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FULL PAPER

Acute hematological toxicity during post-operative bowel sparing image-guided intensity modulated radiation with concurrent cisplatin

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Objective To report acute hematological toxicity (HT) in patients receiving post-operative bowel sparing intensity-modulated radiotherapy (IMRT) and cisplatin and its dosimetric predictors.

Methods Clinical database of Phase III trial (NCT01279135), that randomized patients to post-operative conformal or intensity modulated radiation therapy, was searched to select patient strata that received bowel sparing IMRT (50 Gy/25#/5 wks) and concurrent cisplatin (40 mg m⁻²). Pelvic bone marrow (BM) was retrospectively delineated in two sets: whole bone (WB), and freehand (FH) inner cavity of bone. Dose volume histograms (DVH) of BM were obtained. Receiver operating characteristic (ROC) curve identified DVH thresholds that predicted for Grade ≥ II HT with highest specificity. Univariate and multivariate analysis was performed.

Results Overall 75 patients received concurrent cisplatin. Grades I–V HT was observed in 38.7%, 42.7%, 14.7%, 0%, and 0% patients, respectively. Grade ≥ II leucopenia, neutropenia, anemia, and thrombocytopenia were observed in 26%, 40%, 26.5%, and 1.4% respectively. None of the HT resulted in treatment break. On univariate analysis, whole pelvis+ lumbar FH V30 >55%

& V40 >35%, whole pelvis WB and FH V40 > 35%, and lower pelvis WB and FH V40 >20% correlated for Grade ≥ II leucopenia and neutropenia. None of the BM dose volume constraints predicted for overall HT or neutropenia on multivariate analysis.

Conclusion The IMRT arm of NCT01279135 (PARCER study) that employed strict bowel constraints had unintentional but desirable BM sparing. None of the BM subvolume DVH parameters could be validated on multivariate analysis.

Advances in knowledge The prospective study reports feasibility of bone marrow sparing with bowel sparing post-operative pelvic IMRT and concurrent chemotherapy for cervical cancer. The present study reports low incidence of hematological and gastrointestinal toxicity during post-operative chemoradiation with IMRT. As both whole bone and freehand pelvis BM contours predicted for HT, hence an easier method of whole bone contouring should continue to be used till further validation of more specific BM subvolumes becomes available. The study results highlight the need for further research into dose volume constraints during post-operative IMRT.

INTRODUCTION

Radiation is an integral component of treatment of cervical cancer in both definitive and adjuvant setting.^{1,2} Post-operative radiation with or without concurrent chemotherapy has shown to improve outcomes in patients with intermediate or high-risk features.^{2–4} The addition of platinum-based chemotherapy in both radical and adjuvant setting improves

disease-free and overall survival, albeit at the cost of higher acute hematological and gastrointestinal toxicity.^{5–7} Early data also suggests that cumulative cisplatin dose during concurrent chemoradiation may impact outcomes.⁸

Chemoradiation for locally advanced cervical cancer is associated with high rates of acute Grade ≥ 3 hematological

toxicity (HT) of 23–48% particularly leucopenia and neutropenia.^{2,9–12} Conventional treatment portals include the pelvic bones, lumbar vertebrae, and femoral heads, which constitute about 50% of the functional bone marrow (BM) reserve.^{13,14} Intensity-modulated radiotherapy (IMRT) reduces dose to bowel, bladder, and rectum and has the potential to reduce the volume of BM irradiated.^{15–17} While some research studies investigating relationship between BM irradiation and HT have reported that volume of BM receiving 10 and 20 Gy may correlate $\geq$ Grade II with neutropenia and leucopenia,^(18, 19) other groups including ours have suggested that exposing large volumes of BM to 40 Gy may predict for increased HT.^{18,19}

The international multicenter Phase II clinical trial of BM sparing IMRT in cervical cancer (INTERTECC) that was designed with a primary endpoint of reducing acute Grade $\geq$ III neutropenia or Grade $\geq$ II diarrhea or any $\geq$ Grade III acute gastrointestinal (GI) toxicity with use of BM sparing IMRT, reported a combined primary event rate of 26% as compared to 40% in historical data.²⁰ The overall Grade $\geq$ II HT was 79.5%. While $\geq$ Grade III acute neutropenia was almost similar (19.4 and 22.2%) in radical and post-operative arm, the incidence of clinically significant GI toxicity was higher in postoperative cohort (9.7% 27.3%).²⁰ A study validating dose volume constraints for acute GI toxicity in patients undergoing post-operative IMRT (with or without concurrent chemotherapy) within context of Phase III bowel sparing IMRT trial reported Grade $\geq$ III acute GI toxicity in 9.4% of patients which was lower than INTERTECC trial.²¹ Therefore, it is unclear if simultaneous sparing of BM and bowel is feasible in patients undergoing post-operative IMRT. The present study was therefore undertaken to report the rates of HT in cervical cancer patients undergoing bowel sparing rotational IMRT (tomotherapy) and concurrent cisplatin and to explore the dosimetric parameters that correlate with HT.

METHODS AND MATERIALS

The clinical database of a Phase III trial (NCT01279135) that randomizes cervical cancer patients to receive post-operative IMRT (helical tomotherapy) and Three dimensional conformal radiation therapy to reduce late bowel toxicity was reviewed to select patient strata that received treatment on tomotherapy (50 Gy/25 fractions/5 wks) with concurrent cisplatin (40 mg m⁻²) from January 2011 to June 2016. Tomotherapy is a form of rotational IMRT with 360 degrees of freedom for radiation delivery. The process of radiation simulation, contouring, and planning has been published.²² The IMRT planning was aimed at restricting V15 and V40 small bowel (individual loops) to $\leq$ 200 and $\leq$ 100 cc respectively. No prospective BM constraints were applied. In patients with creatinine clearance between 40 and 50 ml min⁻¹, a 20–25% chemotherapy dose reduction was applied and chemotherapy was stopped in case of any Grade $\geq$ III HT.

As a part of ongoing trial, acute HT and GI toxicity was prospectively captured using common toxicity criteria for adverse events v. 3.0. All patients receiving concurrent chemotherapy were monitored weekly with complete blood count during radiation. The database was reviewed to determine the grades of anemia, leucopenia, neutropenia and thrombocytopenia, and

acute GI toxicity. The worst grade of acute HT was recorded. In addition, grade of acute GI toxicity was also determined across objective and subjective GI subscales (nausea, vomiting, diarrhea, bloating, abdominal pain) of common toxicity criteria for adverse events v. 3.0. HT was recorded up to 8 weeks from initiation of chemoradiation.

As no prospective BM dose constraints were applied, IMRT plans were dearchived and exported to eclipse planning station (Varian medical systems, Palo Alto, CA, v. 8). BM delineation was performed on the eclipse planning station. The pelvic BM was delineated in two sets: whole bone (WB), and freehand (FH) inner cavity of bone from top of L3 vertebra to bottom of ischial tuberosity using previously described methods.^{19,23} The external contours of the bone were delineated as WB contours using auto-segmentation.^{18,23} FH contours included the low density regions inside the bone and were delineated by adjusting the window to bone range (Window width: 1800 HU, Level: 400 HU).¹⁹ The entire contouring was done by two radiation oncologists (SL and PN) and verified by senior radiation oncologist (SC). Various BM subvolumes namely whole pelvis +lumbar (WPL), lumbar vertebra, sacrum, ilium, ischium, femoral head and neck (FHN), whole pelvis (WP), lower pelvis (LP) (includes ischium and FHN) were contoured in both sets. Tomotherapy plans were imported on Eclipse planning station and overlaid on the contours to estimate dose volume parameters. The total volume, mean and median dose, volume receiving 5 Gy, 10 Gy, 20 Gy, 30 Gy, and 40 Gy was estimated for each of the subvolumes in both WB and FH set of contours.

Statistics

SPSS v. 20 was used for statistical analysis. Overall, acute HT was categorized to two groups, Grade 0–1 and Grade $\geq$ II. Similar categorization was performed for anemia, leucopenia, neutropenia, and thrombocytopenia. The sensitivity and specificity of dose volume characteristics to predict for HT was assessed using receiver operating characteristic (ROC) curve. The ROC curve was used to identify dose volume histogram (DVH) thresholds that predicted for Grade $\geq$ II HT toxicity with highest specificity. All data was dichotomized across these cut-offs and univariate analysis (chi-square test) for overall Grade $\geq$ II and Grade $\geq$ III toxicity was performed. Similar analysis was also undertaken for each of the BM components (anemia, leucopenia, neutropenia, and thrombocytopenia). Multivariate analysis was performed with binary logistic regression for dose volume characteristics significant on univariate analysis. A two-sided *p* value of < 0.05 was considered significant. No statistical corrections were applied for multiple tests.

RESULTS

Patient characteristics

The study cohort of patients randomized to tomotherapy arm (*n* = 94) were evaluated to identify patients who received concurrent chemoradiation (*n* = 75). The clinical and tumor characteristics of patients are shown in Table 1. All patients received the planned dose of IMRT (50 Gy/25 fractions). The median age of cohort was 48 years [interquartile range (IQR) 42–55]. All except one patient received cisplatin-based chemotherapy. One patient

Table 1. Clinical characteristics ($n = 75$)

Surgical procedure	
Simple hysterectomy	45 (60%)
Modified radical hysterectomy	30 (40%)
Histology	
Squamous	51 (68%)
Adenocarcinoma	24 (32%)
Chemotherapy	75/ 95
Chemotherapy agent	
Cisplatin	74 (98.5%)
Carboplatin	1 (1.5%)
Median no of cycles (range)	5 (1-6)
Cycles of Cisplatin	
1	1 (1.3%)
2	2 (2.5%)
3	1 (1.3%)
4	18 (24%)
5	52 (69.5%)
6	1 (1.3%)

received carboplatin due to low glomerular filtration rate of 50. The median of five chemotherapy cycles were delivered. [Range 1–6, Median: 5 (IQR 4–5)]. Overall 95% of patients received four or more cycles. Four patients received less than four cycles of chemotherapy (three due to nephrotoxicity and one due to poor compliance). Of the 71 patients, who received more than four cycles of chemotherapy, 5 patients required dose reductions to 75–80% of the planned dose (4 due to nephrotoxicity and 1 due to gastrointestinal toxicity). The fifth chemotherapy cycle was withheld in seven patients due to potential for Grade $\geq$ III HT.

Dose volume parameters

On comparing BM delineation techniques, the FH subvolumes were 25–47% of WB subvolumes. The mean volume for WP for WB contours was 872 cm³ (349–1219 cm³) as compared to FH

contours of 373 cm³ (212–766 cm³), which accounted for 44% of the whole BM contour volume. The difference was statistically significant ($p < 0.05$). A similar difference in volumes was observed for all subvolumes as shown in Table 2. The mean V10, V20, V30, and V40 for WP on WB and FH were 94%, 80%, 60%, and 36%, and 93%, 77%, 60%, and 36%, respectively. The V30, V40 of sacrum and ischium was high due to proximity to the planned target volume. The V30 of ilium was also high likely due to the lateral dose spillage for sparing the bowel. The DVH parameters of all subsites are shown in Supplementary table 1.

The median V15, V40 of small bowel was 200 cc (IQR 165–240) and 65 cc (IQR 39–97) respectively. Overall 75% of patients had body mass index of less than 25. The V15 and V40 of bowel bag was 952cc (IQR 767–1206) and 363 cc (IQR 248–452) respectively.

Acute toxicity

At baseline, Grade 1 and Grade 2 anemia was seen in 36 (48%) and 3 (4%) patients respectively. The number (%) of patients developing any grade of acute anemia, leukopenia, neutropenia, and thrombocytopenia were 63 (84%), 61 (81%), 60 (80%), and 41 (54.7%), respectively. Majority of the HTs were Grade I. Overall Grade I–V HT was seen in 38.7%, 42.7%, 14.7%, 0 and 0% patients, respectively. Grade $\geq$ III anemia, leukopenia, neutropenia, and thrombocytopenia were observed in 6.5%, 5%, 11%, and 0%, respectively. (Table 3) None of the HT resulted in treatment break.

Overall, Grade $\geq$ II and Grade $\geq$ III GI toxicity was observed in 49 (51.5%) and 10 (10.5%) patients. Grade $\geq$ II and Grade $\geq$ III diarrhea was observed in 28 (29.5%) and 4 (4.2%) patients respectively.

Correlation of HT with DVH parameters

On univariate analysis for FH contours, FHN V30 predicted for overall Grade $\geq$ III HT. None of the subvolumes predicted for overall Grade $\geq$ II HT. WPL V30 $>55\%$, V40 $>35\%$, WP V40 $>35\%$, and LP V40 $>20\%$ strongly correlated for Grade $\geq$ II leucopenia and neutropenia. FHN V30 and V40 predicted for Grade $\geq$ II leucopenia, Ilium V40 $>30\%$ predicted for Grade $\geq$ II

Table 2. Volume characteristics

Volume	Whole bone (W) mean (range) cm ³	Freehand-bone cavity (FH) mean (range) cm ³	FH/W $\times$ 100 (%)
Whole pelvis + lumbar	1034 (733–1487)	410 (237–657)	39.6%
Whole pelvis	872 (349–1219)	373 (212–766)	43.8%
Lumbar spine	164 (85–273)	42 (13–78)	25.6 %
Sacrum	172 (20–262)	68 (22–164)	39.5 %
Ilium	286 (183–662)	130 (26–213)	45.4%
Lower pelvis	405 (289–565)	166 (100–285)	41 %
Ischium	192 (35–285)	71 (36–122)	36.9%
Femoral head and neck	199 (28–284)	93 (12–161)	46.7%

FH, freehand;

Table 3. Acute hematological toxicity ($n = 75$)

Toxicity	Anemia	Leukopenia	Neutropenia	Thrombocytopenia	Overall hematological toxicity
Grade 0	12 (16%)	14 (19%)	15 (20%)	34 (45.3%)	3 (4%)
Grade I	43 (57.5%)	41 (55%)	30 (40%)	40 (53.3%)	29 (38.7%)
Grade II	15 (20%)	16 (21%)	22 (29%)	1 (1.4%)	32 (42.7%)
Grade III	5 (6.5%)	4 (5%)	8 (11%)	–	11 (14.6%)
Grade IV	–	–	–	–	–

neutropenia, and LP V20 >55% predicted for Grade $\geq$ II anemia. (Supplementary table 2)

On univariate analysis for WB contours, none of the subvolumes predicted for overall Grade $\geq$ III HT. WP V20 >75% and FHN V40 >5% correlated with Grade $\geq$ II HT. The subvolumes predictive of Grade $\geq$ II leukopenia were WPL V30, WP V40, LP V40, ischium V40, and FHN V40. The subvolumes predictive of Grade $\geq$ II neutropenia were WP V40, LP V40, ilium V40, and FHN V40. Ilium V20 >90% was predictive of Grade $\geq$ II anemia. (Supplementary table 3)

The established parameters from existing data like WP V10 <90%, WP V20 <80%, WP V40 $\leq$ 37%, and WP median dose $\leq$ 34.2 Gy (both whole bone and freehand) were assessed for the toxicity end points. None of them were predictive on univariate analysis.

On multivariate analysis, only WB Ilium V20 >90% was predictive of Grade $\geq$ II anemia. FH WP V40 >35% showed a trend to significance for Grade $\geq$ II neutropenia ($p = 0.057$). None of the other whole bone or freehand subvolumes predicted for either overall HT or neutropenia. (Tables 4 and 5)

DISCUSSION

High incidence of $\geq$ Grade III HT (23–48%) have been reported in the early randomized trials of concurrent chemoradiation in locally advanced cervical cancer patients treated with conventional portals.^{9–12} In post-operative setting, Peters *et al* noted that about 74% developed Grade $\geq$ II and higher leukopenia in patients receiving chemoradiation.² Gonzalez *et al* compared cisplatin with the combination of cisplatin and gemcitabine concurrent with pelvic RT.²⁴ Although higher response rates were noted with doublet chemotherapy, a significantly higher incidence of $\geq$ Grade III leukopenia (60% *vs* 17.5%) and

Table 4. Multivariate analysis of bone marrow (freehand) contours with toxicity

Toxicity	Volume	Percentage	Odd ratio (95% CI)	<i>p</i> value
Any HT Grade 2 and above	WP + LS V30	>55%	1.2 (0.27–5.9)	0.75
	WP + LS V40	>35%	0.46 (0.04–4.6)	0.51
	Ilium V20	>90%	1.43 (0.45–4.5)	0.53
	WP V40	>35%	3.9 (0.32–46.2)	0.28
Any HT Grade 3 and above	LP V20	>55%	0.48 (0.04–4.8)	0.54
	FHN V5	>99%	0	0.99
	FHN V30	>10%	0.18 (0.01–2)	0.16
	FHN V40	>1.5%	0.9 (0.13–6.04)	0.91
Hemoglobin Grade 2 and above	LS V40	>23%	0.36 (0.11–1.14)	0.08
	LP V20	>55%	3.2 (0.61–17.4)	0.16
	FHN V20	>30%	1.2 (0.3–5.09)	0.75
WBC Grade 2 and above	WP + LS V30	>55%	0	0.99
	WP + LS V40	>35%	0.34 (0.04–2.44)	0.28
	WP V40	>35%	7.33 (0.69–77.2)	0.09
	LP V40	>20%	1.4 (0.34–6.02)	0.60
Neutrophil Grader 2 and above	WP + LS V30	>55%	2.46 (0.31–19.2)	0.38
	WP + LS V40	>35%	0.34 (0.03–3.49)	0.36
	WP V40	>35%	11.96 (0.93–153.8)	0.057
	LP V40	>85%	1.03 (0.27–3.8)	0.96

FHN, femoral head and neck ; HT, hematological toxicity ; LP, lower pelvis; WP, whole pelvis;WB, whole bone; WBC, white blood cells;

Table 5. Multivariate analysis of whole bone contours with toxicity

Toxicity	Volume	Percentage	Odds ratio (95% CI)	P value
Any HT Grade 2 and above	WP +LS V20	>70%	3.2 (0.3–34.6)	0.32
	WP V20	>75%	0.08 (0.005–1.3)	0.08
	WP V30	>60%	1.04 (0.28–3.7)	0.94
	FHN V40	>5%	0.33 (0.11–1)	0.051
Any HT Grade 3 and above	WP + LS V30	>55%	2.3 (0.14–39.5)	0.54
	WP V30	>60%	2.3 (0.15–36.3)	0.54
	FHN V30	>15%	1.5 (0.18–12.9)	0.68
	FHN V40	>5%	1.68 (0.2–14.08)	0.63
Hemoglobin Grade 2 and above	Ilium V20	>90%	7.15 (1.6–30.3)	0.008
	LP V5	>99%	0.27 (0.06–1.12)	0.07
	LP V40	>25%	0.50 (0.06–3.8)	0.51
	Ischium V40	>45%	0.65 (0.09–4.2)	0.65
WBC Grade 2 and above	WP + LS V30	>55%	2.02 (0.35–11.6)	0.42
	WP V40	>35%	4.7 (0.79–27.8)	0.08
	LP V40	>25%	0.22 (0.02–2.63)	0.23
	Ischium V40	>45%	2.6 (0.39–17.7)	0.31
	FHN V 40	>5%	5.7 (0.98–33.3)	0.05
Neutrophil Grade 2 and above	WP V40	>35%	3.38 (0.6–17.4)	0.14
	Ilium V40	>25%	1.5 (0.36–6.5)	0.57
	LP V40	>25%	0.63 (0.13–3.009)	0.56
	FHN V40	>5%	2.6 (0.69–10.2)	0.15

HT, hematological toxicity ; WP, whole pelvis; LP, lower pelvis;LS, lumbar spine; WBC, white blood cells;

neutropenia (25% vs 17.5%) was noted. The Grade III-IV HT was higher in the multiagent chemotherapy arm (72% vs 24%). Patients receiving multiagent chemotherapy also had a lesser likelihood of completing the planned number of cycles (63% vs 82%). As distant metastasis continue to be one of major sites of failure, ongoing Phase III trials are evaluating platinum-based consolidation chemotherapy after chemoradiation in both post-operative and definitive settings and it is prudent to investigate radiation techniques that minimize radiation dose to both bowel and bone marrow.^{25–27}

In recent years, post-operative IMRT has been investigated for reducing acute and late toxicity following pelvic radiation.¹⁵ In RTOG 0418, the incidence of Grade III HT was 25% in patients with cervical cancer who received chemoradiation.¹⁸ INTERTECC-2 reported reduced rates of HT particularly Grade ≥ III neutropenia after adjuvant chemo-radiation (22.2%).²⁰ However, the acute GI toxicity was higher in post-operative cohort (27.3%). Unlike INTERTECC-2, that primarily used constraints for minimizing high dose in bowel (V45 <200 cc), the present study employed strict bowel constraints for both low dose (V15 <200 cc) and high dose (V40 <100 cc) regions. Therefore it's likely that minimizing low dose spillage in bowel was also associated with unintentional BM sparing and hence the reduced rates of both BM and HT. Though the compliance to four or more cycles of concurrent chemotherapy was >95% in the present study, the lower rates

of Grade ≥ III HT within our cohort could be attributed to omission of fifth cycle of chemotherapy in seven patients in anticipation of higher grade of HT. Nevertheless, even if all these patients progressed to develop a higher clinical grade of HT the rate of BM toxicity would be no more than that observed in RTOG 0418 and INTERTECC-2 suggesting that in post-operative setting simultaneous sparing of bowel and BM is feasible and that may result in reduced hematological and gastrointestinal toxicity.

For implementing marrow sparing post-operative IMRT, WB contouring assumes WB as a surrogate for BM.²³ This can be autocontoured and is more reproducible. This has been used in majority of the trials exploring BM sparing IMRT. However, this includes significant quantity of bone that does not contain active BM therefore reducing precision of BM sparing IMRT planning. Active BM can be better delineated with advanced imaging like single photon emission CT, fluoro-thymidine positron emission tomography (PET) and MRI. With lack of easy access to these advanced imaging, FH contouring has been explored as a surrogate for active BM.¹⁹ In the present study, although FH volumes strongly correlated for grade ≥ II leucopenia and neutropenia on univariate analysis, none of the factors were significant on multivariate analysis and FH and WB showed similar results. Thus, WB remains as a surrogate for BM. Further studies exploring active BM delineated with PET and MRI and its correlation with planning CT are needed.

Though our study represents largest post-operative cohort of cervical cancer patients, it has few limitations. This is an unplanned exploratory analysis from patients recruited on the IMRT arm of a Phase III trial that investigates bowel sparing. There is also a risk of significant findings by chance due to the multiple comparisons. While we could not validate any of the established or hitherto identified BM dose volume constraints for reducing HT, the emerging clinical and toxicity data on PET-based BM sparing IMRT is encouraging and shows even further reduction in hematological

toxicity.²⁰ This may suggest that BM constraints may require either independent validation in other data sets or further evolution and is a subject of research in ongoing BM sparing studies.

CONCLUSION

The chemo-IMRT cohort of NCT01279135 that employs strict bowel constraints had unintentional dosimetrically desirable BM sparing. This was associated with low absolute rates of both GI and hematological toxicity.

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