil counts during the second week showed statistical significance between IMRT and 3D-CRT. IMRT significantly reduced the dose to the bone marrow as compared to 3D-CRT. In our study, critical organs and total bone marrow (BM) were received lower doses in the IMRT arm than 3D- CRT arm. When the doses received by total bone marrow V20 (p<0.001), bladder V40 (p<0.001), bladder mean dose (p<0.001), rectum V40 (p<0.001), rectum mean dose (p<0.001), small bowel V40 (p=0.01) were compared, statistical significance was found in the IMRT arm.

Conclusion

Based on the results of our study, three-dimensional conformal radiotherapy is a safe treatment with acceptable low toxicity levels in patients and does not adversely affect quality of life. IMRT significantly reduces the dose to the bone marrow and other OARs as compared to 3DCRT. Delineation and avoidance of bone marrow and other OARs with functional imaging will probably result in reduced acute hematological toxicities.

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