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Original Research

Low-dose range of pelvic irradiation leads to acute hematological toxicity in early-stage cervical cancer with intermediate risk factors by postoperative intensity-modulated radiotherapy

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Summary

Purpose: To analyze the correlation between acute hematological toxicity (HT) due to the irradiation volume to the pelvis low-dose region (PLDR) from postoperative intensity-modulated radiotherapy (IMRT) for intermediate-risk early-stage cervical cancer. *Materials and Methods:* The medical records of 125 patients with intermediate-risk IA-IIA cervical cancer treated with postoperative radiotherapy were retrospectively reviewed. The nadir of leukocyte, neutrophil, lymphocyte, erythrocyte, hemoglobin, and platelet counts were collected from the beginning of radiotherapy to three months after radiotherapy.The volume of pelvic bone marrow ≥ 5 Gy, 10 Gy, and 20 Gy (V5, V10, and V20) of the PLDR in IMRT were obtained using a dose volume histogram. *Results:* V10 and V20 were independent factors of grade ≥ 2 leukopenia and neutropenia. V10 was an independent risk factor of grade ≥ 3 lymphopenia. V10 > 86%, V20 > 73%, V10 > 88%, and V20 > 73% can cause grade ≥ 2 leukopenia and neutropenia. A V10 of > 80% is more likely to occur than grade 3 lymphopenia. Preoperative neoadjuvant chemotherapy will aggravate HT after pelvic radiotherapy, especially leukocytes. *Conclusion:* In patients with early cervical cancer with intermediate risk factors by postoperative IMRT, the volume of V10 and V20 in the low-dose pelvic region should be limited to reduce HT.

Key words: Cervical cancer; IMRT; Pelvis; Low-dose area; Hematological toxicity

Introduction

The incidence of cervical cancer is the second most prevalent female malignant tumors in China, and its age-standardized morbidity and mortality are increasing [1]. Postoperative radiotherapy (PORT) is required for patients with early-stage cervical cancer who have two or more intermediate risk factors (tumor size of > 4 cm, lymphovascular space invasion (LVSI), and stromal invasion middle or deep one-third) [2]. However, acute hematological toxicity (HT), gastrointestinal toxicity, bladder toxicity, and other complications occur in different degrees during pelvic radiotherapy. In ensuring good efficacy without increasing the volume of normal tissue in the radiation response is the principle of radiotherapy for malignant tumors. In gynecological oncology, dosimetry investigations have demonstrated that intensity-modulated radiotherapy (IMRT) can reduce the dose distribution in the bladder, gastrointestinal tract, rectum, and bone marrow [3, 4]. More than 40% of the active bone marrow in the body is located in the pelvis and lower spine. When patients with cervical cancer are treated with PORT, they receive some dose of irradiation in the pelvis low-dose region (PLDR). However, bone marrow stem cells are characterized by high sensitivity to radiation exposure, and the destruction of these cells by radiotherapy is the main cause of acute HT [5]. Among patients with early cervical cancer after pelvic IMRT, most of the pelvis is in the low-dose irradiation area, so the present authors speculate that the volume of low-dose pelvic irradiation is related to HT. In radiotherapy for cervical cancer, the dose limit to the rectum, bladder, and other organs has been quite perfect. However, the limit of radiation dose to the pelvis is still inconclusive. Strategies to limit the irradiation volume to the PLDR, which reduces the patient's HT, deserve to be discussed.

Materials and Methods

The 125 patients with early cervical cancer who were treated in the First Affiliated Hospital of Fujian Medical University between September 2009 and October 2015 were evaluated. All the patients were treated with radical hysterectomy and pathologically diagnosed. Then, after three to four weeks, postoperative IMRT was performed. Simultaneously, all the patients had a Karnofsky performance status score of ≥ 70, no histories of pelvic radiotherapy and other malignant tumors, and successfully completed radiotherapy.

Age, IMRT dose, body mass index (BMI = body weight

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[kg]/height [m]), hematological parameters (white blood cell [WBC] count, neutrophil [NEU] count, leukocyte [LEU] count, hemoglobin level, and platelet [PLT] count). Hematological toxicities were assessed in accordance with the Radiation Therapy Oncology Group grading criteria.

According to the International Commission on Radiation Units and Measurements Report No. 62, the postoperative IMRT target area of cervical cancer includes clinical target volume (CTV), planning target volume (PTV), and organs at risk (OAR). The CTV included one-half of the vagina, parametrial tissues of the original uterus, and regional lymph nodes (common, internal, external iliac, and obturator nodes). The PTV was generated from the CTV expanded 0.5 cm in the three-dimensional space. A 95% PTV was required to enclose 100% of the target volume, but the maximum dose of PTV was ≤ 110%. The OAR includes the small intestine, rectum, bladder, pelvis, and bilateral femoral head. The fifth lumbar vertebra, sacral vertebra, bilateral ilium, ischial, pubis, bilateral femoral head, and upper femur were defined as the range of the pelvis. The doses stipulated for the OAR were as follows: the volumes of the small intestine, rectum, and bladder to receive > 40 Gy were limited to < 30%, < 50%, and < 40%, respectively, and < 50% of the bilateral femoral head was to receive > 20 Gy. All the patients underwent IMRT with daily fractions of 1.8 to 2 Gy by 6-MV line irradiation. The total dose rendered to the PTV was 40–50.4 Gy.

Neoadjuvant chemotherapy (chemotherapy regimens: paclitaxel 135 mg/m^2 + cisplatin 75 mg/m^2 per three weeks for two cycles) was administered to patients with a tumor size of > 4 cm before radical surgery.

The possible underlying factors resulting in HT were analyzed using the c^2 test and multiple logistic regression model. The correlation between the volume in the PLDR of postoperative IMRT and acute HT was investigated using the receiver operating characteristic (ROC) curve.

Results

Of the 125 patients enrolled in the study, seven were in FIGO Stage IA (4.8%); 54, in Stage IB (44%); 48 in Stage IIA1 (38.4%); and 16 in Stage IIA2 (12.8%). The median age was 47 (range, 30–67) years. The BMIs were <18.5, 10 (8%), 18.5–24.99, 95 (76%), and > 25.20 kg/m^2 (16%), respectively. Of the cases, 58 (46.44%) had neoadjuvant chemotherapy (preoperative tumor size of > 4 cm) and 67 (53.6%) did not receive chemotherapy. The radiotherapy dose was 45 Gy in 45 cases (36%) and 46–50.4 Gy in 80 cases (64%; Table 1).

During the beginning of radiotherapy until three months after radiotherapy, grade 1 leukopenia occurred in 26 cases (20.8%), grade 2 in 47 cases (37.6%), grade 3 in 29 cases (23%), and grade 4, in two cases (1.6%). The reduction rates of grades 1–4 neutrophils were 36%, 11.2%, 30.4%, 18.4%, and 4%, respectively, and the reduction rates of grade 1–4 lymphocytes were 9.6% (12 cases), 19.2% (24 cases), 63.2% (79 cases), and 6.4% (8 cases), respectively. The incidence rates of grade 1–3 anemia and thrombocytopenia were 41.6% and 13.6%, respectively. None of the cases caused grade 4 anemia and thrombocytopenia (Table 2).

Table 1. — *Clinical characteristics of the 125 cases.*

Project	n	Percentage (%)
Age (years)		
≤ 40	28	22.4
40–60	87	69.6
> 60	10	8.0
BMI (kg/m^2)		
< 18.5	10	8.0
18.5–24.99	95	76.0
≥ 25	20	16.0
Clinical FIGO Stage		
Ia	6	4.8
Ib	55	44.0
IIa1	48	38.4
IIa2	16	12.8
Neoadjuvant chemotherapy		
Yes	58	46.4
No	67	53.6
Total radiotherapy dose (Gy)		
45	45	36.0
46-50.4	80	64.0

The c^2 test was used to analyze the factors that might influence acute HT, including age, BMI, FIGO stage, chemotherapy, and radiotherapy dose. The result indicated that chemotherapy was associated with acute HT ($p < 0.05$; Table 3).

By using the HT grading indexes and low-dose pelvic irradiation volumes of 5, 10, and 20 Gy (V5, V10, and V20) in the single-factor analysis, the results showed that irradiation with low-dose volumes of V5 > 94%, V10 > 85%, and V20 > 73% can reduce leukocyte, neutrophil, and lymphocyte counts ($p < 0.05$; Table 4). Two segments of the PLDR (V5: 0–94, 94–100; V10: 0–85, 85–100; V20: 0–73, and 73–100).

The binary logistic regression model was used to analyze these potential factors. Results of the independent risk fac-

Table 2. — *Acute HT in the 125 patients.*

Circulating blood cells	Acute HT classification				
	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
WBC	21 (16.8%)	26 (20.8%)	47 (37.6%)	29 (23.2%)	2 (1.6%)
NEU	45 (36.0%)	14 (11.2%)	38 (30.4%)	23 (18.4%)	5 (4.0%)
LEU	2 (1.6%)	12 (9.6%)	24 (19.2%)	79 (63.2%)	8 (6.4%)
ANE	73 (58.4%)	32 (25.6%)	18 (14.4%)	2 (1.6%)	0
PLT	108 (86.4%)	10 (8%)	6 (4.8%)	1 (0.8%)	0

Table 3. — *The effect of clinical characteristics on acute HT in the 125 patients in a single-factor analysis.*

Factor	Acute HT	
	c^2	*p*
Age (years)	0.125	0.723
BMI (kg/m^2)	0.653	0.419
FIGO Stage	0.001	0.981
Chemotherapy	4.625	0.032
Radiotherapy dose (Gy)	2.154	0.142

tors for grade ≥ 2 leukopenia were chemotherapy (odds ratio [OR], 2.42; 95% confidence interval [CI], 1.03, 5.72; $p = 0.044$), and V10 and V20 in the PLDR. When V10 was > 85% and V20 was > 73%, the ORs of grade ≥ 2 leukopenia were 4.27, (95% CI, 1.45–12.55; $p = 0.008$), and 3.45 (95% CI, 1.17–10.12; $p = 0.024$), respectively. V10 and V20 were independent risk factors for grade ≥ 2 neutropenia. The ORs were 4.77 (95% CI, 1.73–13.09; $p = 0.002$) and 3.34 (95% CI, 1.21–9.19; $p = 0.019$), respectively. When V10 was > 85%, the OR was 2.80 (95% CI, 1.28–6.17; $p = 0.010$) for grade ≥ 3 lymphocytopenia (Table 5).

Grading for leukocytopenia and neutropenia: 0 or 1 one stage, 2–4 one stage, grading for lymphocytopenia: 0–2 one stage, and 3 or 4 one stage. Anemia and thrombocytopenia: divided into two stages.

To determine the cut-off value between the PLDR and acute HT, ROC curves were used to analyze the relationships among V10, V20, leukopenia, and neutropenia. The indicated a relationship between V10 and lymphocytopenia. The present authors can conclude that when V10 was > 86% and V20 was > 73%, grade ≥ 2 leukopenia can be induced ($p < 0.01$; area under the curve (AUC), > 0.7). When V10 was > 88% and V20 was > 73%, grade ≥ 2 neutrophils can be induced ($p < 0.01$; AUC, > 0.7; Figures 1 and 2).

Discussion

HT reaction to postoperative cervical cancer radiotherapy and chemotherapy is more serious than radioactive cystitis, radioactive enteritis, and other adverse reactions [6]. Many clinical patients cannot continue treatment for diseases because of severe myelosuppression. Although treatment was completed, the patients' quality life did not improve. Studies have shown that low-dose bone marrow irradiation is the main cause of acute myelosuppression [7-9]. More than half of the bone marrow of the human body is located in the hip, sacrum, proximal femur, and lower lumbar spine (Figure 3). In the pelvic IMRT, the low-dose range of 5–20 Gy almost contains these areas. The tissue damage caused by radiotherapy depends on two factors: dose and volume. The volume of the irradiation of 20 Gy in the pelvis is related to HT [9, 10].

Table 4. — *The relationship between circulating blood cell reduction and radiation volumes V5, V10, and V20 in the PLDR.*

Circulating blood cells	Grade	V5		*p*	V10		*p*	V20		*p*
		≤ 0.94	>0.94		≤ 0.85	>0.85		≤ 0.73	>0.73	
WBC	0	20	1	< 0.01 (30.59)	21	0	<0.01 (38.53)			< 0.01 (35.39)
	1	14	12		14	12				
	2	15	32		17	30				
	3	8	21		5	24				
	4	0	2		0	2				
NEU	0	31	14	< 0.01 (31.60)	33	12	<0.01 (39.67)	33	12	< 0.01 (36.12)
	1	10	4		10	4		12	2	
	2	14	24		13	25		15	23	
	3	2	21		1	22		2	21	
	4	0	5		0	5		1	4	
LEU	0	2	0	0.029 (10.81)	2	0	0.025 (11.133)	2	0	0.077 (8.44)
	1	6	6		6	6		7	5	
	2	14	10		16	8		15	9	
	3	35	44		32	47		38	41	
	4	0	8		1	7		1	7	
ANE	0	30	43	0.497 (2.38)	33	40	0.787 (1.06)	36	37	0.196 (4.69)
	1	15	17		13	19		13	19	
	2	11	7		10	8		13	5	
	3	1	1		1	1		1	1	
	4	0	0		0	0		0	0	
PLT	0	47	61	0.519 (2.26)	47	61	0.519 (2.26)	52	56	0.531 (2.201)
	1	6	4		6	4		6	4	
	2	3	3		3	3		4	2	
	3	1	0		1	0		1	0	
	4	0	0		0	0		0	0	

Table 5. — *Analysis of factors that reduce circulatory hemocytes.*

Factor		WBC	NEU	LEU	ANE	PLT
V5	OR (95% CI)	2.13 (0.64–7.08)	1.83 (0.55–6.13)	0.88 (0.27–2.88)	0.55 (0.26–1.17)	0.19 (0.22–6.62)
	P	0.215	0.326	0.840	0.123	1.216
V10	OR (95% CI)	4.27 (1.45–12.55)	4.77 (1.73–13.09)	2.80 (1.28–6.17)	1.66 (0.49–5.57)	0.17 (0.20–6.99)
	P	0.008	0.002	0.010	0.410	1.183
V20	OR (95% CI)	3.45 (1.17–10.12)	3.34 (1.21–9.19)	0.988 (0.31–3.15)	0.79 (0.27–2.34)	0.63 (0.44–7.94)
	P	0.024	0.019	0.983	0.673	1.873
BMI	OR (95% CI)	2.32 (0.95–5.68)	0.815 (0.33–1.99)	1.20 (0.53–2.72)	1.66 (0.76–3.62)	0.86 (0.76–7.35)
	P	0.065	0.655	0.662	0.207	2.364
Age	OR (95% CI)	0.92 (0.37–2.32)	1.65 (0.66–3.96)	0.59 (0.26–1.36)	0.90 (0.41–1.99)	0.29 (0.46–3.97)
	P	0.872	0.258	0.220	0.802	1.345
Radiotherapy dose	OR (95% CI)	1.00 (0.39–2.55)	1.65 (0.66–4.13)	1.32 (0.58–3.03)	1.91 (0.91–3.98)	0.49 (0.50–5.28)
	P	0.999	0.281	0.512	0.085	1.628
FIGO stage	OR (95% CI)	0.95 (0.39–2.28)	1.20 (0.49–2.90)	1.67 (0.76–3.69)	2.01 (0.96–4.18)	0.41 (0.87–2.60)
	P	0.906	0.680	0.202	0.063	1.500
Chemotherapy	OR (95% CI)	2.42 (1.03–5.72)	1.53 (0.65–3.59)	0.78 (0.36–1.74)	0.73 (0.34–1.56)	0.64 (0.82–4.98)
	P	0.044	0.326	0.540	0.419	1.341

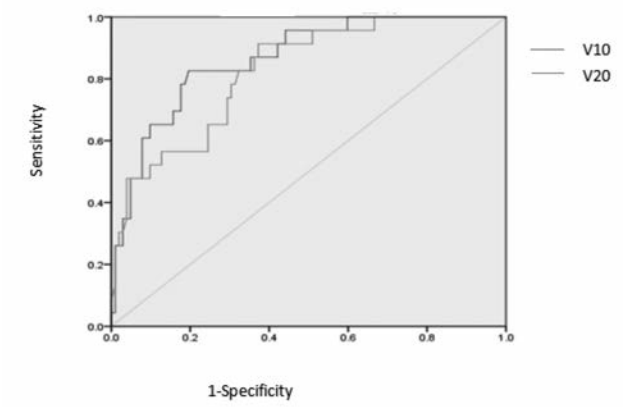

Figure 1. — The ROC curve of V10 and V20 for grade ≥ 2 leukopenia. V10: AUC = 0.754; V20: AUC = 0.762; cut-off value of V10 = 86%, V20 = 73%, (V10: $p < 0.01$; V20: $p < 0.01$).

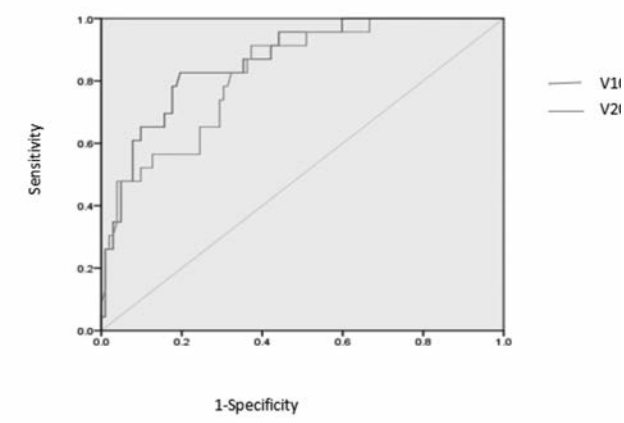

Figure 2. — The ROC curve of V10 and V20 for grade ≥ 2 neutropenia. V10: AUC = 0.865, V20: AUC = 0.824; cut-off values of V10 = 88% and V20 = 73%, (V10: $p < 0.01$; V20: $p < 0.01$).

Compared with radiotherapy alone, simultaneous radiotherapy and chemotherapy aggravated acute and chronic HT [11, 12]. Pelvic external beam radiotherapy (EBRT) is recommended with (or without) concurrent cisplatin-based chemotherapy for patients with Stage IA2, IB1, or IIA1 disease who have negative lymph nodes after surgery but have large primary tumors, deep stromal invasion, and/or LVSI [13]. Similarly, in this study, patients with early cervical cancer with intermediate risk factors were treated with simple pelvic radiotherapy after operation, and no concurrent chemotherapy was performed. As chemotherapy (neoadjuvant chemotherapy) before radical operation may cause tumors to shrink, it may make the operation easier and help to remove any very small tumor that is not easy to see, which can improve the total overall survival rate [14, 15]. Cho *et al.* observed that after neoadjuvant chemotherapy of cervical cancer with a diameter over 4 cm, the complete pathological reaction rate was 7.1%, which can also significantly reduce the depth of tumor invasion and avoid hemoglobin reduction after operation [16]. Therefore, in the present research, 58 patients had a tumor diameter of > 4 cm and two cycles of neoadjuvant chemotherapy with paclitaxel plus cisplatin before the radical operation. Intermediate risk factors remain after operation, so adjuvant pelvic radiotherapy is necessary. The results showed a significant increase in HT ($p < 0.05$) and especially in the total WBC count.

Radiation can induce mitotic arrest of hematopoietic stem/progenitor cells and their progeny cells, resulting in cell reduction and hypoplasia in bone marrow, which can lead to apoptosis of other hematopoietic cells in lymphocytes [17]. EBRT in radical radiotherapy of locally advanced cervical cancer significantly reduced the absolute number of circulating leukocytes and lymphocytes [9]. MELL *et al.* reported that when the PLDR V10 was ≥ 90%, 32% of the patients had grade 2 neutropenia [8]. When V10 was < 90%, only 5.6% had grade 2 neutropenia. Brent *et al.* [18] found that in the concurrent chemoradiotherapy for

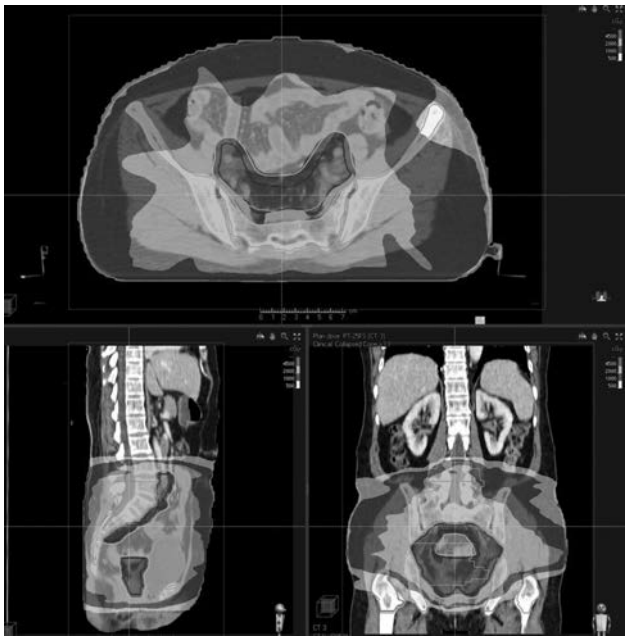

Figure 3. — The cross-sectional, sagittal, and coronal show the pelvic bone marrow low dose areas of 5 Gy (yellow), 10 Gy (red gold,) and 20 Gy (light blue).

cervical cancer, pelvic V10 of < 95% and V20 of < 76% helped to reduce the probability of grade 3 leukocytopenia in 50% of the patients. This study focused on the effects of radiotherapy on cervical cancer after radical resection and PLDR on leukocyte, lymphocyte, and neutrophil counts. The results showed that in the IMRT of postoperative cervical cancer, when the PLDR was controlled at V10 of < 86% and V20 of < 73%, the incidence rates of grade ≥ 2 leukocytopenia and neutropenia could be reduced. To enhance the number of leukocytes and neutrophils of patients with grade ≥ 2 leukocytopenia and neutropenia, the granulocyte colony-stimulating factor should be injected in the clinic. For grade 3 or 4 cases, radiotherapy should be suspended or discontinued, which not only increases expenditure, but also may delay or affect the overall treatment effect. The control of V10 of < 80% in the pelvis can reduce the incidence of grade ≥ 3 lymphopenia. No effective drugs have been developed yet for decreased lymphocyte count. At the same time, the present research also showed no significant correlation between the low-dose volume accepted by the pelvis and anemia and thrombocytopenia in the clinical setting, which is similar to the results of most studies [5, 18, 19].

In clinical practice, an in-depth study on the pelvic irradiation dose limit for postoperative intensive radiotherapy for cervical cancer is still lacking. This study found that for early cervical cancers whose postoperative pathology showed an intravascular tumor thrombus, after one cycle of adjuvant chemotherapy, the degree of myelosuppression was significantly higher than that in patients without chemotherapy. Through the ROC curve, the volume of the PLDR that leads to acute HT was obtained. Therefore, individualized pelvic restricted dose should be individualized in accordance with the different treatment options for patients and the number of basic blood cells before radiotherapy to achieve the goal of reducing HT and ensuring a smooth radiotherapy course.

This research is a retrospective study that used data from treated patients, only analyzing acute HT without evaluating the long-term effects of HT. Owing to the retrospective nature of this study, it cannot be randomized in statistics, which resulted in certain limitations. In the future, prospective studies can be made to determine the grouping criteria and increase the sample size to further verify the feasibility of the results.

Conclusion

For patients who were receiving IMRT for postoperative early-stage cervical cancer, when restricted to V10 of < 86%, V20 of < 73%, V10 of < 88%, and V20 of < 73%, it can reduce grade ≥ 2 leukopenia and neutropenia, and when V10 was < 80%, it can reduce grade ≥ 3 leukopenia lymphopenia ($p < 0.01$). Therefore, the radiation volumes of PLDR of 10 and 20 Gy can be used as a predictor of acute HT. In according with the different treatment regimens of patients before radiotherapy, the volumes of V10 and V20 individualized to reduce the incidence of acute HT can be limited.

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References

[1] Chen W.Q., Zheng R.S., Baade P.D, Zhang S.W., Zeng H.M., Bray F., *et al*: "Cancer Statistics in China, 2015". *CA Cancer J. Clin.*, 2016, *66*, 115.

[2] Sedlis A., Bundy B.N., Rotman M.Z., Lentz S.S., Muderspach L.I., Zaino R.J.: "A randomized trial of pelvic radiation therapy versus no further therapy in selected patients with stage IB carcinoma of the cervix after radical hysterectomy and pelvic lymphadenectomy: A Gynecologic Oncology Group Study". *Gynecol. Oncol.*, 1999, *73*, 177.

[3] Brixey C.J., Roeske J.C., Lujan A.E., Yamada S.D., Rotmensch J., Mundt A.J.: "Impact of intensity-modulated radiotherapy on acute hematologic toxicity in women with gynecologic malignancies". *Int. J. Radiat. Oncol. Biol. Phys* , 2002, *54*, 1388.

[4] Mundt A.J., Mell L.K., Roeske J.C.: "Preliminary analysis of chronic gastrointestinal toxicity in gynecology patients treated with intensity-modulated whole pelvic radiation therapy". *Int. J. Radiat. Oncol. Biol. Phys.*, 2003, *56*, 1354.

[5] Mell L.K., Kochanski J.D., Roeske J.C., Haslam J.J., Mehta N., Yamada S.D., *et al*.: "Dosimetric predictors of acute hematologic toxicity in cervical cancer patients treated with concurrent cisplatin and intensity-modulated pelvic radiotherapy". *Int. J. Radiat. Oncol. Biol Phys.*, 2006, *66*, 1356.

[6] Song S., Song C., Kiln H.J., Wu H.G., Kim, J.H., Park N.H., *et a1*.: "20 year experience of postoperative radiotherapy in IB-IIA cervical cancer patients with intermediate risk factors: impact of treatment period and concurrent chemotherapy". *Gynecol. Oncol.*, 2012, *124*, 63.

[7] Gatcliffe T.A., Tewari K.S., Shah A., Brewster W.R., Burger R.A.,

Kuo J.V., *et al*. : "A feasibility study of topotecan with standard-dose cisplatin and concurrent primary radiation therapy in locally advanced cervical cancer". *Gynecol. Oncol.*, 2009, *112*, 85.

[8] Mell L.K., Schomas D.A., Salama J.K., Devisetty K., Aydogan, B., Miller R.C., *et al*.: "Association between bone marrow dosimetric parameters and acute hematologic toxicity in anal cancer patients treated with concurrent chemotherapy and intensity-modulated radiotherapy". *Int. J. Radiat. Oncol. Biol. Phys.*, 2008, *70*, 1431.

[9] Albuquerque K., Giangreco D., Morrison C., Siddiqui M., Sinacore J., Potkul R., Roeske J.: "Radiation-related predictors of hematologic toxicity after concurrent chemoradiation for cervical cancer and implications for bone marrow-sparing pelvic IMRT". *Int. J. Radiat. Oncol. Biol. Phys.*, 201, *79*, 1043.

[10] Fajardo L.F., Berthrong M., Anderson R.E.: "Hematopoietic tissue". *In:* Fajardo L.F, Berthrong M., Anderson R.E., (eds). *Radiation pathology*. Oxford: Oxford University Press, 2001, 379.

[11] Sood B.M., Timmins P.F., Gorla G.R., Garg M., Anderson P.S., Vikram B., Goldberg G.L.: "Concomitant cisplatin and extended field radiation therapy in patients with cervical and endometrial cancer". *Int. J. Gynecol. Cancer,* 2002, *12*, 459.

[12] Kirwan J.M., Symonds P., Green J.A., Tierney J., Collingwood M., Williams C.J.: "A systematic review of acute and late toxicity of concomitant chemoradiation for cervical cancer". *Radiother. Oncol.*, 2003, *68*, 217.

[13] National Comprehensive Cancer Network: "Cervical Cancer (Version 1.2017-October 10,2016)".

[14] Rydzewska L., Tierney J., Vale C.L., Symonds P.R.: "Neoadjuvant chemotherapy plus surgery versus surgery for cervical cancer". *Cochrane Database Syst. Rev.*, 2010, *1*, CD007406.

[15] Li R., Lu S.T., Si J.G., Liu B., Wang H., Mei Y.Y., Ling H.H.: "Prognostic value of responsiveness of neoadjuvant chemotherapy before surgery for patients with stage IB2/IIA2 cervical cancer". *Gynecol. Oncol.*, 2013, *128*, 524.

[16] Cho Y.H., Kim D.Y., Kim J.H., Kim Y.M., Kim Y.T., Nam J.H.: "Comparative study of neoadjuvant chemotherapy before radical hysterectomy and radical surgery alone in stage IB2-IIA bulky cervical cancer". *J. Gynecol. Oncol.*, 2009, *20*, 22.

[17] Dainiak N., Gent R.N., Carr Z., Schneider R., Bader J., Buglova E., *et al.*: "First Global Consensus for Evidence-Based Management of the Hematopoietic Syndrome Resulting From Exposure to Ionizing Radiation". *Disaster Med. Public Health Prep.*, 2011, *5*, 202.

[18] Rose B.S., Aydogan B., Liang Y., Yeginer M., Hasselle M.D., Dandekar V., *et al*.: "Normal tissue complication probability modeling of acute hematologic toxicity in cervical cancer patients treated with chemoradiotherapy". *Int. J. Radiat. Oncol. Biol. Phys.*, 2011, *79*, 800.

[19] Mell L.K, Sirák I., Wei L., Tarnawski R., Mahantshetty U., Yashar C.M., *et al.*: "Bone Marrow-sparing Intensity Modulated Radiation Therapy With Concurrent Cisplatin For Stage IB-IVA Cervical Cancer: An International Multicenter Phase II Clinical Trial (INTERTECC-2)". *Int. J. Radiat. Oncol. Biol. Phys.*, 2017, *97*, 536.

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