Table 5 Clinical predictors of vaginal ulcer

Characteristic		Vaginal ulcer (+) (n = 5)	Vaginal ulcer (-) (n = 39)	p value
Prior pelvic RT*		3	5	
	Yes	2	34	0.035*
	No			
Concurrent chemotherapy				
	Yes	0	10	0.256
	No	5	29	
Median number of needles used in HDR-ISBT[ʃ] (range)		14 (10-24)	15 (5-29)	0.293
Median CTV[†] (ml, range)		54.7 (17.7-114.0)	34.7 (2.4-142.1)	0.271
Median rectum D_{2cc}[††] (EQD_2[‖], Gy, range)		84.2 (34.0-100.7)	57.9 (30.5-114.3)	0.118
Median bladder D_{2cc}[††] (EQD_2[‖], Gy, range)		69.3 (37.4-113.5)	57.7 (7.3-120.3)	0.091
Median vaginal wall $D_{0.5cc}$[††] (EQD_2[‖], Gy, range)		206.4 (106.6-349.3)	149.4 (47.9-310.1)	0.243
Median vaginal wall D_{1cc}[††] (EQD_2[‖], Gy, range)		169.1 (91.6-277.5)	127.9 (33.6-220.8)	0.096
Median vaginal wall D_{2cc}[††] (EQD_2[‖], Gy, range)		152.5 (71.1-247.5)	109.0 (31.7-201.9)	0.025*
Median vaginal wall D_{4cc}[††] (EQD_2[‖], Gy, range)		115.5 (83.8-200.8)	110.6 (34.0-153.2)	0.152
Median vaginal wall D_{6cc}[††] (EQD_2[‖], Gy, range)		102.5 (60.4-173.7)	99.5 (20.4-146.3)	0.266
Median vaginal wall D_{8cc}[††] (EQD_2[‖], Gy, range)		82.0 (47.6-144.4)	84.3 (10.3-140.3)	0.511

*RT: radiation therapy.
[ʃ]HDR-ISBT.
[†]CTV: clinical target volume.
[‖]EQD2: equivalent dose in 2 Gy fractions.
[††]D0.5cc, D1cc, D2cc, D4cc, D6cc, D8cc: most exposed 0.5, 1, 2, 4, 6, and 8 cm3 of tissue.

the current study, which was composed of EBRT and ICBT/ISBT and normalized to 2 Gy per fraction (EQD_2) using the linear-quadratic model with α/β of 3 Gy for the vaginal morbidities [10-12,16]. The difference between Vienna group and the current study was that there were more patients with severe vaginal morbidities in the current study, presumably because there were more patients who received re-irradiation and current study excluded the patients treated with HDR-ICBT. HDR-ISBT delivers higher dose to the vaginal wall than HDR-ICBT because the multiple needle applicators directly contact vaginal wall. According to the current results, after vaginal wall $D_{0.5cc}$, D_{1cc}, D_{2cc}, D_{4cc}, D_{6cc}, and D_{8cc} having been compared, vaginal wall D_{2cc} was found to be the most relevant DVH parameter predicting the incidence of vaginal ulcer. ROC analysis also showed that vaginal wall D_{2cc} of 145 Gy in EQD_2 can be used as clinical cutoff dose predicting vaginal ulcer. This figure is quite similar to the vaginal tolerance dose of 150 Gy derived from a retrospective study of LDR brachytherapy which was previously mentioned [15]. The current report is the first one concerning about vaginal DVH parameter and complication using modern era of three-dimensional image-guided brachytherapy. It was also found in this study that the history of prior pelvic irradiation was another significant predictive factor for vaginal ulcer (Table 5). Lee et al. reported a patient with colovaginal fistula with previous EBRT [5,7]. As shown in Table 3,

Table 6 Dosimetric predictors for the development of vaginal ulcer

Parameter	ROC[†] AUC*	Cutoff[¶]	2-y incidence ofvaginal ulcer (%)	P value[#]
Vaginal wall $D_{0.5cc}$[‖] (EQD_2[††])	0.667	≤195 Gy	0.0	0.058
		>195 Gy	18.5	
Vaginal wall D_{1cc}[‖] (EQD_2[††])	0.682	≤171 Gy	4.2	0.091
		>171 Gy	20.0	
Vaginal wall D_{2cc}[‖] ($EQD2^{††}$)	0.733	≤145 Gy	3.7	0.026*
		>145 Gy	23.5	
Vaginal wall D_{4cc}[‖] (EQD_2[††])	0.618	≤83 Gy	0.0	0.119
		>83 Gy	15.6	
Vaginal wall D_{6cc}[‖] (EQD_2[††])	0.569	≤86 Gy	5.6	0.323
		>86 Gy	15.4	
Vaginal wall D_{8cc}[‖] (EQD_2[††])	0.559	≤75 Gy	5.6	0.323
		>75 Gy	15.4	

*AUC: area under the curve.
[†]ROC: receiver operator characteristic.
[††]EQD2: equivalent dose in 2 Gy fractions.
[‖]D0.5cc, D1cc, D2cc, D4cc, D6cc, D8cc: most exposed 0.5, 1, 2, 4, 6, and 8 cm3 of tissue.
[¶]Cutoff refers to the most predictive value from the AUC of ROC curve.
[#] Univariate analysis by log-rank test.

both rectum and bladder D_{2cc} was significantly higher in patients with prior pelvic irradiation than those without prior pelvic irradiation. However both rectum and bladder D_{2cc} was not in itself a significant prognostic factor for vaginal ulcer and could not be used as a surrogate indicator (Table 5).

There were several limitations in this study. Contouring of the vagina was not based on MRI but CT, which is inferior to MRI in tissue contrast. However because 41 out of 44 patients were inserted either cylinder or mold into their vagina, contouring of vagina was considered to be precise. The time interval between the prior pelvic RT and HDR-ISBT was not taken into consideration for the calculation of the total dose for OARs. Additionally, this study was a retrospective study with small number of patients with heterogeneous tumor origin, heterogeneous treatment applied, small number of events, and with short follow-up period. Therefore we should be cautious about the results of the current study. However even tumor origin differed greatly in current cohorts of study, it is considered to be feasible because the main concern in current study was focused on only the vaginal toxicity.

It should be stressed that with the introduction of HDR-ISBT in gynecological malignancies and increment of vaginal dose, vaginal tolerance dose must be taken into consideration. Further discussion and validation of vaginal DVH parameters in image-guided brachytherapy in a multicenter prospective study is needed.

Conclusions

The DVH parameters for vagina are essential for treatment planning and optimization in image based HDR-ISBT in gynecological malignancies. Vaginal wall D_{2cc} in EQD_2 should be monitored and be kept under 145 Gy in order to avoid vaginal ulcer. Also in patients with prior pelvic irradiation, vaginal wall dose including the prior radiation dose should be kept lower than 145 Gy.

Consent

Written informed consent was obtained from the patient for the publication of this report and any accompanying images.

Abbreviations

HDR-ISBT: High-dose rate interstitial brachytherapy; EQD_2: Dose in equivalent in 2 Gy fractions; ICBT: Intracavitary brachytherapy; ISBT: Interstitial brachytherapy; DVH: Dose volume histogram; EBRT: External beam radiation therapy; GTV: Gross tumor volume; CTV: Clinical target volume; OAR: Organ at risk; AUC: Area under the curve; ROC: Receiver operating characteristics; IGBT: Image guided brachytherapy; PDR: Pulsed dose rate.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

TK, MS, RY, KH, MK, SS, KT, KY, KI, MM, and YI performed the treatment. NM and JI analyzed the data and wrote the manuscript. All authors read and approved the final manuscript.

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A Dosimetric Analysis of Intensity-modulated Radiation Therapy with Bone Marrow Sparing for Cervical Cancer

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Abstract. *Background/Aim: The purpose of the present study was to compare intensity-modulated radiation therapy (IMRT) plan with (Bone Marrow Sparing (BMS) – IMRT) or without (normal-IMRT) an intention of avoiding bone marrow in order to minimize treatment-related toxicity. Patients and Methods: Computed tomography (CT) images of 10 consecutive postoperative cervical cancer patients were used. All patients were already treated by normal-IMRT. BMS-IMRTs were created for this study and dose-volume histogram parameters were compared. Results: Both planning target volume (PTV) D95% and D97% were statistically lower in BMS-IMRT than normal-IMRT, however, the difference was lower than 3%. There were no statistical differences between BMS-IMRT and normal-IMRT in the mean value of rectum V_{30Gy}, V_{50Gy}; bladder V_{45Gy}, V_{50Gy}; Bowel V_{35Gy}, and V_{50Gy}. Both in whole pelvic bone (WPB) and inner cavity of pelvic bone (ICPB), the mean value of V_{10Gy}, V_{30Gy}, and V_{40Gy} of BMS-IMRT were statistically lower than that of normal-IMRT. Conclusion: Both lower and higher dose for WPB as well as ICPB were effectively lowered by BMS-IMRT.*

Postoperative radiation therapy is an established treatment for intermediate-risk and high-risk cervical patients (1, 2) as well as endometrial cancer patients (3, 4). Conventional radiation techniques for whole-pelvic radiation therapy (WPRT) involve 4 static photon fields. These techniques expose most of the contents of the true pelvis including small bowel equal to the prescribed dose as a target volume. The highly conformal technique of intensity-modulated radiation therapy (IMRT) has a potential of delivering radiation dose while avoiding surrounding normal tissues and its advantage has been proven in several anatomical sites such as head and neck cancer (5, 6) or prostate cancer (7, 8). However the profit of using IMRT in the field of gynecological cancer is controversial (9-11). The Radiation Therapy Oncology Group (RTOG) conducted a multi-institutional prospective phase II trial (RTOG 0418) using IMRT for postoperative endometrial and cervical patients in order to determine if IMRT can be performed in multi-institution settings and to test the hypothesis that IMRT can reduce short-term bowel injury and recently positive preliminary results were presented (12, 13). Although in the RTOG 0418 bone marrow sparing was not included in its protocol, weekly cisplatin was administered successfully concurrent with radiation therapy. As much as 83% of patients received 5 or more cycles of weekly cisplatin and 90% at least 4 cycles (13). Compared to results from other series with conventional technique radiation therapy which also used concurrent cisplatin, this result was favorable, although it is difficult to make any direct comparisons (2, 14). Therefore it is supposed that if bone marrow sparing was intended from the beginning, bone marrow protection would lead to better results. The aim of this study is to investigate the difference of dose volume histogram (DVH) parameters between IMRT plan with or without bone marrow sparing intention using computed tomography (CT) images of posthysterectomy cervical cancer patients.

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Key Words: Cervical cancer, radical hysterectomy, postoperative radiation therapy, IMRT, bone marrow sparing.

Patients and Methods

Patients. Ten consecutive patients constitute this retrospective planning study. These subjects underwent radical hysterectomy and pelvic lymphadenectomy and postoperative radiation therapy for

early-stage high-risk cervical carcinoma between May 2012 and June 2013. Eligibility criteria for postoperative adjuvant radiation therapy were: (i) pelvic lymph node metastasis, (ii) parametrial invasion, and (iii) a positive surgical margin.

Radiation therapy. Before simulation CT was taken, a customized immobilization device was fabricated to minimize variability in the daily setup error. Fiducial markers were inserted into the vaginal cuff to visualize it on CT images. CT scans under full and empty bladder were taken in order to account for the motion of vagina influenced by the content of bladder. CT scans of 2-mm slice thickness were taken by Aquilion LB CT scanner (TOSHIBA Medical Systems, Tochigi, Japan). The clinical target volume (CTV) was contoured on the individual axial CT slices of each patient. The overall CTV includes both the vaginal cuff/paracolpium CTV and the nodal CTV. The vaginal cuff/paracolpium CTV was contoured in a manner similar to the Radiation Therapy Oncology Group (RTOG) (15); Cranial margin: 0.5 cm cranial from the upper part of vaginal cuff metallic marker. Anterior margin: posterior border of bladder or retropubic fat pad. Posterior margin: Anterior part of mesorectal fascia or anterior wall of rectum. Lateral margin: medial edge of internal obturator muscle, piriformis muscle, coccygeus muscle and ishial ramus. Caudal margin: 3 cm below from the upper part of vaginal cuff metallic marker. The nodal CTV included lymph nodes that drain the involved site and adjacent perinodal soft tissue. This included the internal (obturator and hypogastric), external, and common iliac lymph nodes; presacral lymph nodes and soft tissues also included down to the level of S3. The upper limit of the nodal CTV was L4/5 interspace. If a common iliac lymph node metastasis was found pathologically, the nodal CTV was extended at the level of L2/3 interspace. The nodal CTV was based on the Japan Clinical Oncology Group Gynecologic Cancer Study Group (JCOG-GCSG) consensus guidelines for the delineation of CTV for pelvic lymph nodes (16). We used the JCOG-GCSG guideline for reference aiding nodal CTV because it included adipose connective tissue between the iliopsoas muscles and the lateral surface of the vertebral body which was not included in RTOG guideline. This area was also included in an atlas of Taylor *et al.* (17, 18). The CTV was expanded by 7 mm to create the planning target volume (PTV). For normal structures, the small bowel (contoured as a peritoneal space), rectum and bladder (both contoured as a whole organ) and femoral head were routinely contoured according to RTOG normal tissue contouring guideline (19). For the purpose of this study, both pelvic bone and pelvic bone marrow were also contoured. Mahantshetty *et al.* demonstrated that inner cavity of pelvic bone (ICPB) was a better surrogate of active bone marrow than whole pelvic bone (WPB) (20); therefore, both WPB and ICPB were prepared in this study. In order to extract WPB from CT images, bone auto-contouring was performed by including tissue with density of higher than 100 on each slice with 'fill' function activated. Before extracting ICPB, a tentative structure was created using auto-contouring function which includes tissue with density between -100 to 200. This structure includes ICPB as well as extra-bone soft tissue. Therefore, the overlap volume of WPB and the tentative structure was created and this structure became the ICPB. Figure 1 shows representative axial figure of the contour for ICPB and WPB. In this figure, WPB was contoured in pink line while ICPB in green.

Prescription dose was 50 Gy in 25 fractions. The planned goals were to provide a homogenous PTV dose while minimizing the dose delivered to the small bowel, bladder and rectum. Typical input parameters for normal-IMRT plans were as follows: PTV mean dose ranges from 100 to 105% while no more than 2% of the volume of PTV to receive a dose that is 60 Gy or greater; no more than 40% of the volume of the small bowel to receive a dose that is greater than 40 Gy and no more volume of small bowel greater than 1 cc to receive more than 55 Gy; no more than 40% of the volume of the rectum to receive more than 50 Gy and no volume within the rectum receives dose that is 55 Gy or greater; no more than 50% of the volume of the bladder to receive more than 45 Gy and no volume within the bladder receives dose that is 55 Gy or greater; and no more than 20% of the volume of the femoral head to receive more than 30 Gy. Dose constraints of BMS-IMRT planning were as follows: the same dose constraints for PTV and organ at risk (OAR) were used. For the use of DVH-based optimization, virtual structures were created; WPB-PTV and ICPB-PTV which were overlap structure of WPB and PTV, and ICPB and PTV, respectively. The general priority for each structure was presented as below: 70, 90, 65, 50, 65, and 65 for PTV, small bowel, rectum, bladder, WPB-PTV, and ICPB-PTV, respectively.

The way of delivering IMRT was by Volumetric Modulated Arc Therapy (VMAT) using 2 arcs via a computer-controlled auto sequence multileaf collimator on a linear accelerator (Clinac iX, Varian Medical System, Palo Alto, CA, USA) using a 15 MV photon beam. Dose calculation with a calculation grid of 1.0 mm was done and the calculation algorism was Acuros (Link or supplier). The radiotherapy was planned using the Eclipse Planning System (version 10.0, Varian Medical System, Palo Alto, CA, USA).

No chemotherapy was used concurrently with radiation therapy in our institution for early stage high-risk post-hysterectomy cervical cancer patients. DVH parameters between normal-IMRT and BMS-IMRT were compared in this study. The difference of the mean value of each parameter was analyzed by paired *t*-test and *p*-value of <0.05 was considered statistically significant. All statistical analyses were performed using the SPSS™ version 18.0 (SAS Institute, Tokyo, Japan). This retrospective study was approved by the local Institutional Review Board.

Results

Since it was not long before IMRT was introduced in the treatment for postoperative cervical cancer patients at our Institution, only 10 patients were included in the current study. Table I shows their characteristics. Median age was 39 (range=25-66) years. Sixty percent of patients were staged as IB1 and there was no IIA patient. Half of the patients had squamous cell carcinoma. Seventy and ninety percent of patients had parametrium invasion and pelvic lymph node metastasis, respectively. All patients were diagnosed as surgical margin negative.

Figure 2a and Table II show boxplots and actual numbers of DVH parameters for PTV. Although in PTV $D_{95\%}$ and $D_{97\%}$ the mean value of BMS-IMRT were statistically lower than that of normal-IMRT, the differences were smaller than 3% and the influence of this very minute difference on clinical result is unknown. On the other hand, the mean value of PTV median in BSM-IMRT was statistically higher than that of normal-IMRT. There was no statistical difference in PTV D_{max}

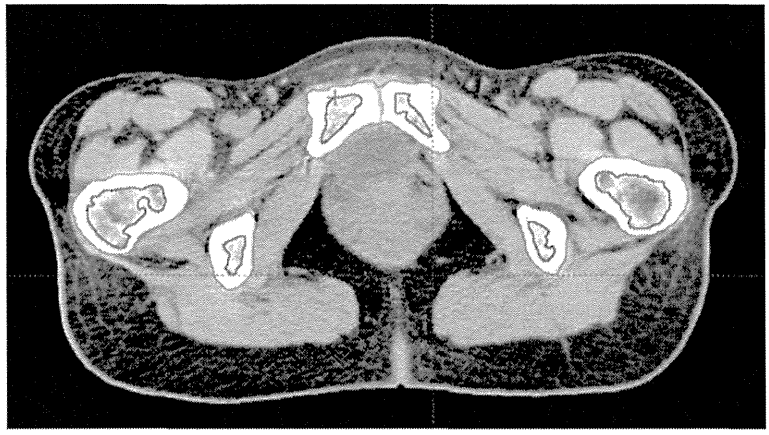

Figure 1. *An axial figure showing contour for inner cavity of pelvic bone (green line) and whole pelvic bone (pink line).*

Table I. *Patients' characteristics (N=10).*

Median age (range)	39 (25-66)
Clinical stage	
IB1	6
IB2	2
IIA	0
IIB	2
Histology	
Scc	5
Adeno	3
Adenosquamous	2
Parametrium invasion	
Yes	7
No	3
Pelvic LN metastasis	
Yes	9
No	1
Median Number of pelvic LN metastasis (range)	2 (0-8)
Surgical margin	
Positive	0
Negative	10
Median tumor size (cm, range)	4.1 (1-5.4)

Table II. *The mean value of DVH parameters for PTV.*

	Normal-IMRT		BMS-IMRT		
	Mean (%)	SD†	Mean (%)	SD†	*p*-Value
PTV D_{max}	109.7	3.7	110.8	1.4	0.258
PTV $D_{95\%}$	94.6	2.3	92.5	1.9	*<0.01
PTV $D_{97\%}$	93.4	2.5	90.8	2.6	*0.05
PTV median	100.4	0.4	100.8	0.5	*0.05

†SD: Standard deviation, PTV: planning target volume, DVH: dose volume histogram.

between both plans. Therefore it was supposed that these small differences would not bring about any clinical relevant differences. For comparison, another plan was created in which the PTV coverage was prioritized to be of the same degree as normal-IMRT. In these plans, favorable sparing of bone marrow did not occur.

Figure 2b shows boxplots of DVH parameters for OARs. There were no statistical difference between normal-IMRT and BMS-IMRMT in the mean value of rectum V_{30Gy}, V_{40Gy}, V_{50Gy}, bladder V_{45Gy}, V_{50Gy}, Bowel V_{35Gy}, V_{40Gy}, V_{45Gy}, and V_{50Gy}. There was a statistically significant difference between the mean value of bladder V_{35Gy} and femoral head V_{30Gy}. Although a statistical significance was found between normal- and BMS-IMRT in bladder V_{35Gy}, as shown in the Figure 2 the difference was quite small; therefore it was not known whether this small difference would be connected to clinically evident difference. The dose of femoral head was effectively lowered in BMS-IMRT than that of normal-IMRT. It was supposed that this difference was caused because the femoral head was included in the structure of pelvic bone.

Figure 3a and 3b show boxplots of DVH parameters for WPB and ICPB. Both in WPB and ICPB, the mean value of V_{10Gy}, V_{20Gy}, V_{30Gy}, and V_{40Gy} of BMS-IMRT were statistically lower than that of normal-IMRT. Figure 4 shows an example of dose distribution of BMS-IMRT and normal-IMRT. In this Figure, the area receiving a dose of 40 Gy or higher was colored. Visually, it was clear that the spinal body was effectively avoided in BMS-IMRT compared with normal-IMRT. Because the 15 MV photon beam is not used in the majority of institutions in the United States, another BMS-IMRT plan was created in 3 representative patients using a 6 MV photon beam and the DVH was compared. Table III summarizes the difference of DVH parameters

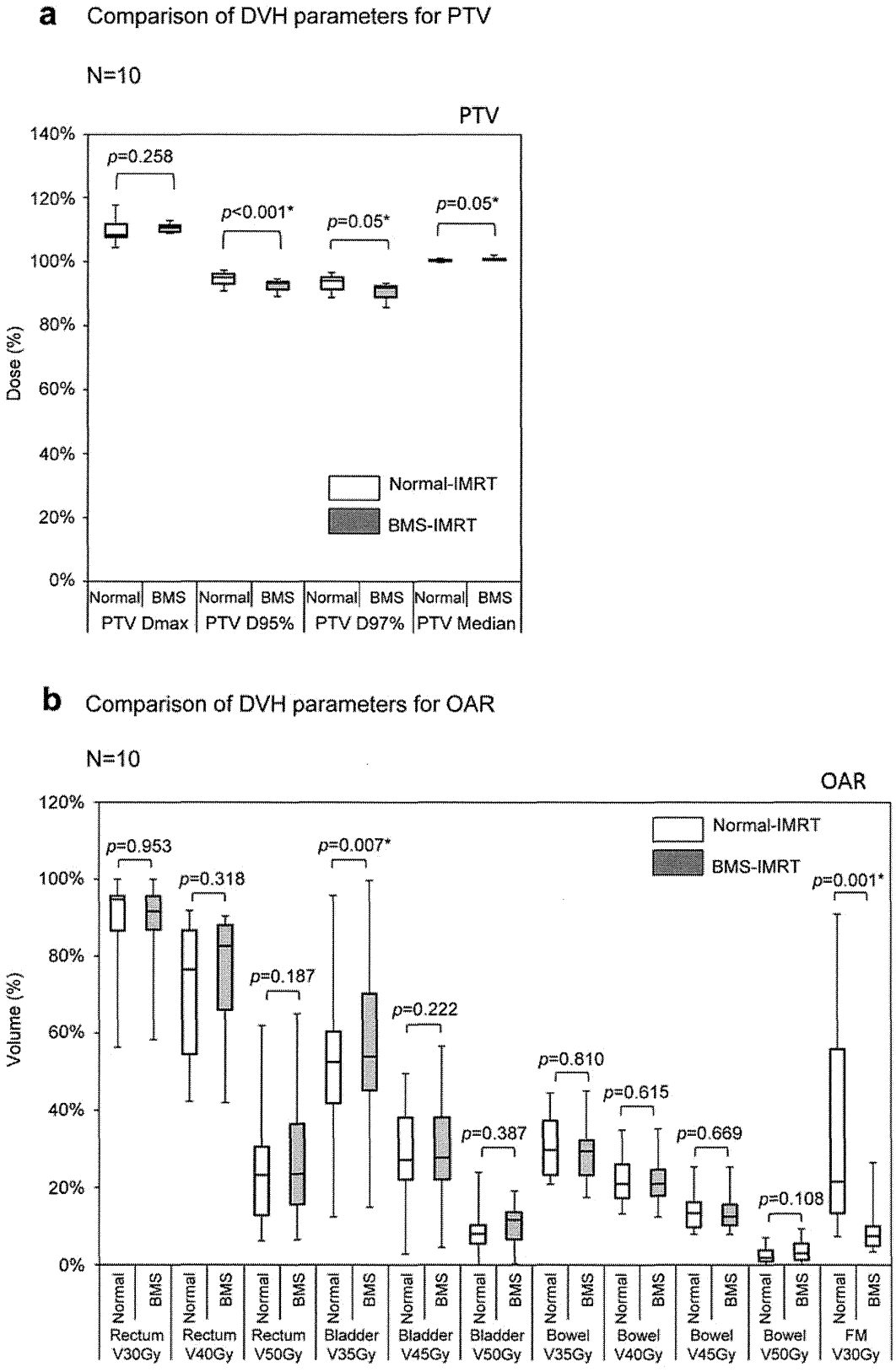

Figure 2. *Boxplots of dose volume histogram (DVH) parameters for planning target volume (PTV) (a) and organ at risks (OARs) (b).Note: spell out Femoral head (FM).*

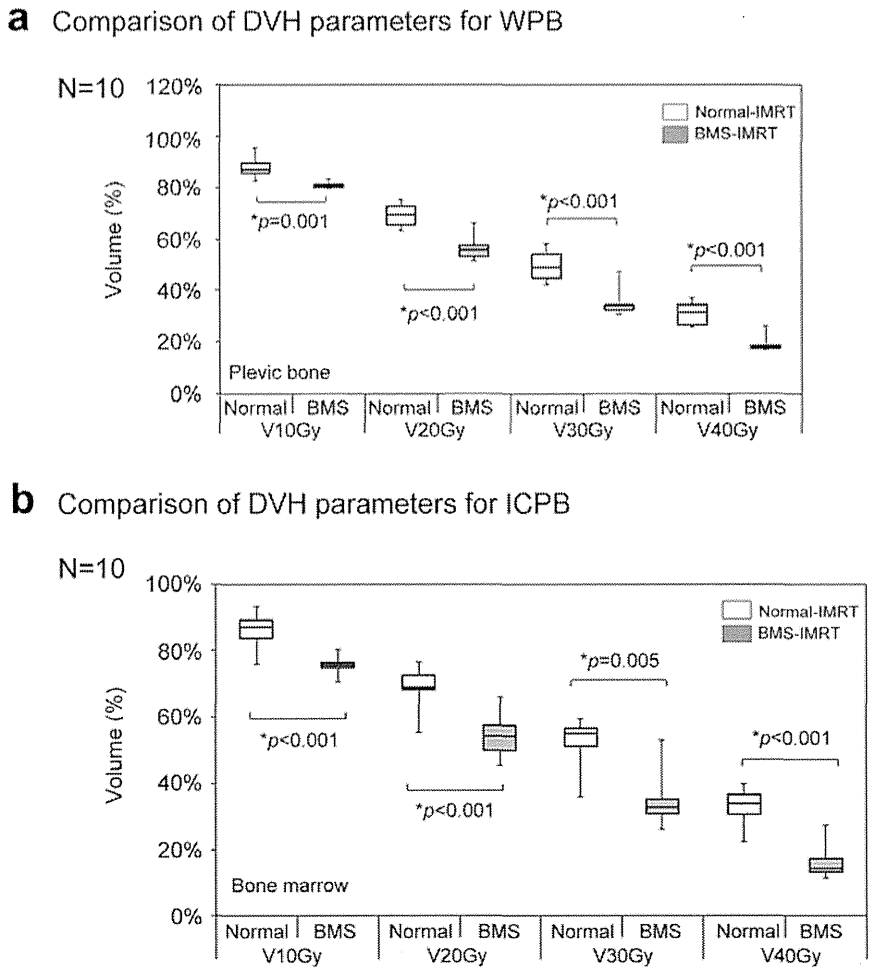

Figure 3. *Boxplots of dose volume histogram (DVH) parameters for whole pelvic bone (WPB) (a) and inner cavity of pelvic bone (ICPB) (b).*

between the 6-MV and 15-MV photon beams. The same degree of BMS and OAR sparing was achieved by using the 6-MV photon beam, while the monitor unit of this beam was higher because of its lower photon energy.

Discussion

It was demonstrated that early-stage cervical cancer patients who underwent radical hysterectomy and exhibited high-risk feature(s) could benefit postoperative concurrent chemoradiotherapy by a multicenter prospective phase III randomized clinical trial (2). It was also shown in this study that it was important to deliver as many chemotherapy cycles as possible. In the RTOG 0418 trial (12), postoperative endometrial and cervical cancer patients were entered and treated by postoperative radiation therapy by IMRT. In the present study, cervical cancer patients were treated by concurrent chemoradiotherapy using weekly cisplatin 40 mg/m^2. Although bone marrow sparing was not intended in the protocol of RTOG 0418, favorable hematological profiles were shown; 83% received 5 or more cycles of cisplatin and 90% received at least 4 cycles of cisplatin (13). The RTOG 0418 data demonstrated that pelvic bone V_{40Gy} >37% was associated with grade 2 or higher hematologic toxicity (13). On the other hand, Rose *et al.* reported that patients with V10Gy ≥95% as well as V_{20Gy} ≥76% were more likely to experience grade ≥3 leukopenia (21). Mell *et al.* also showed from a small sized retrospective study that bone marrow V_{10Gy} was a strong predictor for grade 2 or worse leukopenia (22). Albuquerque *et al.* reported the importance of the volume of bone receiving 20 Gy (23). Therefore, V_{10Gy}, V_{20Gy}, V_{30Gy} and V_{40Gy} were extracted and compared in the current study since controversies still remain over whether lower or higher

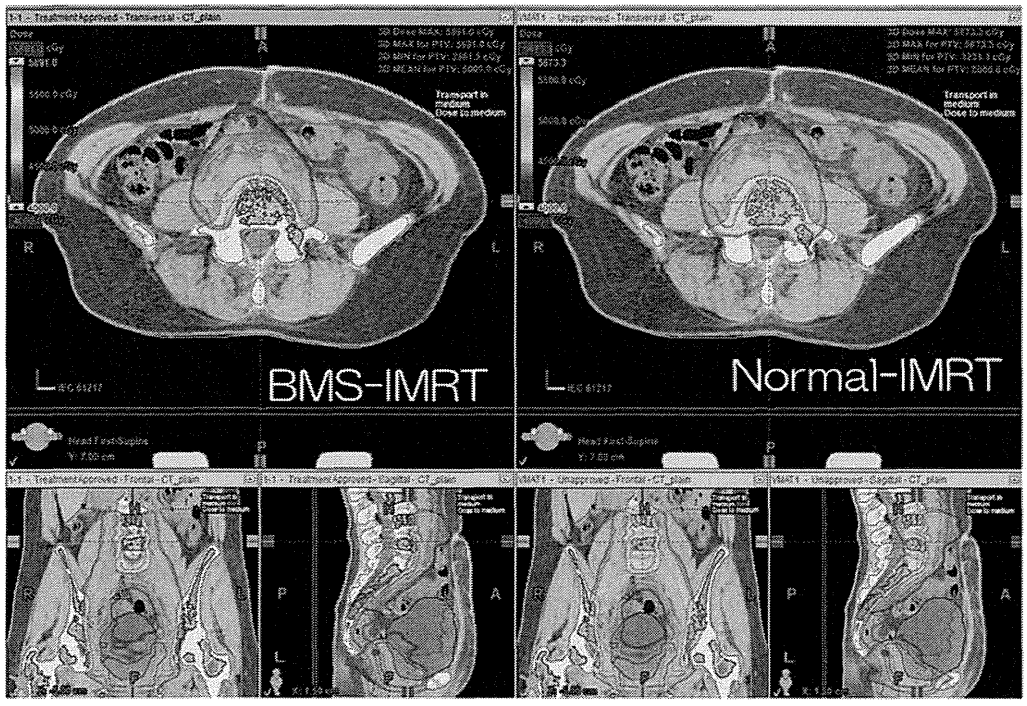

Figure 4. *An example of dose distribution of bone marrow sparing (BMS)–IMRT and normal-IMRT. The area which received 40 Gy or more is colored.*

dose on bone marrow affects its function. Mahantshetty *et al.* demonstrated that ICPB was a better surrogate of active bone marrow than whole pelvic bone WPB (20); therefore, both WPB and ICPB were examined in this study.

In the current study, it was clearly demonstrated that both lower and higher dose for WPB as well as ICPB were significantly lower in the BMS-IMRT plan compared to the normal-IMRT plan without changing the coverage of target volume and other organs at risk. Therefore, it is important to include bone marrow structures into dose-constraint structures for post-hysterectomy radiation therapy by IMRT especially with concurrent use of chemotherapy. Our institution uses a 15-MV photon beam for irradiating the pelvic region because a high energy photon beam has an advantage of delivering photons to deep-seated organs with less attenuation; however, the 15-MV photon beam has a concern about creating neutrons along with photons. Therefore, another BMS-IMRT plan was created using a 6-MV photon beam. Since the same trend was obtained by using the 6-MV photon, BMS-IMRT may protect the patient's bone marrow function in institutions where such a beam is used for cervical cancer.

Among the limitations of this work it has to be noted that it was a single-institution retrospective study with small number of patients that analyzed only DVH parameters virtually based on CTs taken before radiotherapy. Also, it is important to maintain the patient's anatomical relationship as planning CT, namely monitoring the filling of bladder and the emptiness of rectum because otherwise intended OAR sparing will not be achieved. Since this study was represents a "plan-to-be" approach, we have to verify the efficacy of BMS-IMRT in a clinical setting. Recently RTOG

Table III. *Comparison of dose-volume histogram parameters of bone marrow sparing intensity-modified radiation therapy plans between 6 MV and 15 MV photon beams.*

	6X-15X (%)		6X-15X (%)
PTV D_{max}	0.80	Rectum V_{30Gy}	–2.07
PTV $D_{95\%}$	0.07	Rectum V_{40Gy}	–0.33
PTV $D_{97\%}$	0.10	Rectum V_{50Gy}	2.17
PTV Median	–0.01	Bladder V_{35Gy}	0.97
PB V_{10Gy}	0.53	Bladder V_{45Gy}	0.53
PB V_{20Gy}	0.60	Bladder V_{50Gy}	1.67
PB V_{30Gy}	0.10	Bowel V_{35Gy}	0.73
PB V_{40Gy}	0.23	Bowel V_{40Gy}	0.50
BM V_{10Gy}	0.37	Bowel V_{45Gy}	0.70
BM V_{20Gy}	–0.57	Bowel V_{50Gy}	0.83
BM V_{30Gy}	–0.03	FM V_{30Gy}	0.80
BM V_{40Gy}	0.50	MU	93 (MU)

PTV: Planning target volume, PB: pelvic bone, BM, bone marrow, FM: femoral head, MU: monitor unit.

1203 was launched in order to validate whether IMRT could decrease acute gastrointestinal toxicity compared to conventional radiotherapy with bone marrow-sparing included in the protocol. Therefore, important information about the influence of IMRT over bone marrow will be available soon.

Whether WPB or ICPB is more appropriate in surrogate structures for bone marrow function(s) will be confirmed by future prospective studies. Also, the appropriate doses for bone marrow's protection need to be further investigated in the near future.

Conclusion

Both lower and higher dose for WPB, as well as ICPB were effectively decreased by IMRT with an intention of avoiding damage of bone marrow structure without compromising the coverage of target volume and other organs at risk.

Conflicts of Interest

There are no conflicts of interest to be declared.

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ORIGINAL ARTICLE – CLINICAL ONCOLOGY

Severe gastrointestinal bleeding in patients with locally advanced head and neck squamous cell carcinoma treated by concurrent radiotherapy and Cetuximab

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Abstract
Purpose Concurrent administration of Cetuximab with radiotherapy (Cetuximab-radiation) has been accepted as an alternative option for locally advanced head and neck squamous cell carcinoma (HNSCC). The purpose of this study was to retrospectively compare complications of Cetuximab-radiation with those of concurrent chemoradiation (cCRT) with a special concern on gastrointestinal (GI) hemorrhage associated with Cetuximab-radiation.
Methods Indication of Cetuximab-radiation/cCRT for locally advanced HNSCC was primary, postoperative adjuvant, or salvage after recurrence. Our first choice for patients with advanced HNSCC was cCRT; however, if patients did not have enough organ function but with a favorable performance status, Cetuximab-radiation was applied.
Results From April 2013 to March 2014, 30 patients were identified who were treated with Cetuximab-radiation or cCRT and each cohort consisted of 15 patients. Patients in Cetuximab-radiation cohort suffered from a statistically higher rate of G3/4 dermatitis compared with cCRT cohort (80 vs. 13.3 %, respectively, $p < 0.001$). More patients required unexpected hospitalization due to deterioration of their general condition and total parenteral nutrition in Cetuximab-radiation cohort ($p = 0.011$ and $p = 0.025$, respectively). While none experienced GI bleeding in cCRT cohort, four patients experienced GI bleeding including two grade 4 bleeding in Cetuximab-radiation cohort ($p = 0.05$).
Conclusions It is probable that there exists a group of patients who are susceptible for Cetuximab-radiation not only in terms of well-known dermatitis and mucositis but also of gastrointestinal complications.

Keywords EGFR inhibitor · Cetuximab · Radiation therapy · Gastrointestinal bleeding · Adverse effect · Head and neck squamous cell carcinoma

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Introduction

Targeted therapies are recently emerged type of anticancer treatment which can be used as single agent or in combination with cytotoxic chemotherapy and/or radiotherapy (RT) (Ciardiello and Tortora 2008; Hudis 2007; Maloney 2012). In targeted therapies, anticancer agents inhibit a particular target molecule on tumor cells which is involved in tumor proliferation or progression. Therefore, in contrast to conventional chemotherapy which targets certain cellular mechanisms common to both malignant as well as normal healthy cells, targeted therapy agents are directed highly selectively at specific target and considered to be more well tolerated than conventional chemotherapy. The epidermal growth factor receptor (EGFR) is one of the tyrosine kinase receptors

of the ErbB family which is a transmembrane glycoprotein that regulates various cellular processes, such as cell proliferation, differentiation, and survival (Lacouture 2006). Its dysregulation in various cancers such as head and neck, lung, and gastrointestinal tumors has been correlated with unfavorable prognosis (Brockstein et al. 2008; Ang et al. 2002; Hitt et al. 2005). Cetuximab (Erbitux; Merck-Serono, Darmstadt, Germany) is a human-murine chimeric monoclonal antibody against the extracellular domain of the EGFR which competitively inhibits endogenous ligand binding and enhances the sensitivity of tumor cells to radiation therapy (Baselga et al. 2005). Because head and neck squamous cell carcinoma (HNSCC) generally expresses high levels of EGFR, clinical trials demonstrated that addition of Cetuximab to RT resulted in a significant increase in both locoregional and survival rates compared with RT alone, even on a long-term follow-up (Pfister et al. 2006; Bonner et al. 2006, 2010; Curran et al. 2007). Not only demonstrating favorable survival benefit, but also Bonner trial did not show any statistically significant difference in terms of acute radiation dermatitis (either all grades or grade ≥ 3) between with or without Cetuximab arms (Bonner et al. 2006). Consequently, concurrent administration of radiation therapy and Cetuximab (Cetuximab-radiation) has become an alternative option for locally advanced HNSCC other than the conventional cisplatin-based concurrent chemoradiation (cCRT). However, severe dermatitis correlated with Cetuximab-radiation has recently been reported by several authors (Lord et al. 2008; Bölke et al. 2008; Budach et al. 2007; Valeriani et al. 2012; Studer et al. 2011).

Since April 2013, our institution began to use Cetuximab-radiation for advanced head and neck squamous carcinoma patients. We experienced not only severe dermatitis, mucositis, and severe distress which required total parenteral nutrition (TPN), but also severe gastrointestinal bleeding which has not been reported ever before as a complication of Cetuximab-radiation. The purpose of this study was to retrospectively compare treatment-related acute toxicities of Cetuximab-radiation with a concurrent chemoradiation (cCRT) with triweekly cisplatin (CDDP) with a special focus on the gastrointestinal (GI) hemorrhage associated with Cetuximab-radiation.

Materials and methods

In our institution, multidisciplinary tumor board is held to determine the treatment strategy for advanced stage HNSCC. Cetuximab-radiation/cCRT for locally advanced HNSCC was employed as a primary, postoperative adjuvant, or salvage therapy after disease recurrence. Inclusion criteria for postoperative adjuvant RT were positive margin, multiple lymph node metastasis, and extra-capsular extension. Because until now there exists on evidence supporting the superiority of Cetuximab-radiation over platinum-based cCRT in the management of advanced HNSCC, our first choice was cCRT. However, if patients did not have enough organ function but still sustained good performance status, Cetuximab-radiation was applied. All patients included in this study were histologically confirmed advanced HNSCC and evaluated as feasible for curative treatment. One patient with preauricular skin cancer had neck lymph node as well as orbit metastasis which can be recognized as distant metastasis; however, because his disease was confined within head and neck region, it was decided that he could tolerate curative treatment. Because this study was intended to assess the acute toxicity of Cetuximab-radiation or cCRT, this patient was included in this study.

Cetuximab-radiation cohort

All Cetuximab-radiation patients were treated according to the Bonner Protocol (Bonner et al. 2006). Administration of intravenous Cetuximab was initiated seven days prior to radiotherapy at a loading dose of 400 mg/m^2, followed by weekly 250 mg/m^2 until the end of radiotherapy. Intended cycles of Cetuximab were eight cycles. Premedication consisted of intravenous chlortrimeton (10 mg) and dexamethasone (6.6 mg). Cetuximab was discontinued in the case of severe hypersensitivity reaction but not delayed because of radiation-related toxic effects. Patients with Cetuximab-radiation also received oral prophylaxis of acne with minocycline (100 mg/day) (Scope et al. 2007).

cCRT cohort

Patients in cCRT cohort were selected from those who were treated by cCRT in the same time period as Cetuximab-radiation cohort (from April 2013 to March 2014). Administration of first CDDP (80 mg/m^2) was on the same day of radiotherapy start, followed by triweekly CDDP (80 mg/m^2) administration. Three cycles of CDDP were intended to be administered.

Radiotherapy

RT was prescribed in 2-Gy fractions with 6-MV photons in either conformal three-dimensional technique (3DCRT) or intensity-modulated radiation therapy (IMRT). When target volume did not contain large volume of major salivary gland, oral cavity, larynx, or pharynx, 3DCRT was selected; otherwise IMRT was applied. Target volumes were defined as follows: The gross tumor volume (GTV) included the gross extent of the primary disease and involved lymph node metastasis, taking physical

examinations and endoscopic/radiological findings into account. The clinical target volume 70 Gy (CTV_{70Gy}) was defined by adding a 10–15 mm margin to the GTV, subtracting those volume which is considered to be anatomically impossible to contain disease (e.g., outside of the body or inner part of pharyngeal lumen). The CTV_{54Gy} included the clinically negative cervical lymphatic pathways which are considered to be at risk for potential microscopic disease. For the postoperative treatment, the CTV_{66Gy} was defined areas considered as high risk for having microscopic disease such as positive surgical margin or metastatic lymph node with extracapsular extension based on preclinical imaging, preoperative physical exam/endoscopy, operative findings, and final pathologic findings. The CTV_{54Gy} was defined similar to the primary treatment. The planning target volume (PTV) for each CTV structure was created adding 5 mm margins to the CTV.

Simultaneously integrated boost (SIB)-IMRT was performed as follows:

(a) Primary or salvage radiotherapy

PTV_{70Gy}: 2 Gy per fraction to a total dose of 70 Gy/35 fr in five fractions per week.

PTV_{54Gy}: 1.54 Gy per fraction to a total dose of 54 Gy/35 fr in five fractions per week.

(b) Postoperative radiotherapy

PTV_{66Gy}: 2 Gy per fraction to a total dose of 66 Gy/33 fr in five fractions per week.

PTV_{54Gy}: 1.63 Gy per fraction to a total dose of 54 Gy/33 fr in five fractions per week.

Toxicity assessment

Before the initiation of the treatment, individual instructions for self-management about skin care and nutrition at home was provided. Patients were examined three times a week by radiation oncologists during radiotherapy. Patients' oral hygiene and mucositis were also monitored weekly by a dentist. Patients who developed greater than grade 2 dermatitis were intensively seen by our nurse-led skin care team. Severe dermatitis greater than grade 3 was treated with zinc oxide ointment after all planned RT course finished (Lansdown et al. 2007). Mucositis was managed according to the guideline developed by the European Society for Medical Oncology (ESMO) clinical practice guidelines (Peterson et al. 2010). Treatment-related toxicities were classified according to the National Cancer Institute common toxicity criteria version 4.0 (http//ctep.cancer.gov/forms/CTCAEv4.pdf).

Statistical analysis

Treatment-related toxicities were compared between two cohorts of Cetuximab-radiation and cCRT. Because both sample size and number of events were too small, it was impossible to analyze predictive factor for GI bleeding. Statistical analysis was performed using SPSS Statistics (version 18.0; SPSS, Inc., Chicago, IL). Student's unpaired t test was used to compare the continuous variables and Pearson's chi-square test to compare categorical variables. A p value of <0.05 was considered as statistically significant.

This retrospective study was approved by the institutional ethical review board of the National Cancer Center Hospital. This retrospective study was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Results

From April 2013 to March 2014, 30 patients were identified who were treated by Cetuximab-radiation or cCRT and each cohort consisted of 15 patients. Pretreatment patient characteristics are summarized in Table 1. Cetuximab-radiation cohort included more elderly patients older than 75 years compared with cCRT cohort ($p = 0.003$) because some elderly patients who were considered not feasible to undergo cCRT were selected for Cetuximab-radiation. Two and six patients had prior history of GI-related disease in both cohorts; however, this difference did not reach statistical significance ($p = 0.107$). Regular medications which could possibly cause gastrointestinal bleeding, such as anticoagulants, steroids, and non-steroidal anti-inflammatory drugs (NSAIDs), and which were started before radiation therapy were reviewed. There was no difference between two cohorts with regard to the intake of medications which could potentially be harmful to gastrointestinal tract ($p = 0.868$). In Cetuximab-radiation cohort about half of the patients had oropharynx cancers while only three in cCRT cohort, but this difference did not reach statistical significance. Table 2 shows treatment details of the two cohorts. No patient was treated as postoperative adjuvant radiotherapy in Cetuximab-radiation cohort possibly because patients who could undergo operation could also fit for cCRT. In Cetuximab-radiation cohort, four patients were treated by 3DCRT technique because in these patients irradiation fields did not include large volume of oral cavity nor pharyngeal cavity, while none in cCRT cohort was treated by 3DCRT ($p = 0.05$). While three patients (20 %) could not finish the intended cycles of systemic agent administration in cCRT cohort, as many as eight patients (53.3 %) could not in Cetuximab-radiation cohort. All

Table 1 Patient and tumor characteristics

	RT + CDDP ($n = 15$)	RT + Cetuximab ($n = 15$)	p
Median age (years, range)	69 (51–73)	70 (54–85)	0.081
Age group			
≤75	15	8	0.003*
>75	0	7	
Gender			
Male	13	13	0.701
Female	2	2	
Comorbidities[a]			
Colon cancer	0	2	0.439
Gastric cancer	0	2	
Esophageal cancer	2	1	
Liver cirrhosis	0	1	
Hepatitis	0	1	
Hypertension	5	3	
Diabetes mellitus	3	2	
Atrial fibrillation	0	3	
Dementia	0	1	
None	9	7	
GI[b]-related comorbidities			
Yes	2	6	0.107
No	13	9	
Regular mediation			
Anti-coagulants	1	2	0.868
Steroid	0	1	
NSAIDs[c]	4	4	
Site			
Hypopharynx	4	1	0.303
Oropharynx	3	8	
Larynx	5	3	
Oral cavity	1	2	
Others	2	1	
T-stage			
1–2	7	9	0.631
3	4	5	
4	4	1	
N-stage			
0	4	3	0.056
1	4	0	
2	7	12	
3	0	0	
M-stage			
0	15	14	0.5
1	0	1	
AJCC stage			
I	1	0	0.591
II	2	1	
III	3	2	
IV	9	12	

* A p value of <0.05 was considered as statistically significant

[a] Some patients had more than one comorbidities; therefore, the sum of the number exceeded 15

[b] *GI* gastrointestinal tract

[c] *NSAIDs* non-steroidal anti-inflammatory drugs

patients could finish the intended RT in cCRT cohort, on the other hand two (13.3 %) could not in Cetuximab-radiation cohort.

Toxicity assessment

Treatment-related acute toxicities of the two cohorts are summarized in Table 3. Patients in Cetuximab-radiation cohort suffered from statistically higher rate of G3/4 dermatitis compared with cCRT cohort (80 vs. 13.3 %, respectively, $p < 0.001$). Figure 1 shows typical grade 3 dermatitis with superficial infection in patient treated by Cetuximab-radiation. Confluent moist desquamation with yellowish surface which indicated superficial infection developed in the left side of the neck corresponding to radiation field. This patient eventually developed systemic infection which required systemic administration of antibiotics. Nine out of 15 patients (60 %) required zinc oxide ointment to deal with their severe dermatitis in Cetuximab-radiation cohort while none in cCRT cohort ($p < 0.001$). Although the difference did not reach statistical significance, in cCRT cohort grade 2/3 leukopenia was seen more frequently than in Cetuximab-radiation cohort. More patients required unexpected admission to the hospital due to deterioration of their general condition and total parenteral nutrition (TPN) such as feeding tube placement, gastrostomy tube placement, or central venous catheter insertion in Cetuximab-radiation cohort than cCRT cohort ($p = 0.011$ and $p = 0.025$, respectively). While none experienced GI bleeding in cCRT cohort, four patients in Cetuximab-radiation cohort experienced GI bleeding within two weeks after the completion of the radiation therapy ($p = 0.05$). One of these patients with grade 4 rectal bleeding had a prior operation for sigmoid colon cancer and another with grade 2 bleeding from

Table 2 Treatment detail

	RT + CDDP ($n = 15$)	RT + Cetuximab ($n = 15$)	p
Indication of RT			
Primary definitive radiation	6 (40.0 %)	10 (66.7 %)	0.059
Postoperative adjuvant radiation	5 (33.3 %)	0 (0 %)	
Salvage radiation	4 (26.7 %)	5 (33.3 %)	
Reason to choose RT + Cetuximab			
Advanced age	–	7 (46.7 %)	–
Kidney disfunction	–	3 (20 %)	
The others	–	5 (33.3 %)	
Median administered cycles of systemic therapy (range)	3 (1–3)	7 (4–9)	<0.001*
Patients who could not finish intended cycles of systemic therapy	3 (20.0 %)	8 (53.3 %)	0.058
Type of radiotherapy technique			
IMRT[a]	15 (100 %)	11 (73.3 %)	0.05*
3DCRT[b]	0 (0 %)	4 (26.7 %)	
Median total RT dose (Gy, range)	70 (60–76)	70 (60–70)	0.915
Patients who could not finish intended RT	0 (0 %)	2 (13.3 %)	0.241

* A p value of <0.05 was considered as statistically significant

[a] *IMRT* intensity-modulated radiation therapy

[b] *3DCRT* three-dimensional conformal radiation therapy

Table 3 Treatment-related toxicity

	RT + CDDP ($n = 15$)	RT + Cetuximab ($n = 15$)	p
G3/4 dermatitis (%)	2 (13.3)	12 (80.0)	<0.001*
Zinc oxide ointment usage (%)	0 (0)	9 (60.0)	<0.001*
G3/4 mucositis (%)	3 (20)	10 (66.7)	0.01*
G2/3 leukopenia (%)	8 (53.3)	3 (20.0)	0.136
GI bleeding (%)	0 (0)	4 (26.7)	0.05*
TPN[a] (%)	3 (20)	8 (53.3)	0.025*
Unexpected hospitalization (%)	4 (26.7)	11 (73.3)	0.011*
Period of hospitalization (days, range)	19 (10–57)	19 (0–57)	0.513

* A p value of <0.05 was considered as statistically significant

[a] *TPN* total parenteral nutrition

hemorrhoid had prior history of endoscopic submucosal dissection for gastric cancer. The other two patients did not have a past history for major gastrointestinal tract disease. Only patient with bleeding from hemorrhoid used NSAIDs daily for his neck pain before the start of Cetuximab-RT; the other three patients did not use any drugs before the start of Cetuximab-RT potentially harmful for GI such as anticoagulants, steroids, and NSAIDs. Because three out of four of these patients had macroscopic hemorrhage with hemoglobin decrease of 2 g/dl or more, these three patients underwent endoscopy (Fig. 2). Among patients with GI bleeding, two patients experienced grade 4 GI bleeding requiring emergency endoscopic hemostasis and blood infusion for hypovolemic shock (one had bleeding from upper body of stomach, the other from rectum ampulla). The reason to select Cetuximab-radiation for the patients with GI bleeding was advanced age for three patients and slight kidney dysfunction for one patient. Because of small number of events, it was not possible to find potential clinical factors correlated with GI bleeding.

Discussion

It is well known that EGFR inhibitor itself causes dermatitis including acne-like rash, papulopustular rash, dry and itchy skin, and periungual inflammation. Such dermatitis potentially causes infection especially in seborrheic regions such as the scalp, face, neck, and chest (Eilers et al. 2010; Thomas 2005; Lacouture 2006). Therefore, Cetuximab-radiation for HNSCC patients requires an intensive prevention for skin reaction. Initially conducted clinical trials with combination regimens of Cetuximab and radiotherapy did not report severe radiotherapy-related toxicities (Pfister et al. 2006; Bonner et al. 2006, 2010; Curran et al. 2007). In Bonner's study (Bonner et al. 2006), the typical acneiform

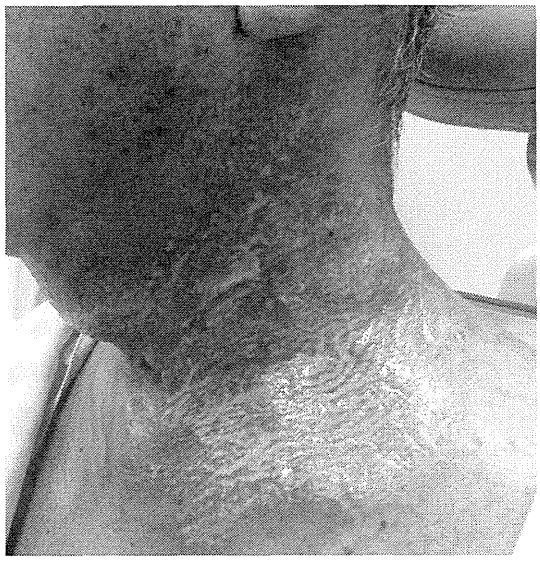

Fig. 1 A representative picture of a patient who was treated with Cetuximab-radiation and developed grade 3 dermatitis with superficial infection. In the radiation field area, moist desquamation with yellowing developed. This patient eventually developed systemic infection

rash was reported in 17 % (grade 3/4) of the patients, while the rate of grade 3/4 radiation dermatitis did not significantly increase compared with RT alone group (23 vs. 18 %). On the other hand, current observation of 12 out of 15 cases (80 %) of grade 3/4 dermatitis in Cetuximab-radiation cohort (Table 3) seemed to be in contradiction to these data. However, accumulating literature reported severer dermatitis than what was reported in Bonner's trial (Lord et al. 2008; Bölke et al. 2008; Budach et al. 2007; Valeriani et al. 2012; Studer et al. 2011). Bölke et al. (2008) reported that skin necrosis may occur at total doses at the epidermal basal cell layer of <31 Gy if Cetuximab-radiation was applied to patients. Studer et al. (Studer et al. 2011) pointed out that patients' ability to complete all intended cycles of Cetuximab in Cetuximab-radiation cohort was lower than that of in cCRT cohort because of substantial mucositis and painful dermatitis, which was similar to the current study.

Because radiation field did not include stomach, rectum, and anal canal, it was reasonable to consider that GI bleedings which occurred in our patients were not attributed to radiotherapy alone. Many reports exist about hemorrhage from gastrointestinal as well as upper airway tract as complications of monoclonal antibody targeted against the vascular endothelial growth factor (VEGF) (Ranpura et al. 2011; Saif and Mehra 2006). Up to now, the mechanism of abnormal hemorrhage is still unclear; however, the risk of bleeding may be due to an effect of VEGF on vascular endothelium because VEGF is a major regulator of endothelial renewal. Therefore, inhibition of VEGF may decrease the renewal capacity of the endothelium in response to trauma, thereby increasing the tendency to bleed (Saif and Mehra 2006). However, as far as author's knowledge there exists no report concerning with GI bleeding caused by Cetuximab and this report is thought to be the first one. In our country, Cetuximab was first introduced in the treatment of colon cancer and single use or combination use with chemotherapy was not reported to cause GI bleedings. Therefore, it is possible to suppose that there exists some kind of interaction between RT and Cetuximab under the mechanisms of GI bleeding. In current study, most of the patients with GI bleeding also experienced severe dermatitis and mucositis requiring TPN, suggesting that these patients might have had susceptibility for Cetuximab not only in their gastrointestinal tract, but also skin epithelium and pharyngeal mucosa. Although there is no report ever, it is not surprising that Cetuximab may cause GI bleeding, because EGFR is normally expressed also in gastrointestinal epithelium (Alison and Sarraf 1994). It is possible that there exists racial disparities between Asian and Western people over the responses of GI tract against EGFR inhibitor; however, this remains to be solved.

In this study, patients with Cetuximab-radiation required significantly higher rate of unexpected admission due to deterioration of their general condition. This could be explained that more patients experienced severe mucositis in Cetuximab-radiation cohort than in cCRT cohort (Table 3, $p = 0.01$). Another possible reason for this higher hospitalization rate was that Cetuximab-radiation cohort included more elderly patients than cCRT cohort. It is well known that many physiological deteriorations occur with aging (Aapro et al. 2000). Age-related changes could influence pharmacodynamics as well as pharmacokinetics and may exaggerate the manifestation of severe adverse events induced by anticancer agents including Cetuximab. Therefore, it is dangerous to consider that elderly patients who are not fit for cCRT could be easily treated by Cetuximab-radiation.

Recently, Bernier et al. (2011) suggested modifications to the current NCI-CTCEA version 4.0 grading system for accessing radiation dermatitis caused by Cetuximab-radiation and proposed grade-specific management guidelines. In this modification, they recommended early intervention using moisturization, topical steroid, or topical antibiotics as well as provided management strategy for crust which can cause superficial infection. Furthermore, in contrast to protocol of Bonner trial (Bonner et al. 2006), this guideline suggested treatment interruption when grade 4 dermatitis occurred. By applying this guideline, it could be expected that feasibility of Cetuximab-radiation would be improved. Adverse events of new targeted agents must be further explored.

There were several limitations in this study. Because the sample size and events of this study was small, it was not possible to analyze statistically what were the predictive factors for GI bleeding. The background between two cohorts

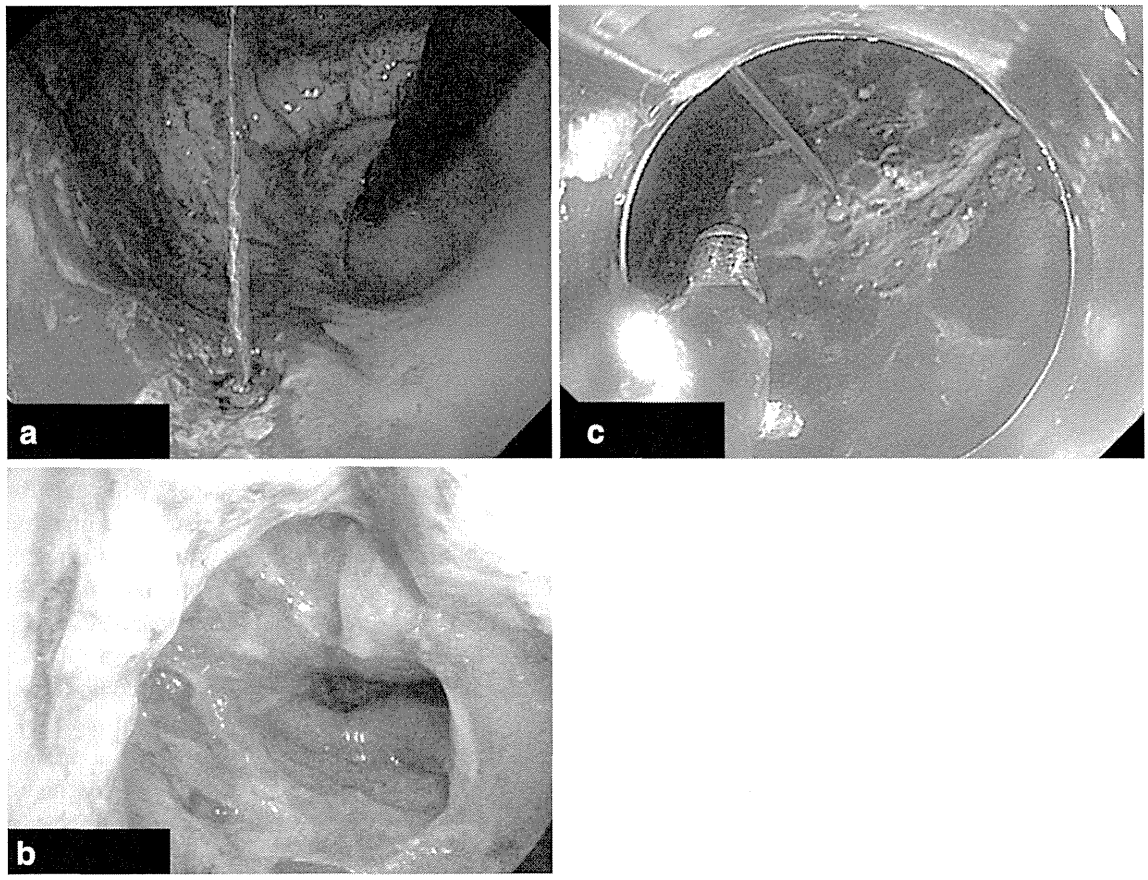

Fig. 2 Endoscopic findings of those who developed gastrointestinal (GI) bleeding. **a** Grade 4 arterial bleeding from upper body of stomach. Two times of emergency endoscopic hemostasis was required. **b** Grade 2 venous bleeding from rectum. It resolved conservatively. **c** Grade 4 arterial bleeding from rectum ampulla. Single emergency endoscopic hemostasis was required

was different. Because there exists no evidence supporting the superiority of Cetuximab-radiation over cCRT and the efficacy of cCRT in the field of HNSCC has been proved for a long time, our first choice for advanced HNSCC was to apply cCRT. Only patients who were not fit for cCRT entered Cetuximab-radiation cohort. Therefore, the feasibility of Cetuximab-radiation in comparison with cCRT in Japanese patients should be accessed in the future clinical trials with equivalent backgrounds. Finally, this study was a retrospective study from a single institution. However, attention must be paid for possible occurrence of GI complication associated with the use of Cetuximab-radiation.

Conclusion

It is possible to suppose that there exists a group of patients who are susceptible for Cetuximab-radiation not only in terms of dermatitis and mucositis but also of gastrointestinal complications. Cautions must be required when Cetuximab-radiation is applied especially in elderly HNSCC patients.

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Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest. Authors have full control of all primary data and authors agree to allow the journal to review their data if requested.

Ethical standard This retrospective study was approved by the institutional ethical review board of the National Cancer Center Hospital. This retrospective study was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. All persons gave their informed consent prior to their inclusion in the study.

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Commissioning of 6 MV medical linac for dynamic MLC-based IMRT on Monte Carlo code GEANT4

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Abstract Monte Carlo simulation is the most accurate tool for calculating dose distributions. In particular, the Electron Gamma shower computer code has been widely used for multi-purpose research in radiotherapy, but Monte Carlo GEANT4 (GEometry ANd Tracking) is rare for radiotherapy with photon beams and needs to be verified further under various irradiation conditions, particularly multi-leaf collimator-based intensity-modulated radiation therapy (MLC-based IMRT). In this study, GEANT4 was used for modeling of a 6 MV linac for dynamic MLC-based IMRT. To verify the modeling of our linac, we compared the calculated data with the measured depth-dose for a 10 × 10 cm^2 field and the measured dose profile for a 35 × 35 cm^2 field. Moreover, 120 MLCs were modeled on the GEANT4. Five tests of MLC modeling were performed: (I) MLC transmission, (II) MLC transmission profile including intra- and inter-leaf leakage, (III) tongue-and-groove leakage, (IV) a simple field with different field sizes by use of MLC and (V) a dynamic MLC-based IMRT field. For all tests, the calculations were compared with measurements of an ionization chamber and radiographic film. The calculations agreed with the measurements: MLC transmissions by calculations and measurements were 1.76 ± 0.01 and 1.87 ± 0.01 %, respectively. In gamma evaluation method (3 %/3 mm), the pass rates of the (IV) and (V) tests were 98.5 and 97.0 %, respectively. Furthermore, tongue-and-groove leakage could be calculated by GEANT4, and it agreed with the film measurements. The procedure of commissioning of dynamic MLC-based IMRT for GEANT4 is proposed in this study.

Keywords Commissioning · Monte Carlo simulation · GEANT4 · IMRT · MLC · Tongue-and-groove

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1 Introduction

In radiotherapy, intensity-modulated radiation therapy (IMRT) is a modern technique for delivering the optimum dose distributions to patients, i.e., a high dose to the target volume with simultaneous sparing of doses to healthy organs by modulated intensity with use of the movement of the multi-leaf collimator (MLC). However, MLC has a complex motion during irradiation, and the patterns of movement of MLC for each patient are variable. Therefore, to ascertain whether critical errors of the delivery systems during irradiation and critical errors in the dose calculation accuracy of radiotherapy treatment-planning systems (TPS) happen abruptly, the delivered dose distributions are generally measured with radiographic films and ionization chambers, and verified with Monte Carlo simulation [1–3].

In many studies, the Monte Carlo simulation has been a useful tool not only for calculation of dose distributions for