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ORIGINAL RESEARCH

A Phase II prospective nonrandomized trial of magnetic resonance imaging-guided hematopoietic bone marrow-sparing radiotherapy for gastric cancer patients with concurrent chemotherapy

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Purpose: This study aimed to spare hematopoietical bone marrow (BM) identified by magnetic resonance (MR) radiation in order to alleviate acute hematologic toxicity (HT) for gastric cancer patients treated with postoperative chemoradiotherapy (CRT).

Methods: A prospective, open-label, single-arm Phase II study (Clinicaltrials.gov; NCT 01863420) was conducted in 25 patients with gastric cancer who were eligible for postoperative concurrent CRT. The MR images of vertebral body T8-L4 were fused with images of simulating computed tomography. Hematopoietical BM was contoured according to the MR and spared in radiotherapy plan. The CRT regimen consisted of daily capecitabine (1600 mg/m^2/d) and 45 Gy of radiation at 1.8 Gy per day. Primary endpoints were grade ≥3 HT that occurred within 2 months of initiation of CRT. The relationship between HT and dose–volume of BM was estimated by multivariable linear regression model.

Results: Twenty four patients (96%) had T3–4 disease and 22 (88%) had disease with node positive. The median age was 53 years (range, 28–73 years). Before concurrent CRT, adjuvant chemotherapy was administered with a mean cycle of 4.3±0.5. Only five patients (20%) developed grade 3–4 HT during treatment, among whom two (8.0%) patients experienced grade 3–4 leucopenia, two (8.0%) experienced neutropenia, and two (8.0%) experienced thrombocytopenia, respectively. None of the patients showed grade 3–4 anemia. Multivariable linear regression revealed increased BM-V5 (P=0.03) and BM-V20 (P=0.002) were found to be significantly associated with decreased white blood cells nadirs in multivariable regression; increased BM-V20 (P<0.001) with decreased absolute neutrophil count nadirs, increased BM-V30 (P=0.002) and volume of BM (P=0.001) with decreased platelet count nadirs.

Conclusion: Irradiation of active BM identified by MR is associated with HTs. Techniques to limit low-dose radiation, especially V20, to BM could reduce HT in gastric cancer patients.

Keywords: gastric cancer, radiotherapy, magnetic resonance, bone marrow, hematologic toxicity

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Introduction

As the outcomes for patients with locally advanced gastric cancer are still suboptimal, concurrent chemotherapy with external beam radiotherapy is the standard adjuvant treatment,[1,2] especially in patients with T3–4 tumors and/or tumor-positive lymph nodes. Despite improved therapeutic results, acute hematologic toxicity (HT) is common with this regimen.[3–5]

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However, both radiation and chemotherapy are myelosuppressive and approximately 50% of the body's hematopoietically active (red) bone marrow (BM) is located in the pelvic bones and lower spine,[6–10] which is surrounding the area of radiotherapy (RT) in rectal and gastric cancers. For gastric cancer patients receiving RT alone, severe HT is rare during RT course, as unirradiated active BM could compensate to increasing hematopoiesis. When concurrent chemotherapy is added to RT as standard treatment, however, additional BM injury and myelosuppression increased HT to grade ≥3, 30–54%,[1,2,11] because of myelosuppression of unirradiated active BM. Despite predisposing patients to more risk of infection and hospitalization, HT can also lead to delayed RT and missed chemotherapy cycles, which might compromise disease control. Thus, control of HT is important for concurrent chemoradiotherapy (CRT).

The application of highly conformal RT techniques, such as intensity-modulated radiation therapy (IMRT), is one strategy to reduce BM irradiation. Several studies have examined IMRT with respect to spare BM irradiation and HT in gynecologic and other cancers.[12–21] However, the effect of vertebra active BM-sparing (BMS) IMRT (BMS-IMRT) plans to reduce HT has never been investigated in gastric cancer patients.

Therefore, we have planned to spare the active BM identified by T1-weighted magnetic resonance (MR) in the RT planning process[7,22–25] in order to reduce the grade ≥3 HT to 25%.

Materials and methods

We conducted a prospective, single-arm Phase II study in patients with histologically proven adenocarcinoma of the stomach and who were in need of a postoperative concurrent CRT. This study was approved by the Institutional Ethic Committee of Cancer Hospital & Institute, Chinese Academy of Medical Sciences (CAMS). We obtained written informed consent from all the enrolled patients. (Clinicaltrials.gov: NCT 01863420).

Eligibility criteria

Patients who met the criteria to receive the postoperative CRT were recruited for the study. The eligibility criteria of postoperative CRT were as follows: histologically confirmed adenocarcinoma of the stomach; cancer resected without residual disease (R0 gastrectomy), at least a D1 lymph-node dissection; T3–4 any N0 M0 or any TN+ M0 according to seventh edition of the American Joint Committee on Cancer TNM Classification; at least four cycles of adjuvant chemotherapy; >18 years and ≤75 years old; a performance status of 1 or lower according to Eastern Cooperative Oncology Group (ECOG) criteria; adequate function of major organs (including cardiac, hepatic, and renal functions), adequate bone marrow function (hemoglobin [Hb] >11 g/dL; absolute neutrophil count [ANC] ≥2,000/μL; platelet count ≥100,000/μL; leukocyte count ≥4,000/μL); caloric intake greater than 1,500 kcal/day by oral route; treatment beginning no later than 4 weeks after the last cycles of chemotherapy; and no previous abdominal radiation and no history of any other tumors except for basal cell carcinoma of the skin and carcinoma in situ of the uterine cervix.

Active BM delineation and treatment planning

Before 1 week of computed tomography (CT) simulation (CT-sim), all patients underwent MR scanning. Then the active BM was contoured as organ at risk (OAR) on the MR images and fused with CT-sim images. The procedures of active BM identification and targets delineation are as follows.

Simulation

Patients were required to fast for 4 hours and take an oral positive contrast (300 mL) 30 minutes before CT-sim to make the small intestine visible. To decrease variability in distention due to gastric filling, a standard meal (300 mL of ready-to-eat canned porridge) was given to the patients 15 minutes before CT scanning and before each daily treatment. Intravenous administration of contrast was added for CT-sim; the patients were placed in a supine position with thermoplastic immobilization during IMRT with a 6-MV photon beam.

MR scanning

The patients were scanned in the supine position on a 1.5 T Genesis-Sigma MR scanner (General Electric Medical Systems; Waukesha, Wisconsin, USA) no later than 7 days before CT-sim. Care was taken to reproduce the simulation position at the time of the MR. The images were obtained from T8 vertebral body to L4 vertebral body. The scanning parameters consisted of TE =15 ms and TR =500 ms, with a slice thickness of 6 mm according to John and Roeske.[7]

Image fusion

The MR images were subsequently fused with the CT-sim images using Pinnacle system and Syntegra image fusion software. The interactive mode of the fusion software was used whereby the user manually translates and rotates the MR scan to produce the best visual overlay of the two image sets.

Then CT and MR images (resliced along the planes of the CT scan) were subsequently displayed side by side.

Active BM and target volume delineation

Active BM regions on the T1-weighted images showing signal intensity equal to or slightly higher than that of muscle were contoured as active BM.[7,26] The range of active BM was 2.5 cm beyond the upper limit of planning target volume (PTV) and 2.5 cm below the lower limit of PTV. The delineation of the clinical target volume (CTV) for each patient depended on the extension and location of the primary tumor and corresponding lymph node regions issued by the Japanese Gastric Cancer Association.[27] In general, the CTV includes anastomoses, duodenal stump, tumor bed (only for stage T4b, if present), and relative regional lymph node regions. The remnant stomach was not routinely included within the radiation field. The PTV was produced by expanding the CTV by 0.7–1.0 cm in all directions. The isocenter was placed at the geometric center of the PTV.

Dose and OAR definition

The prescribed dose in all patients was 45 Gy in 1.8 Gy daily fractions, 5 days per week for 5 weeks. The recommended dose limitations for active BM were as follows: V5 (volume receiving a dose of 5 Gy or more) <90%, V10 <85%, V20 <75%, V30 <60%, and V40 <35%. Dose constraints for other OARs were as follows: V30 <40% for the liver; V20 <30% for both kidneys or a mean dose of <20 Gy; V30 <30% for heart; the maximal dose for the spinal cord was 40 Gy; V30 <40% for small bowel and colon. Based on our previous experience, five-to-seven fields, 6 MV, coplanar, IMRT plans were generated on the Pinnacle system, version 3.0.[28]

Chemotherapy

Based on the Phase I trial of maximum tolerated dose of capecitabine combined with postoperative radiotherapy for gastric cancer, concurrent chemotherapy regimen is monotherapy with oral capecitabine at a daily dose of 1,600 mg/m^2, divided into two equal doses given 12 hours apart, from the beginning to the end of the duration of RT.[28]

Prior to CRT, four to six cycles of adjuvant chemotherapy was allowed. Most of them were oxaliplatin-based regimen.

Safety assessment

All patients had complete blood counts weekly during CRT, while liver and renal function was assessed every 2 weeks. Antacid and gastric mucosa protectants were administered on a prophylactic basis. Anti-emetics and antidiarrheal agents were prescribed when needed.

Endpoints and statistics

Endpoints of interest were the white blood cell count (WBC), ANC, Hb, and platelet count (PLT) nadirs within 60 days of initiation of CRT. HT and other morbidity were graded according to the Radiation Therapy Oncology Group acute radiation toxicity scoring criteria.[29]

According to the reductive effect on HT in gynecological cancer patients,[19,30,31] we hypothesized that BMS-IMRT was able to reduce grade ≥3 HT from 50%[1,2,11] to 25%. Thus, based on sample size estimation of optimal two-stage designs for Phase II clinical trials (α=0.05, β=0.02), a minimum of 25 patients were needed to be enrolled.

Statistical analyses were performed using SPSS Package for Windows version 13.0 (SPSS Inc., Chicago, IL, USA). The continuous variables and frequencies were compared by Mann–Whitney *U*-test and chi-square or Fisher's exact test as appropriate. Associations between variables were tested using the chi-square test. Independent prognostic factors were identified using multivariate linear regression analysis for variables with a *P*-value <0.1 in univariate analysis.

Results

Clinical characteristics

A total of 28 patients were enrolled in this study between May 2013 and April 2014. Three patients were excluded from the study before the start of treatment – two because of unexpected decreased PLT and ANC which had recovered after adjuvant chemotherapy and one because of failed BMS-IMRT planning. Therefore, 25 patients were included in the study and received BMS-IMRT combined with capecitabine. Their demographic and tumor characteristics are listed in Table 1. The median age was 53 years (range, 28–73 years). The mean BMI was 21.3 kg/m^2 (range, 15.0–27.3 kg/m^2). Twenty four patients (96%) had stage T3–4 disease and 22 patients (88%) had node-positive disease.

Radiation delivery and dosimetric parameters

Radiotherapy was stopped at 23.4 Gy and 34.2 Gy in two patients because of grade 4 nausea and persistent grade 3 neutropenia. The other 23 patients completed planned concurrent chemoradiation; among these patients, three required treatment break for grade 3 vomiting (n=1) and grade 3

Table 1 Patients' characteristics

Variables	n (%)
Patients, (n)	25
Sex	
Male, n (%)	22 (88.0)
Female, n (%)	3 (12.0)
Median age, years (range)	53 (28–73)
ECOG performance status	
0, n (%)	9 (36.0)
1, n (%)	16 (64.0)
Mean BMI, kg/m^2 (SD)	21.3±2.8
T stage	
T2, n (%)	1 (4.0)
T3, n (%)	12 (48.0)
T4, n (%)	12 (48.0)
Number of positive lymph node, n ± SD	9.5±6.4
Number of dissected lymph node, n ± SD	29.9±11.5
Pathological stage	
IIa, n (%)	2 (8.0)
IIIa, n (%)	2 (8.0)
IIIb, n (%)	13 (52.0)
IIIc, n (%)	8 (32.0)
Adjuvant chemotherapy before CRT (cycles), n ± SD	4.3±0.5

Abbreviations: CRT, concurrent chemoradiation; BMI, body mass index; ECOG, Eastern Cooperative Oncology Group.

thrombocytopenia (n=2). The median total dose was 45.0 Gy (range, 23.4–45.0 Gy) and the median duration of CRT was 34 days (range, 20–42 days).

BMS-IMRT was able to meet the previous constrain of BM except for BM-V5, which were as follows: BM-V5, 91.06%±4.9%; BM-V10, 84.46%±6.97%; BM-V20, 74.73%±8.95%; BM-V30, 59.25%±12.46%; BM-V40, 29.85%±11.24%. The conformity index (CI) and homogeneity index (HI) of PTV[32] were 0.85±0.38 and 1.12±0.06, respectively, and the mean total volume of BM and PTV were 158.52±77.12 and 968.91±261.39 mL. Dose–volume parameters for other OAR were as follows: V30, 22.44%±6.72% for the liver; V20, 21.15%±5.33% for left kidneys; V20, 19.36%±7.23% for right kidneys; V30, 22.43%±4.76% for the heart; V30, 34.88%±14.48% for small bowel; V30, 25.82%±12.6% for colon; and a maximal dose of 35.77±3.46 Gy for the spinal cord.

Hematologic toxicity and its association with dosimetric parameters

HT and other acute morbidities are summarized in Table 2. Five patients experienced acute grade 3–4 HT, which accounts for 20% (5/25) incidence – two (8.0%) experienced grade 3–4 leukopenia, two (8.0%) experienced grade 3–4 neutropenia, and two (8.0%) experienced grade 3–4 thrombocytopenia, respectively. One patient had developed both neutropenia and thrombocytopenia. None of the patients showed grade 2–4 anemia. All variables listed in Table 1 and dose volume metrics of active BM were evaluated for prognostic value of WBC, ANC, and PLT nadirs, but not for Hb as there was no grade 2–4 anemia. Patients with BM-V5 ≤90% had higher WBC nadirs (3.36±0.84 vs 2.57±0.81, P=0.026) and neutrophil nadirs (2.13±0.60 vs 1.52±0.67, P=0.033) than patients with BM-V5 >90%. Similar results were also observed for patients receiving BM-V10 ≤85% or >85% and BM-V20 ≤75% or >75%. For BM-V30, >60% presented a risk to develop lower platelet nadirs (79±30 vs 118±41, P=0.014) than for patients with BM-V30 ≤60%. However, BM-V40 seemed to have no relation with HT. Multivariable linear regression revealed increased BM-V5 (P=0.03) and BM-V20 (P=0.002) were significantly associated with decreased WBC nadirs,

Table 2 Acute hematologic toxicities and other morbidities

Toxicity	Grade 0 n (%)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)
Hematologic toxicity	2 (8.0)	7 (28.0)	11 (44.0)	4 (16.0)	1 (4.0)
Leukopenia	2 (8.0)	9 (36.0)	12 (48.0)	2 (8.0)	0 (0.0)
Neutropenia	8 (32.0)	9 (36.0)	6 (24.0)	1 (4.0)	1 (4.0)
Anemia	17 (68.0)	8 (32.0)	0 (0.0)	0 (0.0)	0 (0.0)
Thrombocytopenia	11 (44.0)	8 (32.0)	4 (16.0)	2 (8.0)	0 (0.0)
Nausea	2 (8.0)	18 (72.0)	2 (8.0)	2 (8.0)	1 (4.0)
Vomiting	13 (52.0)	8 (32.0)	2 (8.0)	1 (4.0)	1 (4.0)
Diarrhea	22 (88.0)	2 (8.0)	1 (4.0)	0 (0.0)	0 (0.0)
Abdominal pain	17 (68.0)	5 (30.0)	3 (12.0)	0 (0.0)	0 (0.0)
Anorexia	4 (16.0)	13 (52.0)	6 (24.0)	1 (4.0)	1 (4.0)
Fatigue	8 (32.0)	13 (52.0)	2 (8.0)	1 (4.0)	1 (4.0)
Body weight loss	21 (84.0)	3 (12.0)	1 (4.0)	0 (0.0)	0 (0.0)
ALT/AST	23 (92.0)	2 (8.0)	0 (0.0)	0 (0.0)	0 (0.0)
TBil	24 (96.0)	1 (4.0)	0 (0.0)	0 (0.0)	0 (0.0)

Abbreviations: ALT/AST, alanine/aspartate transaminase elevated; TBil, total bilirubin elevated.

Table 3 Multivariable analysis of factors associated with WBC, ANC, and PLT nadirs

Factors	WBC nadirs (10^9/L)			ANC nadirs (10^9/L)			PLT nadirs (10^9/L)		
	β	95% CI	*P*-value	β	95% CI	*P*-value	β	95% CI	*P*-value
BM-V5	–0.069	–0.135 to –0.002	0.03	–	–	–	–	–	–
BM-V20	–0.057	–0.092 to –0.021	0.002	–0.060	–0.082 to –0.038	<0.001	–	–	–
BM-V30	–	–	–	–	–	–	–1.666	2.664 to –0.689	0.002
V_{BM}	–	–	–	–	–	–	–0.301	0.461 to –0.141	0.001

Abbreviations: BM, active bone marrow; WBC, white blood cell count; ANC, absolute neutrophil count; PLT, platelet count; V_{BM}, volume of BM; β, regression coefficient (eg, 1% increase in BM V20 corresponds to a reduction in WBC count of 0.057×10^9/L); CI, confidence interval; V5, V20, V30, percent of BM volume receiving >5, 20, 30 Gy.

increased BM-V20 ($P<0.001$) with decreased ANC nadirs, increased BM-V30 ($P=0.002$) and volume of BM ($P=0.001$) with decreased PLT nadirs (Table 3).

Discussion

This is the first trial to evaluate BMS-IMRT in gastric cancer patients treated with concurrent CRT. Our results revealed significant correlations between low radiation and dose volume of active vertebra BM and the severity of HT. BM-V5 >90%, BM-V20 >78%, and BM-V30 >60% were proved to be risk factors for grade ≥2 leukopenia, neutropenia, and thrombocytopenia, respectively. By contrast, no correlation was found between dose volume metrics and anemia, which is in line with the result of pelvic malignancies.[10,20] These data support the feasibility of MR to identify hematologically active BM for radiation avoidance. Our study enhanced our understanding of the distribution of hematopoietically active BM surrounding radiation field of gastric cancer. The results implied that BMS-IMRT may improve patient's outcomes by reducing HT.

It is important to reduce acute HT, which is the major cause to compromise treatment completion and intestification in gastric cancer patients during radiotherapy and chemotherapy.[1,2,11] This study first tested the hypothesis that sparing active BM in radiation could alleviate the severity of HT (grade ≥2 16.0%) in abdominal cancer patients, which is in line with the results of pelvic cancer patients.[10,19,20] The hypothesis is based on laboratory and dosimetric evidences. Basic research has demonstrated that BM stem cells are sensitive to radiation, especially low doses of radiation, and apoptosis to these cells by radiation is the main cause of HT.[33–35] Furthermore, the severity of BM damage induced by radiation is dependent on both dose and volume.[36–39] Prolonged myelosuppression and irreversible functional BM changes can occur at dose above 30 Gy.[35] However, HT is uncommon with RT alone because of compensatory hematopoiesis in unirradiated active BM. When concurrent chemotherapy is added to RT as standard treatment, myelosuppression is obvious causing HT to grade ≥3 by 30%–54% for gastric cancer patients[1,2,11] because of myelosuppression of unirradiated active BM. In clinical practice, several publications have shown that acute HT was significantly associated with the volume of pelvic lower spine BM in pelvic cancers patients who received 10 and 20 Gy radiations.[10,19,20] Thus it is rational the sparing the volume of active BM receiving low-dose RT can reduce HT.

A practical aspect of this study was first to prove the effectiveness of MR identifying active BM after adjuvant chemotherapy. On these images, regions of active (red) marrow exhibit a low-intensity signal (similar to muscle),[7,26] while regions of nonactive (fatty) BM have a high intensity signal similar to fat. According to MR images fused with CT-sim images, customized IMRT plan could be generated based upon an individual patient's active BM distribution.

Another method to spare BM is contouring the entire bone structures as BM in CT-sim in several clinical trials, which is much easier and time-saving than our method.[12–14] However, it is known that these active and inactive regions cannot be distinguished with CT imaging and a considerable portion of bone structure is filled with inactive (yellow) marrow. In fact, Rose et al had already indicated that there was no correlation between radiation dose and volume metrics on the inactive BM and HT.[10] Furthermore, contouring the entire bone structures overestimates the volume of active BM, which brings unnecessary difficulty in IMRT planning. Dosimetric study showed that total pelvic bones sparing-IMRT resulted in poor CI of 0.68±0.10, which is lower than our result (CI =0.85±0.38).[40] So refining IMRT plans to focus on sparing active BM subregions may be a more effective strategy to reduce radiation-induced BM damage. Indeed, contouring active BM based on MR is time consuming. As the total length of CTV for a gastric cancer patient is usually 20–25 cm, it takes about 30 minutes for a physician to delineate active BM based on MR according to our experience. Thus, in our opinion, the extra time taken for the delineation of OAR is acceptable.

The strength of this study was hypothesis-driven, seeking to validate previously observed associations a priori.[12,17–19,24,25] The data in this study were derived from a prospective cohort. However, the question remains as to how much degree of sparing BM is necessary and sufficient to reduce HT while not increasing dose in other normal organs significantly. According to our data, limiting BM-V5 <90%, V10 <85%, V20 <75%, and V30 <60% did not have significant influence on target coverage (CI =0.85±0.38, HI =1.12±0.06) or sparing of other normal tissues. But still care in interpreting these results is warranted. The range of entire BM parameter values in which the relationship between HT and dosimetric parameters is valid is still unclear, and there is still unexplained variation in some patients with high WBC nadirs and high BM-V5 and BM-V20. As clinical factors were also found to be related with HT in CRT, for example, female sex, positive lymph node, and body weight loss,[20] more optimized tailored algorithms may be required to characterize accurately the dependence of HT on the basis of these demographic and dosimetric factors.

There are several limitations in this study – the study is single centered, has no control setting, and contouring the active BM by MR is rather arbitrary as there is no standard signal values in MR images to discriminate active or inactive BM. Reducing the planning margins would also likely improve BMS, but organ motion is a significant problem. Thus, image guidance during RT course should be added in this study to deliver BMS RT plans.

Conclusion

Our results suggest that MR-guided BMS-IMRT is a feasible and straightforward approach to minimize the dose to active BM sites and may reduce HT in gastric cancer patients undergoing CRT. Efforts to maintain BM-V5 ≤90%, BM-V20 ≤78%, and BM-V30 ≤60% could significantly reduce grade ≥3 leukopenia, neutropenia, and thrombocytopenia, respectively. Further validation is needed in a large group of patients to optimize and determine the clinical significance of BMS techniques.

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Disclosure

The authors report no conflicts of interest in this work.

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