Comparison of hematologic toxicity between 3DCRT and IMRT planning in cervical cancer patients after concurrent chemoradiotherapy: a national multi-center study

O.P. Erpolat[1], G. Alco[2], H.B. Caglar[3], S. Igdem[4], A. Saran[5], N, Dagoglu[6], I. Aslay[6], Z. Ozsaran[7], S. Demirci[7], E. Keven[8], Y. Guney[8], M. Akmansu[1], D. Kilic[1], E. Bayman[9], D. Etiz[9], N.M. Mandel[10]

[1]Medical School of Gazi University, Department of Radiation Oncology, Ankara
[2]Florence Nightingale Hospital, Department of Radiation Oncology, Istanbul
[3]Medical School of Acibadem University, Department of Radiation Oncology, Istanbul
[4]Medical School of Bilim University, Department of Radiation Oncology, Istanbul
[5]Acibadem Hospital, Department of Radiation Oncology, Istanbul
[6]Istanbul University Oncology Institute, Department of Radiation Oncology, Istanbul
[7]Medical School of Ege University, Department of Radiation Oncology, Izmir
[8]Dr. Abdurrahman Yurtaslan Oncology Training & Research Hospital, Ankara Department of Radiation Oncology, Ankara
[9]Medical School of Osmangazi University, Department of Radiation Oncology, Eskisehir
[10]American Hospital, Department of Medical Oncology, Istanbul (Turkey)

Summary

Purpose: To compare the incidence and severity of acute and chronic hematologic toxicity (HT) in patients treated with three-dimensional conformal radiotherapy (3DCRT) and intensity modulated radiotherapy (IMRT) for curative treatment of cervical cancer and to ascertain the dosimetric parameters of two techniques associated with acute and chronic HT. *Materials and Methods:* A total of 127 patients with cervical cancer receiving concomitant pelvic radiotherapy (RT) and cisplatin were evaluated. Pelvic bone marrow (BM) was contoured for each patient and divided into five sub-regions: lumbosacrum (LS), ilium (IL), lower pelvis (LP), pelvis (P), and whole pelvis (WP). The volume of each BM region receiving 10,20,30, and 40 Gy was calculated (V10, -V20, -V30, and -V40). The lowest level of hemoglobin, leukocyte, neutrophil, and platelet counts were obtained during chemoradiotherapy and six months after RT. The nadir values were graded according to Common Terminology Criteria for Adverse Events (version 3.0). *Results:* Grade 2 or greater acute anemia, leukopenia, neutropenia, thrombocytopenia was observed in 2%, 41.5%, 12% ,and 0% in 3DCRT group and in 27%, 53%, 24.5%, and 4.5% in IMRT group, respectively. Grade 2 or greater chronic anemia, leukopenia, neutropenia, and thrombocytopenia was observed in 11%, 10%, 6%, and 0% in 3DCRT group and in 11%, 9%, 4.5%, and 0% in IMRT group, respectively. LS-V30,40; IL-V10,20,30,40; LP-V10,20,40; P-V10,20,30,40, and TP-V10,20,30,40 were significantly reduced with IMRT planning compared to 3DCRT planning. Logistic regression analysis of potential predictors showed that none of the dosimetric parameters were significant for predicting acute and chronic HT. *Conclusion:* The present findings showed that IMRT planning reduced irradiated BM volumes compared to 3DCRT planning. However, no difference between the two techniques was observed in terms of acute and chronic HT. Further studies are needed to confirm these results.

Key words: Hematologic toxicity; Cervical cancer; Radiotherapy; Chemotherapy.

Introduction

Concomitant chemoradiotherapy is a standard treatment for locally advanced cervical carcinoma. Although the combination of chemotherapy and radiotherapy (RT) improves the outcomes [1, 2], it may cause hematologic toxicity (HT) [2-4]. The presence of high grade HT, particularly leukopenia and neutropenia, increases the risk of infection, which leads interruption during treatment [5], and it is well known that prolongation of RT decreases the local control of cervical cancer patients [6].

Bone marrow (BM) is one of the most radiosensitive structures of the pelvis and approximately 40% of the total-body BM reserve lies within the pelvic bones [7]. When the two treatment regimes are applied concomitantly, cytotoxic agent may induce stem cells to divide, making these cell populations more radiosensitive [8]. Serious HT, which may negatively affect the course of the treatment, is rare in patients who receive pelvic RT alone, because of increased compensatory hematopoiesis in un-irradiated BM [1]. However, most chemotherapeutic agents used for cervical cancer are myelotoxic [2, 3]. When chemotherapy is concurrently applied with RT, compensatory hematopoiesis is suppressed in un-irradiated BM and this increases the incidence of severe HT [8]. Severe HT may preclude the delivery of chemotherapy and may protract the treatment time.

Recovery of BM depends on RT dose and volume. When larger fields, as 25%-50% of the BM are irradiated, permanent hypoplasia occurs at similar dose levels as for small fields. After greater than 50 Gy, irreversible injury may

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occur due to irreparable damage to the microvasculature manifested by BM fibrosis [8]. Damage to the BM stromal cells due to the irradiation and certain chemotherapeutic agents primarily account for chronic radiation injury by reducing the ability of hematopoietic stem cells to self-renew [9]. Since BM cannot sustain a normal hematopoietic activity, latent damage of BM and chronic HT may become an important issue in gynecological cancer patients who should receive chemotherapy in the setting of recurrence. Several studies showed that higher rates of HT were observed when chemotherapy was delivered to patients who received RT previously. This condition leads clinicians to reduce the drug dose in treatment of recurrent disease thus this may relate to poor outcome [10, 11]. Therefore, preventing HT becomes an important issue in cervical cancer patients to improve tolerance to treatment and enhance outcomes.

The relationship between dose-volume parameters of irradiated BM and acute HT has been reported in patients treated with three-dimensional conformal radiotherapy (3DCRT) or intensity modulated radiotherapy (IMRT) [12-14]. The volume of pelvic BM receiving low doses, such as 10 Gy or 20 Gy, was shown to be associate with acute HT [4, 12, 15]. However, greater doses have not been found as relevant as low doses for acute HT, but they may have a significant effect on chronic HT. The aim of the present study was to compare the incidence and severity of acute and chronic HT in patients treated with 3DCRT and IMRT and to ascertain the dosimetric parameters of two techniques associated with acute and chronic HT.

Materials and Methods

Patient selection

A total of 127 patients with Stage I-IV cervical cancer who received concomitantly cisplatin with pelvic RT between 2004 and 2012 were retrospectively analyzed in this national multi-center study. Five centers contributed to 3DCRT data and one center contributed to IMRT data. Patients who were previously treated with extended-field RT or received chemotherapy or RT for any reason were not included in the study group. The patient and treatment characteristics of the study group are summarized in Table 1.

Radiotherapy

Eighty-two patients (64.5%) received pelvic 3DCRT with a standard four-field 'box' technique and 45 (35.5%) patients received pelvic IMRT. Patients underwent contrast-enhanced planning computed tomography with appropriate immobilization. Clinical target volume (CTV) and organs at risk were contoured on axial slices. The CTV included cervical tumor, paracervical, and parametrial tissues, uterus (if present), upper one-half of the vagina, presacral region, and regional lymph nodes at risk (common, external, and internal lymph nodes). Nodal margins were obtained by adding 0.5 to one cm around the vasculature according to the treating physician. Planning target volume (PTV) was defined as the CTV plus a 0.5 to one-cm margin. Normal tissues including bowel, bladder, and rectum were contoured for each patient. All patients received 45 to 50.4 Gy in 1.8 to two Gy daily fractions by use of 6-18 MV photons. The planning goal of all centers was to give 100% of the prescription dose to at least 95% of the PTV while minimizing the dose delivered to the small bowel, bladder, and rectum. Using standard forward planning methods constituted the plans of 3DCRT. A standard four fields (anteroposterior-posteroanterior, and two lateral beams) were designed by using ten to 18 MV photons. The weights of the individual fields were optimized to achieve dose uniformity.

Intensity modulated RT plans were generated with Varian Eclipse planning software version 8.6. Seven co-planar beams with angles 0, 51, 102, 153, 204, 255, and 306 angles. For the IMRT plans, couch rails were located at the outer edges of the couch, and these beam angles likewise avoided. Dose objectives and priorities defined by user and adjusted interactively during

Table 1. — *Patient characteristics.*

	3DCRT n = 82	IMRT n = 45	*p* value
Age			
Mean ± SD	55 ± 11.5	52	
(range)	(30-80)	(26-77)	0.16
Histology (n, %)			
Squamous cell	74 (90)	43 (95.5)	
Adeno	8 (10)	2 (4.5)	0.49
Stage n (%)			
IA-IIA	13 (16)	7 (15.5)	
IIB-IVA	69 (84)	38 (84.5)	1
Surgery n (%)			
Yes	14 (17)	6 (13)	
No	68 (83)	39 (87)	0.8
Baseline blood counts			
Hemoglobin (g/dl)			
Mean ± SD	12 ± 1.3	12 ± 1.5	0.47
(range)	(10-15.5)	(10-17)	
WBC (μg/dL)			
Mean ± SD	7.3 ± 2.7	7.8 ± 2	0.27
(range)	(4-15.5)	(4-11)	
ANC			
Mean ± SD	4.7 ± 2	5 ± 2	0.57
(range)	(2-10)	(1.5-9.5)	
Platelets (μg/dl)			
Mean ± SD	277 ± 87	300 ± 94.5	0.51
(range)	(130-531)	(140-610)	

3DCRT: three-dimensional conformal radiotherapy, IMRT: intensity modulated radiotherapy, SD: standard deviation, ANC: absolute neutrophil count

Table 2. — *Grade 2 or greater hematologic toxicity during treatment and at six months after completion of radiotherapy.*

≥ Grade 2 HT	3DCRT n, (%)	IMRT n, (%)	*p* value
Hemoglobin			
Acute	17 (21)	12 (27)	p = 0.45
Chronic	9 (11)	5 (11)	p = 0.98
WBC			
Acute	34 (41.5)	24 (53)	p = 0.26
Chronic	8 (10)	4 (9)	p = 0.97
ANC			
Acute	10 (12)	11 (24.5)	p = 0.09
Chronic	5 (6)	2 (4.5)	p = 0.99
Platelet			
Acute	–	2 (4.5)	p = 0.12
Chronic	–	–	–

HT: hematologic toxicity, 3DCRT: three-dimensional conformal radiotherapy, IMRT: Intensity modulated radiotherapy.

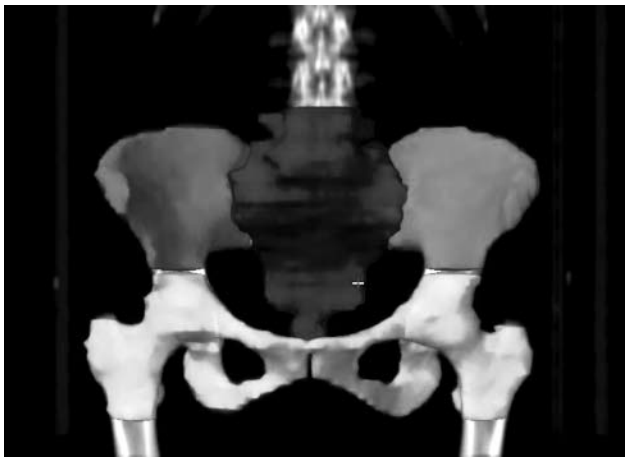

Figure 1. — Three-dimensional rendering of lumbosacral (dark grey), iliac (mid-grey), and lower pelvic (white) BM.

optimization process. Body-PTV structure generated by cropping PTV with 1.2 cm margin from body to reduce low dose region. Six MV photon beams used for all plans and dose calculation were performed using AAA dose calculation algorithm with voxel size 0.25 x 0.25 x 0.25 cm^3. Patient special quality assurance was done prior to each treatment for the IMRT patients.

Chemotherapy delivery

Patients were treated with cisplatin (weekly, 40 mg/m^2) concurrently with pelvic RT. They were planned to receive four to six cycles of cisplatin during RT. Cisplatin was not given under the following conditions: WBC less than 2 x 10^9/l, ANC less than 1 x10^9/l and platelet count less than 50 x 10^9/L.

Bone marrow delineation

The external contour of all bones within the pelvis were contoured on the planning computed tomography (CT) scan for each patient according to the method described by Mell *at al.* [12] and Albuquerque *et al.* [14]. The entire bony contours were defined as the five following sub-sites: 1) Lumbosacral region (LS): including the region from superior border of L5 vertebra to the inferior border of sacrum, 2) Ilium (IL): including iliac crests extending to the superior border of the femoral heads, 3) Lower pelvis (LP): including pubis, ischium, acetabulum, and proximal femurs, 4) pelvis (P): including ilium and lower pelvis, 5) Whole pelvis (WP): including lumbosacrum, ilium, lower pelvis, and pelvis. Three-dimensional rendering of the iliac, lumbosacral, and lower pelvic BM was shown in Figure 1. Dose volume histograms were constituted for each contoured BM regions. The volume of each BM region receiving 10, 20, 30, and 40 Gy was calculated. These parameters were defined as follows: 1) LS-V10, -V20, -V30, -V40 2) IL-V10, -V20, -V30, -V40 3) LP-V10, -V20, -V30, -V40 4) P-V10, -V20, -V30, -V40 5) WP-V10, -V20, -V30, -V 40.

Hematologic toxicity evaluation

The hemoglobin, leukocyte, neutrophil, and platelet counts were obtained before and during RT and six months after RT. Because any treatment related morbidity that occurs later than six months after the beginning of RT is defined as a late reaction [16], blood counts at six months after completion of RT were collected for evaluation of chronic HT. The lowest levels of hemoglobin, leukocyte, neutrophil, and platelet counts were defined as the nadir. The reason for the nadir values were graded according to Common Terminology Criteria for Adverse Events (version 3.0) and grade 2 or greater toxicity was defined as event. Patients with grade 2 or greater HT before chemoradiotherapy were not included in the study.

Table 3. — *Descriptive statistics of dosimetric parameters.*

Bone marrow region	3DCRT (mean ± SD)	IMRT (mean ± SD)	*p value*
Lumbosacrum			
V10	97 ± 5.8	100 ± 0.4	**0.003**
V20	95 ± 7.8	97 ± 3.8	0.1
V30	83 ± 17	75.5 ± 11	**0.01**
V40	70 ± 22.5	50 ± 21	**< 0.0001**
Ilium			
V10	93.5 ± 7.5	90.5 ± 7.3	**0.041**
V20	87.5 ± 10	75 ± 13	**< 0.0001**
V30	58 ± 18	43 ± 15.5	**< 0.0001**
V40	36.6 ± 12.5	18 ± 10.7	**< 0.0001**
Lower pelvis			
V10	90 ± 9	83 ± 10	**< 0.0001**
V20	85 ± 11	70 ± 14	**< 0.0001**
V30	50 ± 18.5	45.5 ± 13.5	0.144
V40	34.5 ± 16	24 ± 13	**< 0.0001**
Pelvis			
V10	92 ± 5.8	86 ± 8	**< 0.0001**
V20	87 ± 7.5	72.5 ± 11	**< 0.0001**
V30	54 ± 17	45 ± 12.5	**0.001**
V40	36.5 ± 14	22 ± 11	**< 0.0001**
Whole pelvis			
V10	93 ± 6	89 ± 6.5	**0.001**
V20	88.5 ± 7	78.5 ± 8.5	**< 0.0001**
V30	61.5 ± 14.5	53.5 ± 11.5	**0.002**
V40	44 ± 14.5	28.5 ± 13	**< 0.0001**

3DCRT: three-dimensional conformal radiotherapy, IMRT: intensity modulated radiotherapy.

Table 4. — *Distribution of number of radiotherapy breaks and chemotherapy cycles missed due to hematologic toxicity and number of transfusions or growth factor administration in treatment groups.*

	3DCRT	IMRT	*p* value
RT breaks, n (%)			
Yes	13 (16)	10 (22)	
No	69 (84)	35 (78)	0.37
No. of RT breaks			
Mean ± SD	5 ± 2.8	4.5 ± 0.7	
Range	2-10	4-5	0.82
CHT cycles missed, n (%)			
Yes	28 (34)	13 (30)	
No	47 (57)	32 (39)	0.34
No. of CHT cycles missed			
Mean ± SD	1.5 ± 0.8	1.5 ± 0.9	
Range	1-4	1-4	0.63
Transfusion received			
Yes, n (%)	15 (18)	10 (22)	
No, n (%)	67 (82)	35 (78)	0.64
Growth factor received			
Yes, n (%)	6 (7)	4 (9)	
No, n (%)	76 (93)	41 (91)	0.78

3DCRT: three-dimensional conformal radiotherapy, IMRT: intensity modulated radiotherapy, RT: radiotherapy, CHT: chemotherapy

The frequency of missed chemotherapy cycles and the fractions of interrupted RT were recorded along with number of using transfusions or growth factors for analyzing the impact of acute HT.

Statistical analyses

Ki-square and Student *t*-tests were used to test the difference in proportion or continuous variables, respectively. Logistic regression analysis was used to correlate the risk of grade 2 or greater HT with the BM volumes.

Results

Hematologic toxicity

There was no significant difference between treatment groups in baseline counts of hemoglobin, white blood cell (WBC), platelet and absolute neutrophil count (ANC). All patients had complete blood counts before and weekly during RT and 79 (62%) patients had complete blood count at six months after completion of RT.

The most common grade 2 or greater acute toxicity was leukopenia, occurring in 34 (41.5%) patients of 3DCRT group, 24 (53%) patients in IMRT group ($p = 0.26$). Grade 2 or greater acute anemia was observed in 17 (21%) patients in 3DCRT group and 12 (27%) patients in IMRT group ($p = 0.45$). Grade 2 or greater acute neutropenia was observed in ten (12%) patients in 3DCRT group and 11 (24.5%) patients in IMRT group ($p = 0.09$). Although no patient developed grade 2 or greater acute thrombocytopenia in 3DCRT group, two (4.5%) patients in IMRT group developed grade 2 or greater acute thrombocytopenia ($p = 0.12$). Results of HT during treatment are shown in Table 2.

Grade 2 or greater HT at sixth month after completion of RT was evaluated and no significant difference was observed between the groups. Grade 2 or greater chronic anemia was observed in nine (11%) patients in 3DCRT group and five (11%) patients in IMRT group ($p = 0.98$). Grade 2 or greater chronic leukopenia occurred in 8 (10%) patients in 3DCRT group and four (9%) patients in IMRT group ($p = 0.97$). Grade 2 or greater chronic neutropenia occurred in five (6%) patients in 3DCRT group and two (4.5%) patients in IMRT group ($p = 0.99$). Results of grade 2 or greater HT at six months after completion of RT are shown in Table 2.

Association between dosimetric parameters and hematologic toxicity

The mean volumes of BM regions for different dose levels in the treatment groups were summarized in Table 3. LS volume receiving 30 and 40 Gy; IL volume receiving 10, 20, 30 and 40 Gy; LP volume receiving 10, 20 and 40 Gy; P volume receiving 10, 20, 30 and 40 and TP receiving 10, 20, 30 and 40 Gy were significantly reduced with IMRT planning compared to 3DCRT planning. However, LS volume receiving 10 Gy was 97% in 3DCRT planning and 100% in IMRT planning ($p = 0.003$). LS volume receiving 20 Gy was 95% in 3DCRT planning and 97% in IMRT planning ($p = 0.1$). Logistic regression analysis of potential predictors showed that none of the dosimetric parameters were significant for predicting acute and chronic HT.

Radiotherapy and Chemotherapy Delivery

In 3DCRT treatment group, 13 (16%) patients had RT breaks mean 5 (2-10) fractions due to HT. Twenty-eight (34%) patients had chemotherapy breaks mean 1.5 (1-4) cycles due to HT. Six (7%) patients received growth factor, 15 (18%) patients received blood transfusions. In one (1.2%) patient cisplatin dose was reduced. In IMRT treatment group, 10 (22%) patients had RT breaks mean 4.5 (4-5) fractions due to HT. Thirteen (30%) patients had chemotherapy breaks mean 1.5 (1-4) cycles due to HT. Four (9%) patients received growth factor, 10 (22%) patients received blood transfusions. In two (4.5) patients cisplatin dose was reduced. No significant difference was shown in terms of RT breaks, missed chemotherapy cycles, number of transfusions and growth factor administrations between treatment groups. Data are summarized in Table 4.

Discussion

Therapeutic strategies combining chemotherapy and RT primarily aim to improve tumor control, however potential side effects are much more complicated when these two treatment modalities are given concomitantly. One of potential side effects that should be taken into consideration is the dose limiting BM suppression.

Most of the knowledge about HT that mentioned above depends on the experimental studies. Few clinical studies evaluate the acute HT of concomitant cisplatin and pelvic RT in cervical cancer patients [2, 4, 12, 14]. Moreover, no trials assess the chronic effects of chemoradiotherapy. For this reason, the impact of 3DCRT and IMRT on acute and chronic HT in cervical cancer patients who received concomitantly cisplatin with pelvic RT were evaluated in the study.

To explain the impact of RT techniques on HT, we assessed the volume of irradiated pelvic BM with 3DCRT and IMRT planning. We found IMRT planning reduced the irradiated volume of BM compared to 3DCRT planning. Our findings are consistent with the results of Brixey *et al.* [4] and Mell LK *et al.* [13] studies; the volume of iliac, lumbar, sacral and pelvic BM irradiation was reduced with IMRT compared to four-field box technique. Although less BM volume was irradiated in IMRT planning, grade 2 or greater acute anemia, leukopenia, neutropenia and thrombocytopenia were higher in IMRT group compared to 3DCRT group. This is possibly because the areas of low dose regions of LS are larger with IMRT in contrast to 3DCRT; low doses such as 10, 20 Gy may cause acute HT because of BM radiosensitivity [12]. Using IMRT did not provide any benefit on reducing RT breaks and missed chemotherapy cycles with requirement of blood transfusions and growth factor. In addition, we evaluated the BM effects of

3DCRT and IMRT at six months after completion of RT. Chronic effects of chemoradiotherapy was observed in few patients and no significant difference was seen between 3DCRT and IMRT and none of the dosimetric parameters were significant for predicting acute and chronic HT.

In contrast to the present findings, Brixey *et al.* reported a non-significant decrease in grade 2 and 3 HT for patients treated with IMRT compared to a conventional whole pelvic RT. IMRT patients were also less likely to miss chemotherapy [4]. Mell *et al.* showed an association between the volume of whole pelvis BM receiving low-dose radiation (V10 and V20) and acute HT in patients receiving concomitant cisplatin and whole pelvis IMRT [12]. Similarly, Albuquerque *et al.* showed a correlation between whole pelvis BM volume received 20 Gy and acute HT in patients treated with concomitant chemotherapy and 3DCRT [14]. As reported in experimental and clinical studies, the present authors could not find any dose predictors for acute and chronic HT. However, the present results need to be interpreted with caution because of retrospective nature of the study. Due to multi-centric nature of the study, there is inevitable heterogeneity in treatment protocols and data of 3DCRT. It should also be considered that dose-volume parameters, which were obtained in this study, were based on a planning protocol from multi-centers using different commercial planning systems. Furthermore, using entire bones as a proxy for BM is another limitation of this study. Active and inactive BM regions cannot be distinguished with CT imaging [17]. Recently functional imaging with ^{18}F-FDG-PET was shown to be one method to identify active BM sub-regions. Irradiation of sub-regions with higher ^{18}F-FDG-PET activity is associated with HT [18]. In the future, optimal SUV thresholds may be introduced to identify active BM sub-regions and new techniques can be developed to spare these regions for reducing HT.

Despite the limitations of the study, the present findings showed that IMRT planning reduced irradiated BM volumes compared to 3DCRT planning. However, no difference between two techniques was observed in terms of acute and chronic HT. A prospective study designed to measure blood counts during treatment and after treatment to evaluate the acute and chronic HT is warranted to compare toxicity across treatment techniques and confirm the present results.

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Address reprint requests to:
O.P. ERPOLAT, M.D.
Ahmet Taner Kıslali Mah, Konutkent 2 sitesi, A8 Blok,
No: 62 Cayyolu, Ankara (Turkey)