

Radiotherapy-induced Haematological and Intestinal Toxicity in Cervical Cancer

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Abstract

Chemotherapy-induced myelosuppression is common and threatening, however, the effect of radiation on bone marrow activity especially leukocyte count has been underestimated in cervical cancer. Pelvic radiation-related intestinal toxicity is prevalent, and the relationship between leukopenia and intestinal toxicity is not clear. The clinical data of 59 patients who underwent conventional radiation alone for cervical cancer were retrospectively analyzed. The patients had normal leukocyte count on admission, and the blood cell count, GTV dose, intestinal toxicity were evaluated. During radiotherapy (RT), 47 patients (79.7%) developed into leukopenia with 38.3% mild and 61.7% moderate. The mean time for leucopenia was 9 days. Compared with leucopenia-negative patients, leucopenia-positive ones had lower baseline leukocyte count, while the neutrophil/lymphocyte (NLR) and monocyte/lymphocyte (MLR) showed no significance. Logistic regression analysis indicated that excluding the factors for age, BMI, TNM stage, surgery and GTV dose, baseline leukocyte count was an important independent predictor of leucopenia ($OR=0.383$). During RT, the significant reduction was found in leukocyte, neutrophil and lymphocyte count at week 2 while monocyte count after 2 weeks. Furthermore, NLR and MLR showed significant and sustained upward trend. About 54.2% patients had gastrointestinal symptoms, however, no significant difference was noted between leukocyte count as well as NLR/MLR and intestinal toxicity. Our results suggest a high prevalence of leucopenia in cervical cancer patients receiving RT, and those with low baseline leukocyte count are more likely for leucopenia, for whom early prevention of infection may be needed during RT.

Introduction

The radical hysterectomy with pelvic lymphadenectomy is acknowledged as the primary therapeutic option for early-stage cervical cancer.^{1–3} For patients with increased risk for disease relapse (intermediate and high-risk pathological factors) postoperative pelvic radiotherapy (RT, with or without platinum-based chemotherapy) is recommended.^{4–6} Compared with patients treated only with surgery, postoperative RT reduces risk for local recurrence to 47%. In the group of elderly patients with late stage, surgery as well as chemotherapy can not bring good curative effect, and then RT is indicated as the preferred treatment modality for cervical cancer.

Compared with chemical agents, the side effects of limited radiation seems mild, but it can not be ignored. The most common postirradiation toxicities in the pelvic are gastrointestinal, genitourinary as well as haematological.⁷ The RT area of cervical cancer covers the whole pelvic cavity, including anterior superior iliac spine and iliac spine, which are important hematopoietic organs. Chemotherapy-induced myelosuppression has been well recognized in solid tumor,^{8–10} however, less study is focused on the role of irradiation alone in bone marrow activity especially in cervical cancer. Furthermore, the effects of RT on the degree of leukopenia is still controversial and the related factors are not fully evaluated.

Pelvic radiation-related intestinal toxicity is also prevalent,¹¹ and the relationship between leukopenia and intestinal toxicity is not clear. In this study, complete blood parameters before and during RT were

collected and the changes of leukocytes, neutrophil/lymphocyte (NLR) and monocyte/lymphocyte (MLR) were assessed. Logistic regression analysis was used to analyze the factors contributing to leucopenia and the correlation between leukocyte cell count and intestinal toxicity. Our study will provide new insight into the irradiation-induced leucopenia and evidence for the prevention of infection complications.

Method

Patients

A total of 59 patients with cervical cancer from Ningbo First Hospital between January 2018 to December 2020 were enrolled. The inclusion conditions were as follows: 1. Patients were diagnosed with cervical cancer by pathology; 2. only received RT without chemotherapy; 3. completed the entire radiation therapy plan; 4. the baseline of leukocyte count before RT was normal ($\geq 3.5 \times 10^9 / L$). We excluded those who had inflammation, intestinal or hematological diseases, or who received prior or concurrent chemotherapy, hyperfractionated RT, or RT to multiple sites concurrently. All patients signed informed consent. The study was approved by the Ethics Committee of Ningbo First Hospital.

Treatment

All patients received RT for at least 5 weeks using Intensity Modulated Radiation Therapy (IMRT) and a three-dimensional treatment planning system (3D-CRT). The median dose for pelvic radiation was 45 Gy, and patients with metastatic pelvic or abdominal lymph nodes had 54-60 Gy.

Blood counts

Blood samples of patients were collected and leukocyte count at baseline (on admission), weekly during RT, and at the end of RT were analyzed. The normal range of leukocyte count was $3.5-9.5 \times 10^9 / L$. Leucopenia was defined as: mild ($3-3.5 \times 10^9 / L$), moderate ($2-3 \times 10^9 / L$) and severe ($< 2 \times 10^9 / L$). Neutrophil to lymphocyte ratio (NLR) and monocyte to lymphocyte ratio (MLR) were also analyzed.

Intestinal toxicity

Intestinal toxicity was mainly defined by clinical symptoms. Systemic enteritis were excluded and patients had symptoms of acute enteritis after radiation as below: 1. nausea, vomiting, abdominal pain, diarrhea, and tenesmus; 2. diarrhea more than 3 times/day and antidiarrheal agents or antibiotics were needed; 3. symptoms of acute enteritis were improved after a rest of RT.

Statistical analysis

Clinical variables of the patients were compared with T test for continuous variables, and chi-squared for categorical variables. Logistic regression analysis was used to assess the degree of association among independent variables. SPSS version 23.0 was used for statistical analyses. Statistical significance was defined as $p < 0.05$.

Results

Leucopenia during RT in cervical cancer

Among the 59 patients with cervical cancer receiving RT, 47 patients (79.7%) developed into leucopenia ($<3.5 \times 10^9/L$) and the mean time was 9 days (Table 1). Eighteen of them had mild leucopenia (38.3%) and 29 developed into moderate leucopenia (61.7%).

Table 1
Clinical characteristics of patients with or without leukopenia

	Leukopenia- (n = 12)	Leukopenia+ (n = 47)	P values
Age (years)	62.17 ± 13.01	62.43 ± 9.52	0.94
BMI (kg/m ²)	23.17 ± 3.54	22.97 ± 4.25	0.88
Surgery	66.67% (8/12)	74.47% (35/47)	0.72
TNM			
I	7	22	0.79
II	3	18	
III	1	2	
IV	1	4	
WBC ($\times 10^9/L$)	5.99 (4.50, 8.03)	4.78 (4.15, 5.53)	< 0.05
NLR (%)	1.81 (1.61, 3.00)	1.87 (1.56, 2.44)	0.53
MLR (%)	0.22 (0.19, 0.33)	0.24 (0.19, 0.31)	0.59
Time (days)	NA	9 (7, 15)	
GTV dose (Gy)			0.83
≤ 45	7	29	
> 45	5	18	
Intestinal toxicity (%)	66.67% (8/12)	51.1% (24/47)	0.33

No significance was found in age, BMI, TNM staging, surgery, radiation dose between the leucopenia-negative and positive groups. Compared with the leucopenia-negative group, the baseline leukocyte count was markedly decreased in leucopenia-positive group. However, the NLR and MLR at baseline showed no significance. Further logistic regression analysis indicated that excluding the factors for age, BMI, TNM

stage, surgery and GTV dose, baseline leukocyte count was an important independent predictor of leucopenia ($OR = 0.383$, 95% CI = 0.193–0.758, $p < 0.01$).

The leukocyte count as well as NLR/MLR at week 1, 2, 4, and 5 after RT were analyzed (Fig. 1). The significant reduction was found in leukocyte, neutrophil and lymphocyte count at week 2 [leukocyte week 1 vs week 2: 3.99 (3.25, 5.31) vs 3.46 (2.72, 4.19), adjusted $p < 0.01$; neutrophil week 1 vs week 2: 2.5 (2.1, 3.2) vs 2.2 (1.6, 2.8), adjusted $p < 0.01$; lymphocyte baseline vs week 2: 1.5 (1.2, 1.8) vs 0.7 (0.5, 0.9), adjusted $p < 0.01$]. While monocyte count decreased after 2 weeks [monocyte week 2 vs week 4: 0.3 (0.3, 0.4) vs 0.4 (0.3, 0.5), adjusted $p < 0.05$]. Furthermore, NLR and MLR showed significant and sustained upward trend.

The association between leucopenia and intestinal toxicity

As shown in Table 2, 54.2% patients had intestinal toxicity during RT, and the data of basic characteristics such as age, BMI, surgery, TNM staging, leucopenia and GTV dose didn't differ between the two groups. Moreover, leukocyte count as well as NLR/MLR before and during RT was compared between patients with or without intestinal toxicity. Mann-Whitney U tests indicated that the changes of leukocyte count as well as NLR/MLR had no significant difference between the two groups (Fig. 2).

Table 2
Clinical characteristics of patients with or without intestinal toxicity

	Intestinal toxicity - (n = 27)	Intestinal toxicity + (n = 32)	P values
Age (years)	60.93 ± 9.10	63.59 ± 11.02	0.32
BMI (kg/m ²)	23.19 ± 4.38	22.87 ± 3.88	0.77
Surgery	21(21/27)	22(22/32)	0.56
TNM			
I	13	16	0.63
II	8	12	
III	3	1	
IV	2	3	
WBC ($\times 10^9/L$)	5.00 (4.12, 5.87)	4.89 (4.44, 6.00)	0.36
NLR (%)	1.85 (1.59, 2.79)	1.87 (1.56, 2.34)	0.43
MLR (%)	0.24 (0.19, 0.28)	0.25 (0.18, 0.33)	0.72
GTV dose (Gy)			0.19
≤ 45	19	17	
> 45	8	15	

Discussion

In this study, we first showed that about 80% patients suffer from leucopenia during RT in cervical cancer. Zachariah B et al reported that in spite of significant decline, the white blood cell count (WBC) of all 108 patients was clinically normal during 6-week pelvic RT.¹² Blank RK also demonstrated that few patients experienced drops in their WBCs below critical nadirs during the period of RT in prostate cancer.¹³ Thus we speculate that though both belonging to the category of pelvic RT, the hematotoxicity of irradiation for cervical cancer is greater than that for prostate cancer. Yang EF et al also found dramatically decreased leukocyte in various types of cancer,¹⁴ however, the change of white blood cells in cervical cancer during RT has not been separately illustrated. Although previous studies have suggested gynecological malignancies receiving whole pelvis irradiation would be at risk for depression of granulocyte reserves,¹⁵ it is indicated that the irradiation-related myelosuppression effect is greatly underestimated in cervical cancer. Moreover, we found more than 60% patients with leucopenia would develop into moderate level, further confirming the severity of myelosuppression by pelvis irradiation. Patients with leucopenia are at risk to experience fever or infection, which prolongs length of hospital stay, delays RT, and increases economic burden.

Secondly, we showed a lower baseline leukocyte count in patients with leucopenia after pelvis irradiation. Previous study demonstrated a strong correlation between starting complete blood counts and nadirs.¹⁴ However, clinical factors that may affect the blood cell count during RT were not ruled out. By univariate and multivariate logistic regression analysis, excluding the factors for age, BMI, TNM stage, surgery and GTV dose, we indicate that baseline leukocyte count is an important independent predictor of RT-induced leucopenia. Furthermore, it is found that the mean value of baseline leukocyte count here is lower than that in previous study. Dovšak Tadej et al has reported that surgery has an effect on the peripheral blood count in oral cancer,¹⁶ and in our study 73% patients underwent surgery before RT, which may contribute to the lower baseline leukocyte count.

Thirdly, we showed that despite a continuing drop trend, the leukocyte, neutrophil and lymphocyte count had significant decrease during 7–14 days (week 2) irradiation, and the adjusted p value of leukocyte, neutrophil and lymphocyte count at baseline and week 1 was of no significance by Friedman test, which is not consistent with previous studies. Yang EF reported the largest decline in leukocytes was seen during the first week.¹⁴ Trask CWL et al also found T cell loss followed an exponential pattern was statistically significant by the end of the first week of pelvic irradiation.¹⁷ However, only 5 patients were included in the pelvis group, and two were of cervical cancer. Two main reasons may explain for the difference: 1. patients included in this study are all with cervical cancer, and RT-induced hematotoxicity in cervical cancer may different from other types of cancer within pelvic irradiation. 2. The data of blood cell count was of non-normal distribution, and thus Friedman test was used to judge the difference between groups by rank analysis and adjusted p value. Furthermore, we for the first time showed NLR and MLR during RT in cervical cancer, and both NLR and MLR were markedly elevated following the RT period. However, by logistic regression analysis, NLR and MLR are not able to predict the risk of leucopenia. We also analyzed other blood parameters like platelets, red blood cells, hemoglobin, C-reactive protein etc., and the results were in consistent with previous studies with no more explanation here.

It is reported that radiation dose and fractionation schedule, treatment field size and intestinal volume irradiated are the key determinant of intestinal radiation induced toxicity.¹⁸ Michael Pinkawa et al demonstrated that early lymphocyte level elevation was protective against late urinary and bowel toxicity,¹⁹ indicating hematologic changes may be also associated with intestinal toxicity during RT. Thus we analyzed the relationship between blood parameters and intestinal toxicity in cervical cancer. However, no significance was found between the changes of leukocyte count as well as NLR/MLR and intestinal toxicity during 5 week-RT.

Administration of G-CSF drugs is a common method for clinical treatment of leucopenia due to the prompt and high efficacy as well as the low price. However, Pape H et al demonstrate that simultaneous treatment with G-CSF during radiotherapy reduces the mobilization of CD34 + progenitor cells and exhaust the bone marrow capacity while peripheral leukocyte counts remain at baseline levels,²⁰ which indicates the hazards for repeat use of G-CSF and the importance for prevention of leucopenia.

Conclusion

Our results suggest that RT-induced haematological toxicity especially leucopenia in cervical cancer is of high prevalence and severity, which shall be paid more attention to reduce the occurrence of other complications and ensure the completeness of RT safely and smoothly.

Abbreviations

RT, radiotherapy; NLR, neutrophil to lymphocyte ratio; MLR, monocyte to lymphocyte ratio; IMRT, intensity Modulated Radiation Therapy; 3D-CRT, three-dimensional treatment planning system; WBC, white blood cell count; BMI, body mass index

Declarations

Ethical Approval and Consent to participate

Not applicable

Consent for publication

Not applicable

Availability of supporting data

Not applicable

Competing interests

The authors report no conflicts of interest in this work.

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Author Contribution

Ruishuang Ma designed the research, made the figures and wrote the paper; Xiaoxian Ye, Jianliang Zhou, Shenchao Guo analyzed data; Ruishuang Ma obtained the funding; Pengrong Lou and Jianxin Guo revised the manuscript and provided partial funding support.

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Ethical Statement

This work is original and none of this work has been published before or is under consideration for publication anywhere else. All authors adhere to discipline-specific rules for acquiring, selecting and processing data.

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Figures

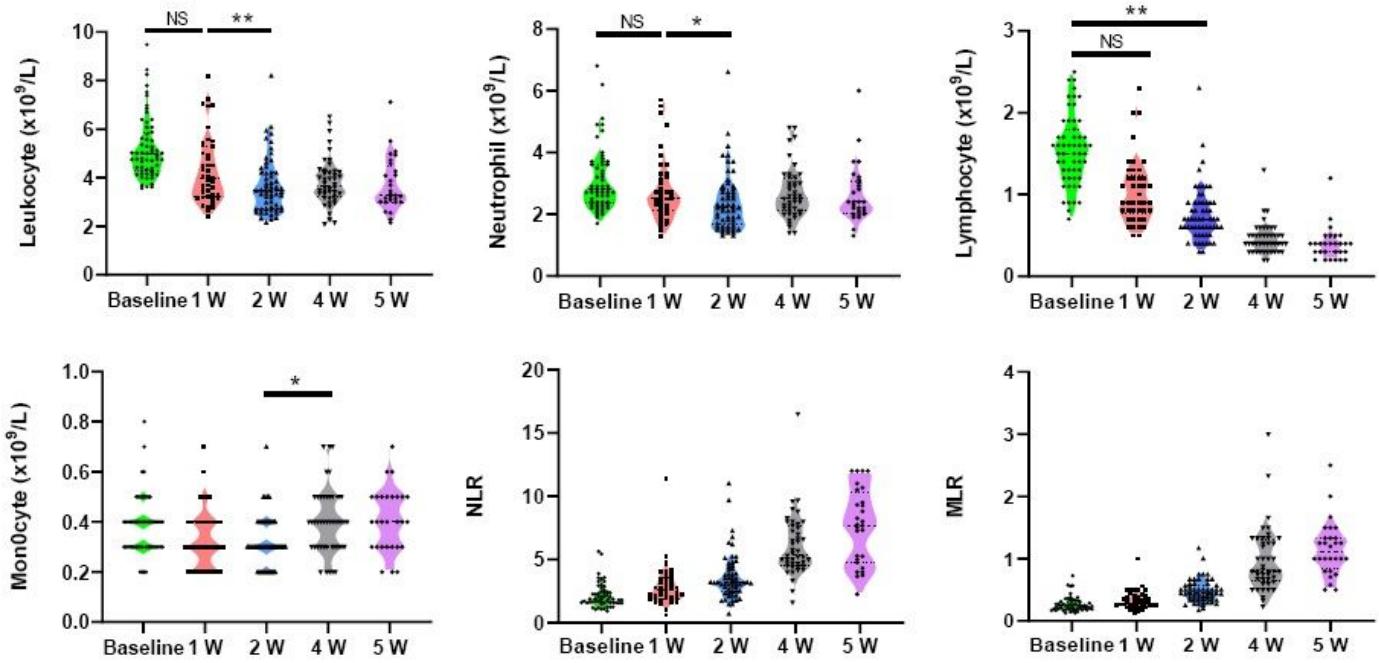


Figure 1

Figure 1

The changes of leukocyte and NLR/MLR during radiotherapy in cervical cancer. * $p<0.05$, ** $p<0.01$, data were present with median and quartile.

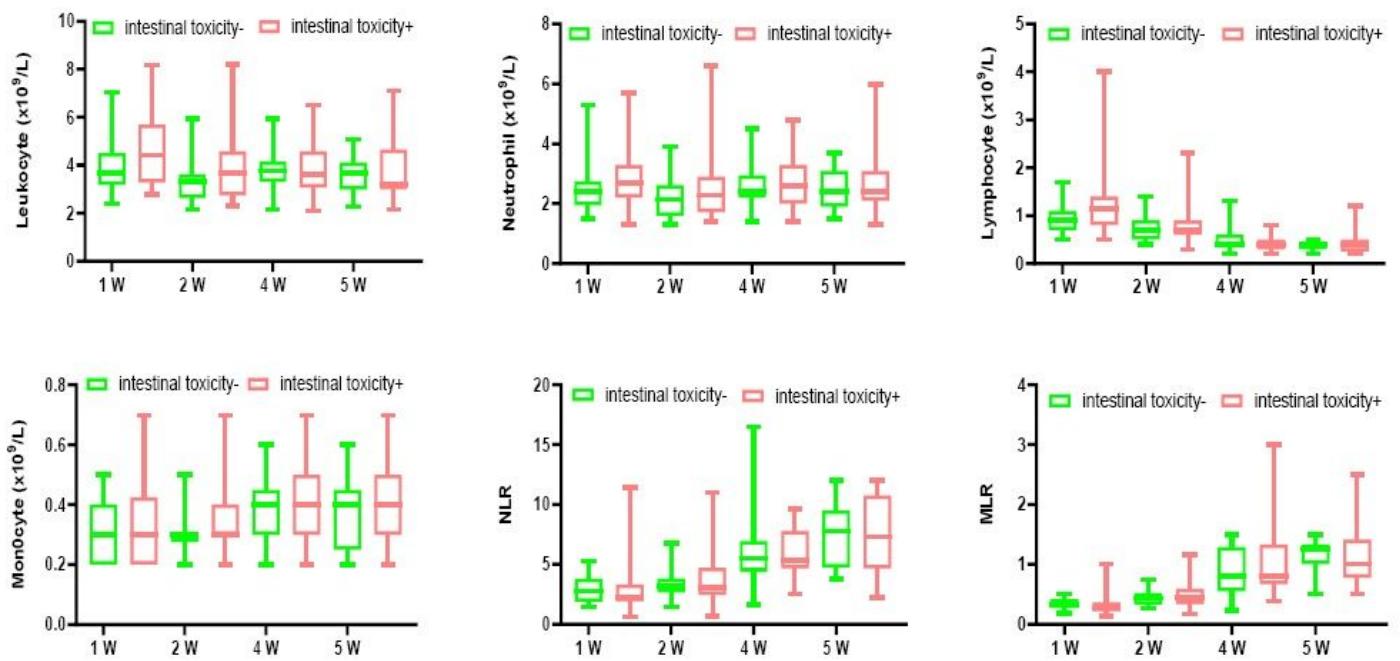


Figure 2

Figure 2

The changes of leukocyte and NLR/MLR during radiotherapy in patients with or without intestinal toxicity. No significance were found in leukocyte as well as NLR/MLR between the intestinal toxicity-negative and positive groups at each week. Data were present with median and quartile.