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FULL PAPER

Dosimetric predictors of acute haematological toxicity in oesophageal cancer patients treated with neoadjuvant chemoradiotherapy

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Objective: Haematological toxicity (HT) is common in patients with oesophageal cancer (EC) treated with chemoradiotherapy (CRT). The Quantitative Analysis of Normal Tissue Effects in the Clinic guidelines provide no dose constraints for the bone marrow (BM) to avoid HT. We aimed to determine dosimetric factors associated with HT during CRT for EC.

Methods: 41 patients with EC treated with neoadjuvant cisplatin and 5-fluorouracil-based CRT were retrospectively reviewed. Associations between the dose-volume histogram parameters of thoracic bones and blood cell count changes during CRT were assessed using logistic regression analyses. Receiver-operating characteristic curves were used to derive optimal dosimetric planning constraints. V_x indicates the total organ volume percentage exceeding a radiation dose of x (Gy).

Results: Greater thoracic vertebrae and rib irradiation doses, including mean vertebral dose (MVD), thoracic

vertebrae V_{5-30} (TVV₅₋₃₀), mean rib dose and rib V_{5-20} , were associated with increased leukopenia (grade ≥ 3) risk. Additional BM sites (sternum, scapulae and clavicles) did not influence HT. White blood cell and absolute neutrophil count nadirs were associated with increased irradiation doses to the thoracic vertebrae, ribs and sternum. Chemotherapy cycle number was not significantly associated with severe neutropenia or leukopenia. Cut-off values with the highest likelihood of avoiding leukopenia were $MVD < 25.9$ Gy, $TVV_{20} < 70\%$ and $TVV_{10} < 77\%$.

Conclusion: Thoracic bone irradiation dose was significantly associated with HT after adjusting for chemotherapy effects. Efforts to maintain $MVD < 25.9$ Gy, $TVV_{10} < 77\%$ and $TVV_{20} < 70\%$ could reduce HT.

Advances in knowledge: This is the first study addressing issues concerning HT in patients with neoadjuvant CRT-treated EC.

INTRODUCTION

Neoadjuvant concurrent chemoradiotherapy (CRT) followed by curative surgery has been shown to improve overall survival in patients with locally advanced oesophageal cancer (EC)¹⁻³ and has therefore become a standard form of treatment. Although CRT affords a better chance of cure, bone marrow (BM) suppression is a common toxicity that has been observed in patients with EC undergoing treatment with CRT. Leukopenia (grade ≥ 3) has been reported to have occurred in several previously published clinical trials, including the Cancer and Leukaemia Group B 9781 study and the Japan Clinical Oncology Group 9516 and 9906 trials, in which 36, 33 and

43% of patients, respectively, were affected. The study protocol of these trials mandated that when leukopenia (grade ≥ 3) occurred, chemotherapy be withheld or reduced until blood counts recovered.^{2,4,5} Furthermore, myelotoxicity has been identified as a significant poor prognostic factor in patients with T4 EC treated with CRT followed by curative resection.⁶

Pelvic radiotherapy and chemotherapy are known to be myelosuppressive in patients with cervical and anal cancers,⁷⁻¹³ and radiation oncologists have implemented efforts to mitigate the degree of haematological toxicity (HT) associated with these treatments. Given that the

thorax contains approximately 35% of the functional BM,¹⁴ irradiation of these thoracic structures could destroy radiosensitive BM stem cells and contribute to HT in patients with EC. However, there is a paucity of data concerning the extent to which thoracic radiation contributes to HT in patients with EC treated with CRT and there are no dose constraints for BM to avoid HT on Quantitative Analysis of Normal Tissue Effects in the Clinic.¹⁵ In order to explore these issues, we examined our institution experience with patients with EC undergoing CRT. The aim of this study was to determine the impact of CRT on BM suppression and to establish potential dosimetric constraints of thoracic bony structures that may be used for thoracic radiotherapy.

METHODS AND MATERIALS

Patients

Patients with EC receiving treatment with neoadjuvant CRT at our institution between 2011 and 2015 were retrospectively reviewed. Eligible patients had biopsy-proven clinical Stage I–III oesophageal carcinoma and no previous history of chemotherapy or irradiation. All of the patients recruited to our study were required to have a World Health Organization performance status of 0 or 1. Reasons for patient exclusion included a previously treated malignancy or evidence of metastatic disease. 46 patients were screened for eligibility; 5 patients were excluded because of a previous history of malignancy, leaving 41 patients eligible.

Pre-treatment evaluations included: a complete medical history, physical examination, complete blood count and biochemistry survey, chest radiography, chest and abdominal CT, oesophagogastrroduodenoscopy with endoscopic ultrasonography and whole-body fluorine-18 fludeoxyglucose positron emission tomography. The pre-CRT clinical stage was determined using the seventh edition of the Union for International Cancer Control/American Joint Committee on Cancer TNM classification system.

The study protocol was granted institutional review board approval. Written informed consent was obtained from all study participants and research was conducted in accordance with the 1975 Declaration of Helsinki, as revised in 1983.

Chemotherapy delivery, transfusions and growth factors

Chemotherapy consisted of two cycles of cisplatin and 5-fluorouracil (5-FU). Cisplatin (60 mg m^{-2}) was delivered by i.v. infusion on Days 1 and 29. 5-FU (600 mg m^{-2} every 24 h) was administered as a continuous infusion on Days 1–4 and 29–32. Chemotherapy was administered as a half dose under the following conditions: (a) white blood cell (WBC) count $<2.0 \times 10^9/\text{l}$, (b) absolute neutrophil count (ANC) between 1.0×10^9 and $1.5 \times 10^9/\text{l}$ or (c) platelet (Plt) count between 5.0×10^7 and $7.5 \times 10^7/\text{l}$. Chemotherapy was omitted under the following conditions: (a) ANC $<1.0 \times 10^9/\text{l}$, (b) Plt count $<5.0 \times 10^7/\text{l}$ or (c) creatinine clearance $<50 \text{ ml min}^{-1}$. None of the patients underwent Plt transfusions or granulocyte/monocyte colony-stimulating factor treatments.

Radiation planning and delivery

All 41 patients underwent CT simulation in the supine position and were immobilized using alpha cradles. Planning CT images with a maximum slice thickness of 3 mm were acquired through the entire neck, thorax and upper abdomen. The gross tumour volume (GTV) consisted of the primary tumour and regional lymph nodes, using imaging studies that included CT, endoscopic ultrasonography and whole-body fluorine-18 fludeoxyglucose positron emission tomography. Two clinical target volumes (CTVs) were defined as follows: the GTV plus regions considered to be at significant risk of microscopic disease (CTV_{High}) and the GTV plus a 1-cm circumferential margin and a 3–4-cm longitudinal margin (CTV_{Low}). Elective nodal irradiation was included in the CTV_{Low}. Elective nodal irradiation was delivered to the supraclavicular fossa (if the primary tumour was located in the upper third of the oesophagus or any enlarged lymphadenopathy was present in the upper mediastinum) or celiac lymphatics (if the primary tumour was in close proximity to the oesophagogastric junction or any lymphadenopathy was present in the perigastric region). The two planning target

Table 1. Baseline characteristics of patients with oesophageal cancer

Characteristic	Number	%
Total	41	100
Gender		
Male	39	95.1
Female	2	4.9
Tumour location		
Upper	12	29.3
Middle	17	41.4
Lower	12	29.3
Clinical T stage		
T1	1	2.4
T2	6	14.6
T3	31	75.6
T4a	3	7.4
Clinical N stage		
N0	2	4.9
N1	23	56.1
N2	12	29.3
N3	4	9.7
Clinical stage		
I–IIA	0	0
IIB	3	7.4
IIIA	24	58.5
IIIB	9	21.9
IIIC	5	12.2
IV	0	0

Table 2. Descriptive characteristics of predictors and outcomes

Characteristic	Case (<i>n</i> = 41)
Age (years)	
Median	58
Range	41–79
Pre-treatment BMI	
Median	21.0
Range	13.8–29.4
Post-treatment BMI	
Median	20.2
Range	14.9–28.5
Chemotherapy	
Cisplatin + 5-FU	41 (100%)
Cycles	
1	41 (100%)
2	38 (92.7%)
Chemotherapy dose reduction	
Yes	11 (26.8%)
No	30 (73.2%)
PTV (ml)	
Median	519
Range	300–1426
Baseline blood count (mean ± SD)	
WBC ($\text{k } \mu\text{l}^{-1}$)	7.7 ± 2.2
ANC ($\text{k } \mu\text{l}^{-1}$)	5.1 ± 1.9
Hgb (g dl^{-1})	12.5 ± 1.9
Plt ($\text{k } \mu\text{l}^{-1}$)	254.2 ± 85.7
Blood cell nadir (mean ± SD)	
WBC ($\text{k } \mu\text{l}^{-1}$)	2.9 ± 1.1
ANC ($\text{k } \mu\text{l}^{-1}$)	1.9 ± 0.8
Hgb ($\text{k } \mu\text{l}^{-1}$)	10.2 ± 1.7
Plt ($\text{k } \mu\text{l}^{-1}$)	137.1 ± 55.8
Whole chest bone DVH (mean ± SD)	
V_{40} (%)	12.6 ± 7.9
V_{30} (%)	26.3 ± 9.8
V_{20} (%)	36.9 ± 11.6
V_{10} (%)	45.6 ± 12.6
V_5 (%)	52.3 ± 13.6
Mean dose (Gy)	15.3 ± 4.2
Thoracic vertebrae DVH (mean ± SD)	

(Continued)

Table 2. (Continued)

Characteristic	Case (<i>n</i> = 41)
V_{40} (%)	22.0 ± 12.7
V_{30} (%)	46.3 ± 19.5
V_{20} (%)	61.0 ± 22.1
V_{10} (%)	66.5 ± 22.3
V_5 (%)	68.6 ± 22.0
Mean dose (Gy)	23.3 ± 7.8
Ribs DVH (mean ± SD)	
V_{40} (%)	3.4 ± 3.2
V_{30} (%)	9.0 ± 5.2
V_{20} (%)	17.1 ± 7.5
V_{10} (%)	27.0 ± 9.6
V_5 (%)	35.5 ± 13.4
Mean dose (Gy)	8.3 ± 2.7
Sternum DVH (mean ± SD)	
V_{40} (%)	21.4 ± 19.6
V_{30} (%)	44.3 ± 28.9
V_{20} (%)	60.7 ± 27.6
V_{10} (%)	76.4 ± 25.9
V_5 (%)	82.2 ± 23.9
Mean dose (Gy)	24.9 ± 10.6
Scapula DVH (mean ± SD)	
V_{40} (%)	0.9 ± 2.5
V_{30} (%)	3.3 ± 7.6
V_{20} (%)	9.3 ± 13.0
V_{10} (%)	19.6 ± 17.2
V_5 (%)	32.8 ± 22.0
Mean dose (Gy)	6.1 ± 4.7
Clavicle DVH (mean ± SD)	
V_{40} (%)	20.5 ± 20.5
V_{30} (%)	33.6 ± 24.2
V_{20} (%)	44.1 ± 30.0
V_{10} (%)	53.3 ± 33.0
V_5 (%)	61.0 ± 35.4
Mean dose (Gy)	18.6 ± 12.3

5-FU, 5-fluorouracil; ANC, absolute neutrophil count; BMI, body mass index; DVH, dose-volume histogram; Hgb, haemoglobin; Plt, platelet; PTV, planning target volume; SD, standard deviation; V_x , percentage of the total organ volume exceeding a radiation dose of x (Gy); WBC, white blood cell.

volumes (PTVs) were defined as follows: the CTV_{High} plus a 0.5–0.7-cm margin in all directions (PTV_{High}) and the CTV_{Low} plus a 0.5–0.7-cm margin in all directions (PTV_{Low}).

The simultaneous integrated boost intensity-modulated radiation therapy (IMRT) regimen was used for all patients. Treatment plans were generated using 6-MV or 10-MV photons (Eclipse Treatment Planning System; Varian Medical Systems Inc., Palo Alto, CA). The prescribed doses were 46–48 Gy for PTV_{High} (delivered in 23–24 fractions of 2 Gy/fraction) and 41.4–43.2 Gy for PTV_{Low} (delivered in 23–24 fractions of 1.8 Gy/fraction). The goals were to deliver the prescribed dose to $\geq 95\%$ of the PTV and deliver 95% of the prescribed dose to $\geq 99\%$ of the PTV, whilst meeting the following normal tissue constraints: (a) ≤ 45 Gy to the spinal cord, (b) lung $V_{20} \leq 30\%$, (c) mean lung dose ≤ 15 Gy and (d) mean heart dose ≤ 30 Gy. BM was not routinely used as an avoidance structure. A dose–volume histogram (DVH) parameter of V_x was defined as the percentage of the total organ volume exceeding a radiation dose of x (Gy). Radiotherapy administration was typically interrupted in cases of severe HT (ANC $< 1.0 \times 10^9/l$ and/or Plts $< 5.0 \times 10^7/l$) or persistent grade 3–4 digestive toxicity. However, there were no dose reductions following the identification of such toxicities.

Bone marrow delineation

The external contours of the whole chest bone were delineated on the planning CT scan as a proxy for the BM. The external contours were selected rather than the low-density regions within the bones, to ensure reproducibility and to minimize dependency of the contours on CT windowing and levelling. The whole chest bone contouring image was divided into five sections: (1) thoracic vertebrae (T1–T12), (2) ribs (1–12), (3) clavicles, (4) scapulae and (5) sternum. DVH data were collected for the whole chest, thoracic vertebrae V_{10-40} (TVV₁₀₋₄₀), ribs V_{10-40} (RV₁₀₋₄₀), clavicle, scapula and sternum V_{10-40} , in increments of 10%. Whole chest V_5 , TVV₅, RV₅, clavicle V_5 , scapula V_5 , sternum V_5 , mean whole chest bone dose, mean vertebral dose (MVD), mean rib dose (MRD), mean clavicle dose, mean scapula dose and mean sternum dose measurements were also collected.

Haematological toxicity evaluation

Haemoglobin (Hgb) and Plt counts, WBCs and ANCs were collected weekly (commencing 1 week before Day 1 of treatment through to the week after CRT for the WBCs and ANCs, or

90 days after CRT for the Hgb and Plt counts). These values were subsequently scored using the Common Terminology Criteria for Adverse Events (v. 4.0). The severest (*i.e.* highest grade) toxicity occurring during CRT was recorded. Additional end points of interest included the Hgb and Plt count, WBC and ANC nadirs during CRT.

Statistical analyses

All statistical analyses were conducted using Statistical Package for the Social Sciences for Windows, SPSS® software v. 21.0 (IBM Corp., New York, NY; formerly SPSS Inc., Chicago, IL). The Shapiro–Wilk test was performed to assess the normality of the haematological cell values. Non-normally distributed haematological values were log-transformed. Simple logistic regression models were used to test for associations between the DVH parameters and HT. Multivariate logistic regression models controlling for age, body mass index and the number of chemotherapy cycles were applied to test the effect of dosimetric parameters on HT. Receiver-operating characteristic (ROC) curves were used to evaluate cut-off values for DVH parameters to avoid HT.¹⁶ The discriminative power of the models was assessed by calculating the area under the ROC curves. The Kaplan–Meier method was used to calculate overall and disease-free survival, which were determined from the date of initiation of CRT to the date of last follow-up. All comparisons were evaluated using a *t*-test and a χ^2 or Fisher's exact test. A two-tailed probability *p*-value of < 0.05 was considered statistically significant.

RESULTS

Patient characteristics

A summary of the baseline characteristics of the 41 patients with EC treated with CRT is provided in Table 1. The median age at diagnosis was 58 years (range, 41–79 years). The majority of patients (92.6%; $n = 38$) had Stage III disease. The median follow-up duration was 31.9 months (range, 4.9–61.4 months).

Treatment compliance and outcomes

In the present study, all patients completed the radiotherapy; radiotherapy interruption occurred in 5 (12.2%) patients because of holidays (by 3 days for 2 patients) or severe HT (by 4 days for 3 patients). With regard to chemotherapy, 41 and 38 patients underwent the first and second cycles of chemotherapy, respectively (Table 2). For the first cycle of chemotherapy, all patients underwent chemotherapy without dose reduction. For the second cycle, eight patients had dose

Table 3. Frequency of haematological toxicities

Toxicity	CTCAE grade [<i>n</i> (%)]				
	0	1	2	3	4
Leukopenia	9 (22.0)	8 (19.5)	14 (34.1)	10 (24.4)	0 (0)
Neutropenia	18 (43.9)	7 (17.0)	13 (31.7)	3 (7.3)	0 (0)
Anaemia	2 (4.9)	20 (48.8)	13 (31.7)	6 (14.6)	0 (0)
Thrombocytopenia	19 (46.3)	18 (43.9)	3 (7.3)	1 (2.4)	0 (0)

CTCAE, Common Terminology Criteria for Adverse Events.
Grade 0 represents normal counts.

Table 4. Multiple logistic regression analysis of factors associated with leukopenia (grade ≥ 3) and neutropenia (grade ≥ 2)

Variable	Grade ≥ 3 WBC		Grade ≥ 2 ANC	
	Odds ratio (95% CI)	<i>p</i> -value	Odds ratio (95% CI)	<i>p</i> -value
Whole chest bone				
V_{40}	1.03 (0.93–1.14)	0.603	1.18 (1.03–1.36)	0.020
V_{30}	1.18 (1.01–1.37)	0.033	1.30 (1.09–1.54)	0.004
V_{20}	1.23 (1.04–1.46)	0.014	1.15 (1.03–1.28)	0.009
V_{10}	1.20 (1.04–1.37)	0.009	1.10 (1.02–1.18)	0.013
V_5	1.16 (1.04–1.30)	0.010	1.07 (1.01–1.14)	0.026
Mean dose	1.01 (1.00–1.02)	0.016	1.00 (1.00–1.01)	0.008
Thoracic vertebrae				
V_{40}	1.05 (0.97–1.14)	0.219	1.09 (1.01–1.16)	0.022
V_{30}	1.11 (1.02–1.21)	0.018	1.16 (1.05–1.27)	0.004
V_{20}	1.11 (1.02–1.21)	0.012	1.09 (1.03–1.16)	0.003
V_{10}	1.11 (1.02–1.20)	0.010	1.08 (1.03–1.14)	0.003
V_5	1.11 (1.02–1.21)	0.013	1.08 (1.03–1.14)	0.003
Mean dose	1.00 (1.00–1.01)	0.015	1.00 (1.00–1.01)	0.004
Rib				
V_{40}	1.08 (0.83–1.41)	0.564	1.29 (1.01–1.65)	0.041
V_{30}	1.22 (1.00–1.49)	0.047	1.23 (1.04–1.47)	0.018
V_{20}	1.23 (1.04–1.46)	0.015	1.11 (1.00–1.24)	0.062
V_{10}	1.66 (1.07–2.55)	0.022	1.08 (0.99–1.16)	0.067
V_5	1.20 (1.01–1.44)	0.040	1.05 (0.99–1.11)	0.110
Mean dose	1.01 (1.00–1.02)	0.010	1.00 (1.00–1.01)	0.010
Sternum				
V_{40}	0.99 (0.95–1.04)	0.868	1.04 (1.00–1.08)	0.073
V_{30}	1.00 (0.97–1.03)	0.976	1.03 (1.00–1.06)	0.040
V_{20}	1.03 (0.99–1.06)	0.173	1.04 (1.01–1.07)	0.016
V_{10}	1.09 (0.99–1.20)	0.074	1.05 (1.01–1.10)	0.013
V_5	1.20 (0.90–1.59)	0.221	1.05 (1.01–1.10)	0.020
Mean dose	1.00 (0.99–1.00)	0.275	1.00 (1.00–1.01)	0.010
Scapulae				
V_{40}	0.23 (0.00–0.28)	0.779	0.72 (0.33–1.54)	0.393
V_{30}	0.95 (0.77–1.18)	0.657	0.93 (0.78–1.10)	0.374
V_{20}	1.02 (0.94–1.10)	0.670	0.97 (0.91–1.05)	0.479
V_{10}	1.02 (0.97–1.08)	0.401	0.98 (0.93–1.03)	0.489
V_5	1.02 (0.97–1.06)	0.514	0.97 (0.93–1.01)	0.187
Mean dose	1.00 (0.99–1.00)	0.548	1.00 (0.99–1.00)	0.434
Clavicle				
V_{40}	1.02 (0.97–1.06)	0.509	1.01 (0.97–1.05)	0.533
V_{30}	1.02 (0.98–1.06)	0.345	1.00 (0.97–1.04)	0.890
V_{20}	1.02 (0.98–1.06)	0.277	1.00 (0.98–1.03)	0.920

(Continued)

Table 4. (Continued)

Variable	Grade ≥ 3 WBC		Grade ≥ 2 ANC	
	Odds ratio (95% CI)	<i>p</i> -value	Odds ratio (95% CI)	<i>p</i> -value
V ₁₀	1.02 (0.98–1.05)	0.314	1.00 (0.98–1.03)	0.901
V ₅	1.03 (0.98–1.04)	0.380	1.00 (0.98–1.02)	0.965
Mean dose	1.00 (1.00–1.00)	0.318	1.00 (0.99–1.01)	0.773

ANC, absolute neutrophil count; CI, confidence interval; V_x, percentage of the total organ volume exceeding a radiation dose of x (Gy); WBC, white blood cell.

reductions and three patients did not undergo chemotherapy because of HT. There were no treatment-related deaths before surgery. Surgery was performed in 41 (100%) patients. The median time between the end of CRT and surgery was 5.7 weeks (range, 3.6–7.9 weeks). The overall survival and disease-free survival curves for all patients are shown in [Supplementary Figure A](#). The median overall survival time was 40.9 months (95% CI, 29.9–51.9) and the 3-year survival rate was 50.9%. The median disease-free survival time was 35.0 months (95% CI, 17.8–52.2) and the 3-year disease-free survival rate was 42.7%.

Haematological toxicity

Descriptive characteristics of the key predictors and outcomes are presented in [Table 2](#). In total, 16 (39.0%) patients developed neutropenia (grade ≥ 2), 10 (24.4%) patients developed leukopenia (grade ≥ 3), 6 (14.6%) patients developed anaemia (grade ≥ 3) and 1 (2.4%) patient developed thrombocytopenia (grade ≥ 3) ([Table 3](#)). The median times to development of neutropenia (grade ≥ 2) and leukopenia (grade ≥ 3) were 4 weeks (range, 2–6 weeks) and 4 weeks (range, 3–6 weeks), respectively.

Dose-volume histogram parameters associated with a risk of haematological toxicity

Simple logistic regression analysis demonstrated that neutropenia (grade ≥ 2) and leukopenia (grade ≥ 3) were associated with increased irradiation doses to the whole chest bone, thoracic vertebrae, ribs and sternum. Conversely, for anaemia (grade ≥ 3) and thrombocytopenia (grade ≥ 3), there were no significant associations with irradiation dose in relation to these bones. When adjusting for age, body mass index and the number of chemotherapy cycles, multiple logistic regression analysis revealed that whole chest V_{5–30}, TVV_{5–30}, RV_{5–30}, mean whole chest bone dose, MVD and MRD were significantly associated with an increased leukopenia (grade ≥ 3) development risk ($p < 0.05$) ([Table 4](#)). Neutropenia (grade ≥ 2) development risk correlated with whole chest V_{5–40}, TVV_{5–40}, RV_{30–40}, sternum V_{5–30}, mean whole chest bone dose, MVD, MRD and mean sternum dose ($p < 0.05$).

Factors associated with haematological nadir

Simple linear regression analysis demonstrated that increased irradiation doses to the whole chest bone, thoracic vertebrae, ribs and sternum were negatively associated with the WBC and ANC nadirs. On multiple logistic regression analysis, DVH parameters of the whole chest bone, thoracic vertebrae, ribs and sternum correlated negatively with the WBC and ANC nadirs ([Table 5](#)). The regression coefficient (β) indicates the change in

WBC or ANC nadir for each unit of change in the dosimetric parameter. Adjusted R^2 measurements were highest for the model incorporating the MVD ($R^2 = 0.66$ and 0.58 for the WBC and ANC nadir, respectively).

Simple linear regression and multiple logistic regression analyses demonstrated that the log-transformed Plt nadir was negatively associated with DVH parameters of the thoracic vertebrae, ribs and sternum ([Supplementary Table A](#)). The majority of patients with EC in this study experienced thrombocytopenia (grade ≤ 1); only 1 (2.4%) patient experienced thrombocytopenia (grade ≥ 3) ([Table 3](#)). The clinical significance of the DVH parameters for the Plt nadir may be minimal. Hgb nadir was not associated with DVH parameters of thoracic bony structures on simple linear regression analysis.

Dose-volume histogram toxicity threshold for haematological toxicity

To identify optimal thresholds for dosimetric planning, we analyzed the ROC curves of the MVD, TVV₂₀ and TVV₁₀ for leukopenia (grade ≥ 3) ([Figure 1a–c](#)) and neutropenia (grade ≥ 2) ([Figure 1d–f](#)). The optimal cut-off values for avoiding leukopenia (grade ≥ 3) and neutropenia (grade ≥ 2) were as follows: an MVD of <25.9 Gy or <22.3 Gy, a TVV₂₀ of $<70\%$ or $<59\%$ and a TVV₁₀ of $<77\%$ or $<63\%$, respectively. These represent the DVH parameter values with the highest accuracy of predicting leukopenia (grade ≥ 3) and neutropenia (grade ≥ 2).

Patients receiving an MVD of ≥ 25.9 Gy (64.3 vs 3.7%; $p < 0.001$), a TVV₂₀ of $\geq 70\%$ (60.0 vs 4.0%; $p < 0.001$) and a TVV₁₀ of $\geq 77\%$ (64.3 vs 3.7%; $p < 0.001$) had increased risk of developing leukopenia (grade ≥ 3). Moreover, patients receiving an MVD of ≥ 22.3 Gy (69.6 vs 0.0%; $p < 0.001$), a TVV₂₀ of $\geq 59\%$ (68.2 vs 5.6%; $p < 0.001$) and a TVV₁₀ of $\geq 63\%$ (68.2 vs 5.3%; $p < 0.001$) had increased risk of developing neutropenia (grade ≥ 2).

DISCUSSION

To the best of our knowledge, this is the first study which addresses the issue of acute HT in patients with EC treated with CRT using simultaneous-integrated boost IMRT. We demonstrated that increasing irradiation doses to thoracic bones was associated with a risk of developing leukopenia and neutropenia, but not anaemia or thrombocytopenia. When analyzed by subsite, the thoracic vertebrae, ribs and sternum were significantly associated with acute HT. Other thoracic BM structures,

Table 5. Multiple linear regression analysis of factors associated with haematological nadir

Variable	WBC nadir			ANC nadir		
	β (95% CI)	<i>p</i> -value	Adjusted R^2	β (95% CI)	<i>p</i> -value	Adjusted R^2
Whole chest bone						
V_{40}	−0.057 (−0.102 to −0.128)	0.013	0.12	−0.047 (−0.076 to −0.018)	0.002	0.18
V_{30}	−0.078 (−0.107 to −0.050)	0.0001	0.44	−0.055 (−0.074 to −0.036)	0.0001	0.44
V_{20}	−0.071 (−0.094 to −0.475)	0.0001	0.49	−0.042 (−0.059 to −0.024)	0.0001	0.34
V_{10}	−0.063 (−0.085 to −0.040)	0.0001	0.45	−0.033 (−0.051 to −0.015)	0.001	0.24
V_5	−0.053 (−0.075 to −0.031)	0.0001	0.37	−0.026 (−0.043 to −0.009)	0.003	0.17
Mean dose	−0.0021 (−0.0027 to −0.0016)	0.0001	0.58	−0.001 (−0.002 to −0.0009)	0.0001	0.45
Thoracic vertebrae						
V_{40}	−0.044 (−0.070 to −0.018)	0.002	0.21	−0.032 (−0.050 to −0.015)	0.001	0.24
V_{30}	−0.044 (−0.057 to −0.031)	0.0001	0.55	−0.030 (−0.038 to −0.021)	0.0001	0.52
V_{20}	−0.041 (−0.052 to −0.030)	0.0001	0.61	−0.026 (−0.033 to −0.018)	0.0001	0.51
V_{10}	−0.041 (−0.052 to −0.030)	0.0001	0.61	−0.025 (−0.033 to −0.016)	0.0001	0.46
V_5	−0.041 (−0.052 to −0.031)	0.0001	0.61	−0.025 (−0.034 to −0.017)	0.0001	0.46
Mean dose	−0.001 (−0.002 to −0.0009)	0.0001	0.66	−0.0008 (−0.001 to −0.0006)	0.0001	0.58
Rib						
V_{40}	−0.094 (−0.210 to 0.022)	0.110	0.03	−0.080 (−0.157 to −0.002)	0.044	0.05
V_{30}	−0.086 (−0.154 to −0.018)	0.014	0.12	−0.057 (−0.103 to −0.011)	0.017	0.09
V_{20}	−0.077 (−0.121 to −0.033)	0.001	0.23	−0.038 (−0.070 to −0.005)	0.024	0.08
V_{10}	−0.052 (−0.087 to −0.017)	0.005	0.23	−0.020 (−0.046 to 0.006)	0.125	0.01
V_5	−0.031 (−0.058 to −0.005)	0.022	0.10	−0.011 (−0.030 to 0.008)	0.257	0.01
Mean dose	−0.002 (−0.003 to −0.001)	0.001	0.25	−0.001 (−0.002 to 0.0002)	0.016	0.10
Sternum						
V_{40}	−0.0017 (−0.0035 to 0.0001)	0.070	0.05	−0.014 (−0.026 to −0.002)	0.024	0.08
V_{30}	−0.014 (−0.027 to −0.002)	0.023	0.10	−0.011 (−0.019 to −0.003)	0.008	0.13
V_{20}	−0.021 (−0.033 to −0.009)	0.001	0.23	−0.014 (−0.022 to −0.006)	0.002	0.20
V_{10}	−0.028 (−0.040 to −0.016)	0.0001	0.37	−0.017 (−0.025 to −0.008)	0.0002	0.26
V_5	−0.031 (−0.043 to −0.018)	0.0001	0.37	−0.018 (−0.027 to −0.008)	0.0004	0.24
Mean dose	−0.0006 (−0.0009 to −0.0003)	0.0001	0.29	−0.0004 (−0.0006 to −0.0002)	0.0001	0.28
Scapulae						
V_{40}	0.120 (−0.029 to 0.269)	0.111	0.03	0.066 (−0.037 to 0.169)	0.201	0.01
V_{30}	0.028 (−0.022 to 0.076)	0.263	0.01	0.018 (−0.015 to 0.052)	0.278	0.02
V_{20}	0.011 (−0.018 to 0.040)	0.461	0.01	0.010 (−0.009 to 0.029)	0.324	0.03
V_{10}	0.003 (−0.019 to 0.025)	0.772	0.03	0.007 (−0.008 to 0.022)	0.354	0.03
V_5	0.002 (−0.015 to 0.020)	0.778	0.03	0.005 (−0.007 to 0.016)	0.414	0.04
Mean dose	0.0002 (−0.0006 to 0.0010)	0.614	0.03	0.0003 (−0.0003 to 0.0008)	0.369	0.03
Clavicle						
V_{40}	−0.007 (−0.026 to 0.012)	0.442	0.02	−0.005 (−0.018 to 0.007)	0.392	0.03
V_{30}	−0.006 (−0.022 to 0.009)	0.408	0.02	−0.004 (−0.014 to 0.007)	0.501	0.04

(Continued)

Table 5. (Continued)

Variable	WBC nadir			ANC nadir		
	β (95% CI)	<i>p</i> -value	Adjusted R^2	β (95% CI)	<i>p</i> -value	Adjusted R^2
V_{20}	-0.005 (-0.018 to 0.007)	0.410	0.02	-0.003 (-0.011 to 0.006)	0.542	0.04
V_{10}	-0.004 (-0.016 to 0.007)	0.439	0.02	-0.002 (-0.010 to 0.005)	0.535	0.04
V_5	-0.003 (-0.014 to 0.008)	0.549	0.03	-0.002 (-0.009 to 0.005)	0.615	0.05
Mean dose	-0.0001 (-0.0004 to 0.0002)	0.513	0.02	-0.0001 (-0.0003 to 0.0002)	0.565	0.04

ANC, absolute neutrophil count; CI, confidence interval; V_x , percentage of the total organ volume exceeding a radiation dose of x (Gy); WBC, white blood cell. β indicates linear regression coefficient (e.g. 1% increase in V_{20} corresponds to a reduction in WBC nadir of $0.041 \text{ k}\mu\text{l}^{-1}$).

such as the scapulae and clavicles, however, did not exhibit a significant association with acute HT. Increasing thoracic vertebrae dose exhibited the strongest association with the WBC and ANC nadirs. Although the ribs and sternum were also associated with the WBC and ANC nadirs, the adjusted R^2 values were low (Table 5).

In the present study, leukopenia (grade ≥ 3) frequency was similar to that noted in previous studies using cisplatin and 5-FU, but higher than the frequency reported by the Chemo-radiotherapy for Oesophageal Cancer Followed by Surgery Study trial, which administered carboplatin and paclitaxel.²⁻⁵ Discrepancies in leukopenia (grade ≥ 3) incidence are likely owing to the use of different chemotherapeutic agents. Bazan et al¹¹ reported that acute HT (grade ≥ 3) incidence was dependent on the type of chemotherapy administered in patients receiving pelvic IMRT and concurrent chemotherapy. Chemotherapy has a myelosuppressive effect; therefore, we conducted simple logistic regression analyses on this potential confounder. However, the number of chemotherapy cycles was not significantly associated with severe neutropenia ($p = 0.12$) or leukopenia ($p = 0.33$). Multiple logistic regression analysis demonstrated that irradiation dose to the thoracic bones alone was significantly associated with HT. This finding may emphasize the importance of limiting thoracic bony irradiation dose to avoid HT in patients undergoing thoracic radiotherapy.

Deek et al¹⁷ have determined the relationships between irradiation doses to the thoracic BM and declines in blood cell counts in patients with non-small-cell lung cancer treated with CRT. The DVH parameters associated with an increased risk of developing leukopenia (grade ≥ 3) were MVD, TVV₃₀ and TVV₂₀. The optimal cut-off values for avoiding acute HT were an MVD of ≤ 23.9 Gy, a TVV₂₀ of $\leq 56.0\%$ and a TVV₃₀ of $\leq 52.1\%$. In their study, it is possible that the thoracic vertebrae had the greatest impact on acute HT during thoracic irradiation, owing to its larger contribution to overall BM function (19.9%) than the sternum (2.9%), scapulae (3.8%) and ribs and clavicles (8.8%).¹⁴ However, in our study, there were slight differences in that not only the thoracic vertebrae, but also the RV₅₋₃₀ and MRD were associated with leukopenia (grade ≥ 3). In our study, all of the patients received IMRT as the radiotherapy technique, indicating that the low-dose irradiation (≤ 20 Gy) to the second most BM-producing structure (*i.e.* the ribs) is likely to impact

on acute HT in the IMRT era. We analyzed the ROC curves to determine the optimal cut-off values of the MRD and RV₁₀ for predicting leukopenia (grade ≥ 3) in the ribs. The optimal cut-off values for avoiding leukopenia (grade ≥ 3) in the ribs were an MRD of ≤ 8.7 Gy and an RV₁₀ of $\leq 32\%$. These represent DVH parameter values with the highest accuracy of predicting leukopenia (grade ≥ 3) in the ribs. However, the area under the ROC curves was higher for the DVH parameter values of the thoracic vertebrae than that of the ribs (0.89 and 0.79 for the MVD and MRD, respectively). These findings suggested that the most accurate dosimetric constraints used for avoiding leukopenia (grade ≥ 3) were associated with the thoracic vertebrae. However, the dosimetric constraints of the ribs should also be taken into consideration. Moreover, our data revealed higher cut-off values for the MVD and TVV₂₀ than those reported by Deek et al.¹⁷ Several differences between the two studies included the cancer type, chemotherapeutic agents, irradiation doses and techniques, as well as thoracic vertebrae delineation. In our study, we delineated thoracic vertebrae from T1-T12 rather than T1-T10, which may lead to the determination of differing cut-off values. Given that the incidence of acute HT (grade ≥ 3) is dependent on the type of chemotherapy, we postulated that different irradiation dose thresholds may need to be considered under different treatment settings. From our findings, dose constraints of MVD < 25.9 Gy, TVV₂₀ $< 70\%$ and TVV₁₀ $< 77\%$ should be considered in patients with EC being treated with CRT, especially when cisplatin and 5-FU are used as chemotherapeutic agents.

Incorporation of the optimal cut-off values determined in this study into IMRT planning may be beneficial in avoiding acute HT (grade ≥ 3) and therefore in increasing the therapeutic ratio for patients with EC. The most commonly used radiotherapy technique in previous randomized trials has been three-dimensional conformal radiation therapy (3D-CRT). Data regarding the impact of different radiotherapy techniques on acute HT have been limited in patients with thoracic cancer. In a retrospective review, Deek et al¹⁷ reported no statistically significant differences in the WBC nadirs among patients treated with 3D-CRT, IMRT or 3D-CRT/IMRT. Roeder et al¹⁸ have also reported on their experience of using IMRT and concurrent systemic chemotherapy as a definitive treatment for locally advanced EC. In this trial, acute HT (grade ≥ 3) occurred in 25.9% of patients. ECs treated with IMRT and concurrent systemic

Figure 1. Receiver-operating characteristic curves for leukopenia [grade ≥ 3 ; (a) mean vertebral dose (MVD), (b) thoracic vertebrae V_{20} (TVV₂₀) and (c) thoracic vertebrae V_{10} (TVV₁₀)] and neutropenia [grade ≥ 2 ; (d) MVD, (e) TVV₂₀ and (f) TVV₁₀]. V_x indicates the percentage of the total organ volume exceeding a radiation dose of x (in gray). The arrows indicate the cut-off values that represent the highest accuracy of predicting leukopenia (grade ≥ 3) and neutropenia (grade ≥ 2).

chemotherapy in these trials have not exhibited higher rates of acute HT as compared with those detected in studies, such as the Cancer and Leukaemia Group B 9781 study, in which only 3D-CRT was used. For pelvic malignancies, BM-sparing IMRT/intensity-modulated proton therapy using specific dose constraints of the BM had theoretic benefit through dosimetric analysis.^{19–22} Desai et al²³ demonstrated that BM-sparing IMRT reduced acute HT in patients with pelvic malignancies. For current IMRT treatment of thoracic malignancies, specific dose constraints of the BM were not followed, as none have been set. Furthermore, Nichols et al²⁴ have demonstrated that when taken into consideration during pre-treatment planning, proton therapy can help reduce irradiation doses to the BM compared with 3D-CRT or IMRT in thoracic malignancies. BM-sparing IMRT/intensity-modulated proton therapy has the potential advantage of avoiding acute HT (grade ≥ 3). Our study has determined thresholds for BM toxicity in patients with EC treated with CRT. However, given the lack of clinical data that consider BM constraints, further studies are warranted.

There are several limitations of this study: (1) the data were derived from a retrospective cohort; (2) all of the patients in this study were diagnosed with EC, so whether our findings are specific to this disease is uncertain; and (3) we assumed that different BM irradiation dose constraints should be considered for different chemotherapeutic agents in CRT. However, we could not establish this definitively because all of the patients in this study received cisplatin. Further prospective studies would be desirable in confirming our findings.

CONCLUSION

In conclusion, we determined that a higher irradiation dose to the thoracic vertebrae and ribs during CRT is associated with an increased risk of developing acute HT. IMRT/intensity-modulated proton therapy with BM sparing may reduce the incidence of acute HT and improve the therapeutic ratio or outcomes in patients with EC treated with CRT. Further prospective studies to identify appropriate dosimetric constraints in thoracic malignancies are necessary.

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