Predicting severe hematologic toxicity from extended-field chemoradiation of para-aortic nodal metastases from cervical cancer

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Introduction

Cervical cancer is the fourth most common cancer in women with the number of cases increasing each year [1]. For cervical cancer, lymph node metastasis, especially para-aortic lymph node metastasis (PALN), is associated with higher treatment failure and distant failures [2]. For these patients, extended-field radiation therapy with concurrent chemotherapy has been shown to give good local control and survival rates; however, hematologic toxicity (HT) was significant due to extensive radiation of the bone marrow in the pelvis and spinal column, leading to prolonged treatment days and missed chemotherapy [3,4]. Bone marrow sparing radiation techniques to prevent HT have been extensively studied for pelvic radiation, but information is lacking for extended-field radiation therapy [5]. The purpose of this study is to determine significant factors predictive for severe HT in cervical cancer patients with PALN metastasis treated with concurrent chemoradiation with a specific focus on radiation parameters.

Methods

1. Patient selection

- 38 patients from 2008-2015
- Extended-field radiation therapy with concurrent chemotherapy

2. Bone Marrow Contouring

- Total bone marrow includes pelvis, femoral head, lumbar and sacral spine.
- Active bone marrow determined by ^{18}F-FDG-PET / CT scan.

3. Data collection

- Retrieved weekly blood counts collected during treatment.
- Determined doses to bone marrow from the treatment plan.

Results

Patient and Cancer Characteristics	
Patients	38
Mean age, years (SD)	49.8 (11.4)
Race, number of people (%)	
White	15 (39.5)
Hispanic	15 (39.5)
Other	8 (21.1)
Mean body mass index, kg/m^2 (SD)	26.8 (6.1)
Diabetes (%)	7 (18.4)
Hypertension (%)	12 (31.6)
FIGO Clinical Stage, number of people (%)	
1B1	1 (2.6)
1B2	4 (10.5)
2A2	2 (5.3)
2B	21 (55.3)
3B	8 (21.1)
4A	2 (5.3)

Treatment Characteristics	
Method of External Radiation	
IMRT (%)	27 (71.1)
3D-CRT 4 Field Technique (%)	11 (28.9)
Mean Dose to BM_{TOT} in Gy (SD)	29.8 (2.9)
Mean Dose to BM_{ACT} in Gy (SD)	33.4 (3.4)
Mean Treatment Days (SD)	57.4 (7.5)
Received Packed Red Blood Cell Transfusion During Treatment (%)	18 (47.4)
Received Platelet Transfusion During Treatment (%)	1 (2.6)
Received Granulocyte Colony Stimulating Factor During Treatment (%)	11 (28.9)

Acute Hematologic Toxicity					
Toxicity	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Neutropenia (%)	11 (28.9)	6 (15.8)	11 (28.9)	9 (23.7)	1 (2.6)
Anemia (%)	0 (0)	9 (23.7)	17 (44.7)	12 (31.6)	0 (0)
Thrombocytopenia (%)	4 (10.5)	26 (68.4)	5 (13.2)	2 (5.3)	1 (2.6)

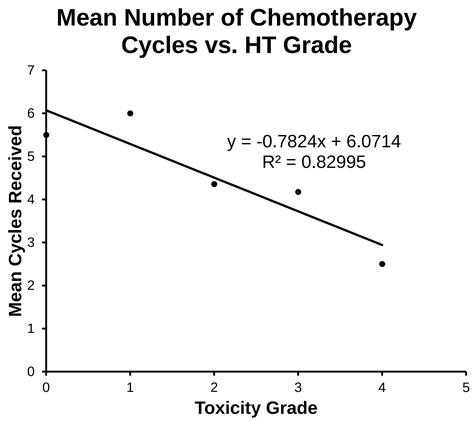
Blood Counts	
Baseline count, mean (SD)	
WBC k/μL (SD)	11.3 (6.5)
ANC k/μL	8.4 (6.0)
Hemoglobin g/dL	11.1 (1.9)
Platelet k/μL	367.8 (161.4)
Nadir count, mean (SD)	
WBC k/μL	2.4 (1.1)
ANC k/μL	1.6 (1.0)
Hemoglobin g/dL	8.9 (1.4)
Platelet k/μL	113.3 (58.7)

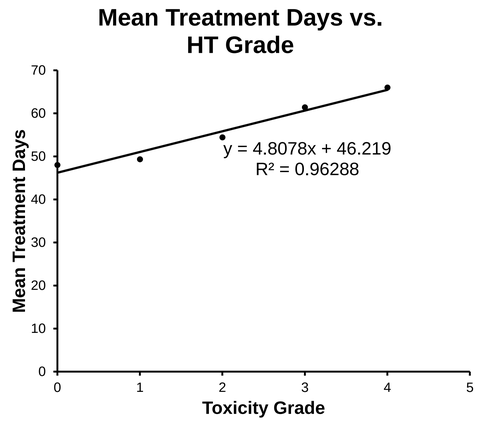
HT3+ Dosimetric Parameter Cutoff Values	
Total Bone Marrow	
Mean Dose (p-value)	30.28 (0.04)
V10 % (p-value)	94.58 (0.11)
V20 % (p-value)	78.56 (0.01)
V30 % (p-value)	47.14 (<0.01)
V45 % (p-value)	20.36 (0.01)
Active Bone Marrow	
Mean Dose (p-value)	32.36 (0.02)
V10 % (p-value)	95.50 (0.03)
V20 % (p-value)	80.52 (0.05)
V30 % (p-value)	59.64 (0.03)
V45 % (p-value)	31.74 (0.01)

	HT Grade 0-2	HT Grade 3-4
Not Obese	4 (10.5%)	14 (36.8%)
Obese	15 (39.5%)	5 (13.2%)

Patients who were obese were less likely to have severe hematologic toxicity compared with patients who were not obese ($p < 0.01$).

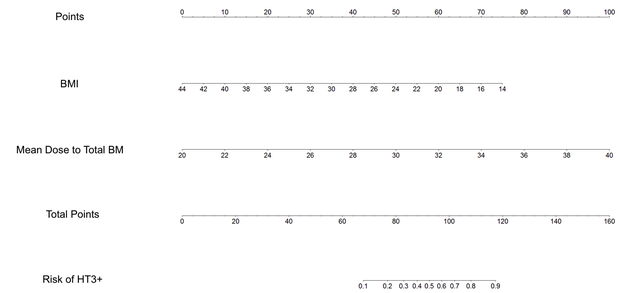
Abbreviations: HT3+ = Hematologic Toxicity Grade 3 and Higher; V10, 20, 30, 45 = percent of bone marrow receiving ≥ 10, 20, 30, 45 Gy.





Conclusions

1. The greater volume irradiated due to extended-field radiation therapy is associated with severe hematologic toxicity in a high proportion of patients.
2. Patients with higher BMI were less likely to get severe hematologic toxicity.
3. Dosimetric parameters have been identified for cervical cancer patients receiving extended-field radiation therapy.
4. A simplified nomogram has been created to predict the risk of developing HT3+ in this patient population.



Abbreviations: HT3+ = Hematologic Toxicity Grade 3 and Higher; BMI = Body Mass Index; BM = Bone Marrow

Future Work

1. Perform planning studies using simulated particle therapies (proton, carbon ion) to reduce bone marrow dose in patients from this sample.
2. Perform phase 1/2 studies exploring bone marrow sparing radiation therapy techniques in patients and compare with previous hematologic toxicity rates.

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References

1. Ferlay, J., et al., *Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012.* Int J Cancer, 2015. **136**(5): p. E359-86.
2. Stehman, F.B., et al., *Carcinoma of the cervix treated with radiation therapy. I. A multi-variate analysis of prognostic variables in the Gynecologic Oncology Group.* Cancer, 1991. **67**(11): p. 2776-85.
3. Kim, Y.S., et al., *High-dose extended-field irradiation and high-dose-rate brachytherapy with concurrent chemotherapy for cervical cancer with positive para-aortic lymph nodes.* Int J Radiat Oncol Biol Phys, 2009. **74**(5): p. 1522-8.
4. Jensen, L.G., et al., *Outcomes for patients with cervical cancer treated with extended-field intensity-modulated radiation therapy and concurrent cisplatin.* Int J Gynecol Cancer, 2013. **23**(1): p. 119-25.
5. Liang, Y., et al., *Prospective study of functional bone marrow-sparing intensity modulated radiation therapy with concurrent chemotherapy for pelvic malignancies.* Int J Radiat Oncol Biol Phys, 2013. **85**(2): p. 406-14.