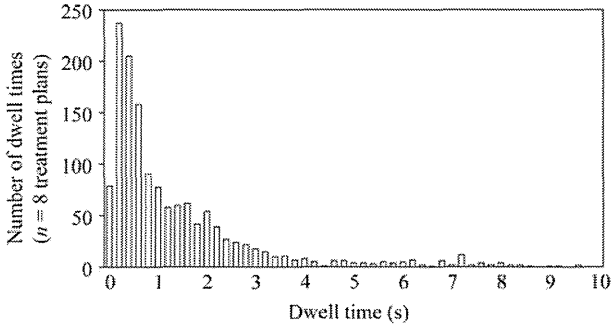

Fig. 6. Distribution of dwell times for the multiple interstitial needle applicators ($n = 8$ treatment plans). Inverse planning and graphical optimization are used to optimize dwell time in the Treatment Planning System.

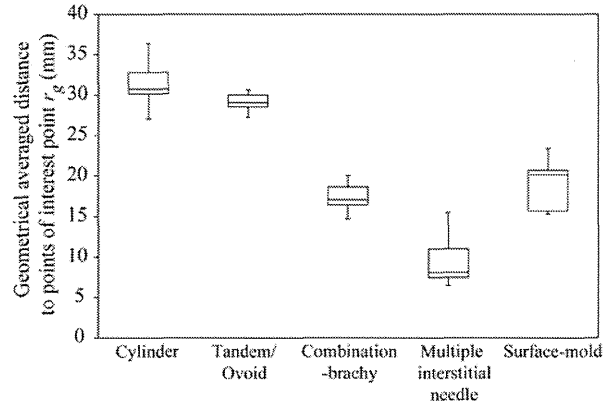

Fig. 7. The box-and-whisker plot of the geometrical averaged distance to the point of interest derived from Eq. (2) for clinical treatment plans (see Table 1).

Table 3. Potential dose errors for clinical treatment plans (see Table 1) with $\Delta T = 32$ ms and $\Delta P = 0.12$ mm from measurements

Applicators or catheters	(ΔT, ΔP) = (32 ms, 0.12 mm) Potential dose error
Cylinder	~0.1%
Tandem/ovoid	~0.2%
Combination-brachytherapy	~0.3%
Multiple interstitial needle applicators	~2.0%
Surface-mold for scalp tumor	~1.3%

DISCUSSION

In brachytherapy, there are many uncertainties in the prescribed dose for the overall treatment process such as the uncertainty in calculating the absolute dose [17–19] and the effect of inhomogeneity [20–24], the mechanical accuracy of the source movement, and the intra- and inter-fractional displacements of the applicators or catheters, which cause substantial dose deviation from the planned dose. Of these uncertainties, we focus upon the dose errors caused only by the mechanical uncertainties of movement of the source in ^{192}Ir HDR-RALS in terms of dwell time and source position.

The dwell time deviation was obtained from the amount of electric charge from the WIC during the irradiation [see Eq. (1)]. This measurement is considered to be influenced by the deviation, both in dwell time and source position. However, we could neglect the influence of deviation in the source position, for the following reason. For this measurement, the ^{192}Ir source was located at a predetermined position in the WIC where the amount of electric charge represented the maximum. The behavior of the amount of electric charge in this region can be comparatively flat for a variable source position. For example, a displacement of 0.1 mm in the source position causes a change in the amount of electric charge by 0.001%. This corresponds to a dwell time of 1 ms. Therefore, the amount of electric charge is weakly dependent on the deviation of the source position.

The Nucletron RALS has high precision control of the dwell time of a source independent of dwell time (Table 2). We determined source position deviation via two methods, and the results obtained from each in this study were similar. Mechanical accuracy of the source movement in the short term was also evaluated. Actually, deterioration of the motor controlling source movement can happen abruptly or can gradually worsen in the long term. The long-term mechanical accuracy needs to be further investigated.

From Fig. 3, it is clear how dose error at the point of interest for a single catheter can change with variable dwell time and distance to the point of interest from a source. In the case of low dwell time and placement of the point of interest near a source, dose error can be expected to be high. Therefore, it is important that the effect of both deviations is taken into account when evaluating potential dose error for different the brachytherapy techniques. Of all the brachytherapy techniques investigated, the smallest and largest dwell times were obtained with the multiple interstitial needle and cylinder applicators, respectively (see Fig. 5). Additionally, the brachytherapy techniques having the smallest and largest distance to the point of interest from the source were also the multiple interstitial needle and cylinder applicators, respectively (see Fig. 7).

As shown in Table 3, all of the catheters or applicators represented fell within a 2% dose error. This is because the Nucletron RALS has high precision control of the movement of the radioactive ^{192}Ir source, $\Delta T = 32$ ms and $\Delta P = 0.12$ mm. The finding is that the potential dose error depends on the kind of brachytherapy technique used. Of all

the techniques investigated, the multiple interstitial needle applicators could introduce the most error, ~2.0% potential dose error. A procedure for evaluation of the potential dose error, applicable for all brachytherapy techniques, was proposed in this study. The authors recommended that the user establish the 2D-plot for dwell time and distance to the point of interest with the measured accuracy of movement of the source, and need to evaluate the potential dose error caused by mechanical uncertainties of movement of the source for the brachytherapy techniques used in a particular institute.

CONCLUSIONS

Mechanical uncertainties in the ^{192}Ir HDR-RALS (Nucletron, an Elekta company), a dwell time deviation ΔT of 32 ms and a source position deviation ΔP of 0.12 mm were obtained from measurements. The finding was that the Nucletron HDR-RALS has high precision control of the movement of the radioactive ^{192}Ir source in terms of dwell time and source position. The potential dose error caused by the two deviations depends on the kind of brachytherapy technique used. Of the techniques studied, multiple interstitial needle applicators have the highest susceptibility to dwell time deviation and source position deviation.

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Radiotherapy for gastric lymphoma: a planning study of 3D conformal radiotherapy, the half-beam method, and intensity-modulated radiotherapy

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During radiotherapy for gastric lymphoma, it is difficult to protect the liver and kidneys in cases where there is considerable overlap between these organs and the target volume. This study was conducted to compare the three radiotherapy planning techniques of four-fields 3D conformal radiotherapy (3DCRT), half-field radiotherapy (the half-beam method) and intensity-modulated radiotherapy (IMRT) used to treat primary gastric lymphoma in which the planning target volume (PTV) had a large overlap with the left kidney. A total of 17 patients with gastric diffuse large B-cell lymphoma (DLBCL) were included. In DLBCL, immunochemotherapy (Rituximab + CHOP) was followed by radiotherapy of 40 Gy to the whole stomach and peri-gastric lymph nodes. 3DCRT, the half-field method, and IMRT were compared with respect to the dose–volume histogram (DVH) parameters and generalized equivalent uniform dose (gEUD) to the kidneys, liver and PTV. The mean dose and gEUD for 3DCRT was higher than for IMRT and the half-beam method in the left kidney and both kidneys. The mean dose and gEUD of the left kidney was 2117 cGy and 2224 cGy for 3DCRT, 1520 cGy and 1637 cGy for IMRT, and 1100 cGy and 1357 cGy for the half-beam method, respectively. The mean dose and gEUD of both kidneys was 1335 cGy and 1559 cGy for 3DCRT, 1184 cGy and 1311 cGy for IMRT, and 700 cGy and 937 cGy for the half-beam method, respectively. Dose–volume histograms (DVHs) of the liver revealed a larger volume was irradiated in the dose range <25 Gy with 3DCRT, while the half-beam method irradiated a larger volume of liver with the higher dose range (>25 Gy). IMRT and the half-beam method had the advantages of dose reduction for the kidneys and liver.

Keywords: primary gastric lymphoma; radiotherapy; IMRT; half-field method; planning study

INTRODUCTION

Primary gastric lymphomas are mainly consists of mucosa-associated lymphoid tissue (MALT) lymphoma and diffuse large B-cell lymphoma (DLBCL). While standard treatment of gastric MALT lymphoma refractory to *Helicobacter pylori* (HP) sterilization is radiotherapy of ~30 Gy with conventional fractionation [1, 2], localized gastric DLBCL is treated with immunochemotherapy and ensuing radiotherapy of ~30–40 Gy with conventional fractionation [3, 4]. The clinical target volume (CTV) for gastric lymphoma is the whole stomach and neighboring peri-gastric lymph node stations. The stomach shows physiological motions due to respiration and peristalsis, which necessitates large margins being added to the CTV to set up the internal target volume (ITV). During radiotherapy of the stomach, the main organs at risk (OARs) are the kidneys and liver. Meticulous attention should be paid to kidney and liver tolerances because they are relatively sensitive to radiation. The tolerance dose is expressed as $TD_{5/5}$ and $TD_{50/5}$, indicating the doses at which

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late morbidity is seen in 5% and 50% respectively in 5 years. $TD_{5/5}$ and $TD_{50/5}$ for whole kidney irradiation are 23 Gy and 28 Gy, respectively. Also, $TD_{5/5}$ and $TD_{50/5}$ for whole liver irradiation have been reported to be 30 Gy and 40 Gy, respectively [5]. Radiation effects to the kidneys and liver were recently summarized in the QUANTEC study [6, 7, 8].

There are numerous reports about treatment planning for the abdominal region, e.g. gastric carcinoma [9] or pancreas carcinoma and/or bile duct malignancies [10, 11], and many reports indicate the advantages of intensity-modulated radiotherapy (IMRT). For gastric lymphoma, however, there are few reports about radiation treatment planning. In one such report, Della *et al.* classified gastric lymphoma into three types according to the amount of overlap between the kidney and the planning target volume (PTV). In cases with a large overlap between the kidney and the PTV, it is difficult to protect the kidney when using radiation of AP/PA opposing fields; in these cases, 3D conformal radiation therapy (3DCRT) is more advantageous. Use of IMRT might lead to further improvement for the left kidney and liver doses [12]. Additionally, Ringash *et al.* reported a five-fields technique for postoperative radiotherapy of gastric cancer. In this technique, the target volume is divided at the isocenter, which is typically placed at the level of the upper end of the left kidney. The volume superior to this isocenter is treated with AP/PA half-beam opposing fields, wheras the inferior volume is irradiated with an anterior and two half-beam wedged lateral fields. The resulting anterior fields irradiate the superior and inferior volumes with a single isocenter. A junctional move of 1 cm superiorly is planned after 10 fractions. This method was used to treat 20 patients, and acute toxicity was reduced to 25%, which is lower than the 41% observed in INT0116 [13]. INT0116 was a phase III study of chemoradiotherapy (fluorouracil plus leucovorin and 45 Gy/25 fractions to the tumor bed, regional nodes and 2 cm beyond the proximal and distal margins of resection) after surgery versus surgery alone for adenocarcinoma of the stomach or gastroesophageal junction [14]. We modified the method of Ringash *et al.* by deleting the lower half of the anterior field so as to reduce the dose to the left kidney. This half-beam method uses superior AP/PA half-beam fields and inferior LR/RL half-beam fields.

The current planning study was conducted on difficult cases with a large overlap between the kidney and the PTV, comparing the three planning techniques of 3DCRT, the half-beam method and IMRT.

MATERIALS AND METHODS

The radiation oncology database was searched for gastric DLBCL treated with radiotherapy of ~40 Gy/20 fractions from 1 January 2000 to 31 December 2012, whose 3D CT data was available for radiation planning. Eligible patients had an overlap of >50% between the left kidney and the PTV in an AP projection in digitally reconstructed radiography (DRR).

Patients were instructed to fast before treatment. In some patients, scopolamine butylbromide was used to suppress peristalsis. For X-ray simulation, a small amount of barium was swallowed to examine the degree of peristalsis. The CTV was defined as the whole stomach plus the neighboring peri-gastric lymph nodes. Planning CT was obtained in shallow exhale and inhale phases, and CTVs in both phases were fused and margins of peristalsis were added to obtain the ITV. The PTV was expanded 1 cm in all directions from the ITV to cover inter- and intra-fractional gastric motion and the set-up margin. On-board imaging (OBI) was used to confirm the fields covered the target sufficiently with a small amount of barium during treatment. During radiotherapy planning, the kidneys were contoured as the renal parenchyma excluding renal calyces. The three plans of 3DCRT, the half-beam method and IMRT were constructed using beam data generated by 15-MV X-rays from a linear accelerator (Clinac iX Linear accelerator, Varian, Palo Alto, CA). In 3DCRT, AP/PA or oblique fields and LR/RL fields or oblique fields were set up that covered the PTV adequately. In the half-beam method, the isocenter was set at the upper end of the left kidney, and the upper half of the PTV was treated using half-beam AP/PA or oblique fields with the reference point set to the central point of the field, while the lower half was irradiated with half-beam RL/LR or oblique lateral fields with the reference point set to the central point of the field. The junction was moved once a week. In the 3DCRT and half-beam methods, 40 Gy was applied to the isocenter. Nine fields at gantry angles of 0°, 35°, 60°, 110°, 165°, 210°, 290°, 315° and 340° were used in the IMRT treatment plan. Doses to the kidney and the liver were reduced to as low as possible, and the dose prescription in the IMRT treatment plan was defined by 95% of the PTV (D95) being irradiated to an equal dose to the 3DCRT planning.

Dose–volume histograms (DVHs) of the PTV, the liver, the right kidney, left kidney and both kidneys were analyzed. The mean dose and generalized equivalent uniform dose (gEUD) were compared between the three treatment plans. The gEUD is the uniform whole-organ dose that would cause equivalent biologic effect to the inhomogeneous dose distribution in the relevant organ. The gEUD can be obtained using the formula

$$\mathrm{gEUD} = \left(\sum_i v_i D_i^a\right)^{1/a} \text{ [15],}$$

where v_i is the fractional organ volume receiving a dose D_i and a is a tissue-specific parameter that represents the volume effect.

In the statistical analysis, each parameter was analyzed by non-parametric comparison. A P value < 0.0167 was considered significant when two of the three plans were evaluated (multiple comparison, Bonferroni method). Our institutional review board (the National Cancer Center Institutional Review

Board) approved this study, and treatment was carried out with written informed consent.

RESULTS

A total of 92 patients with gastric DLBCL underwent post-chemotherapy radiation therapy in the study period; 17 of the 92 patients (18.5%) were classified as 'difficult' cases with a large overlap of the left kidney and the PTV, and were thus included in this study. Average DVHs for the three plans are shown in Fig. 1. The mean dose and the gEUD of the three plans are summarized in Table 1.

Comparing the DVHs in the dose range <15 Gy, an increasing volume of the right kidney was irradiated by the half-beam method, 3DCRT and IMRT (in that order). In the dose range >25 Gy, the DVHs of the three plans converged with one another. The resulting mean dose and gEUD of the right kidney for IMRT was higher than for 3DCRT and

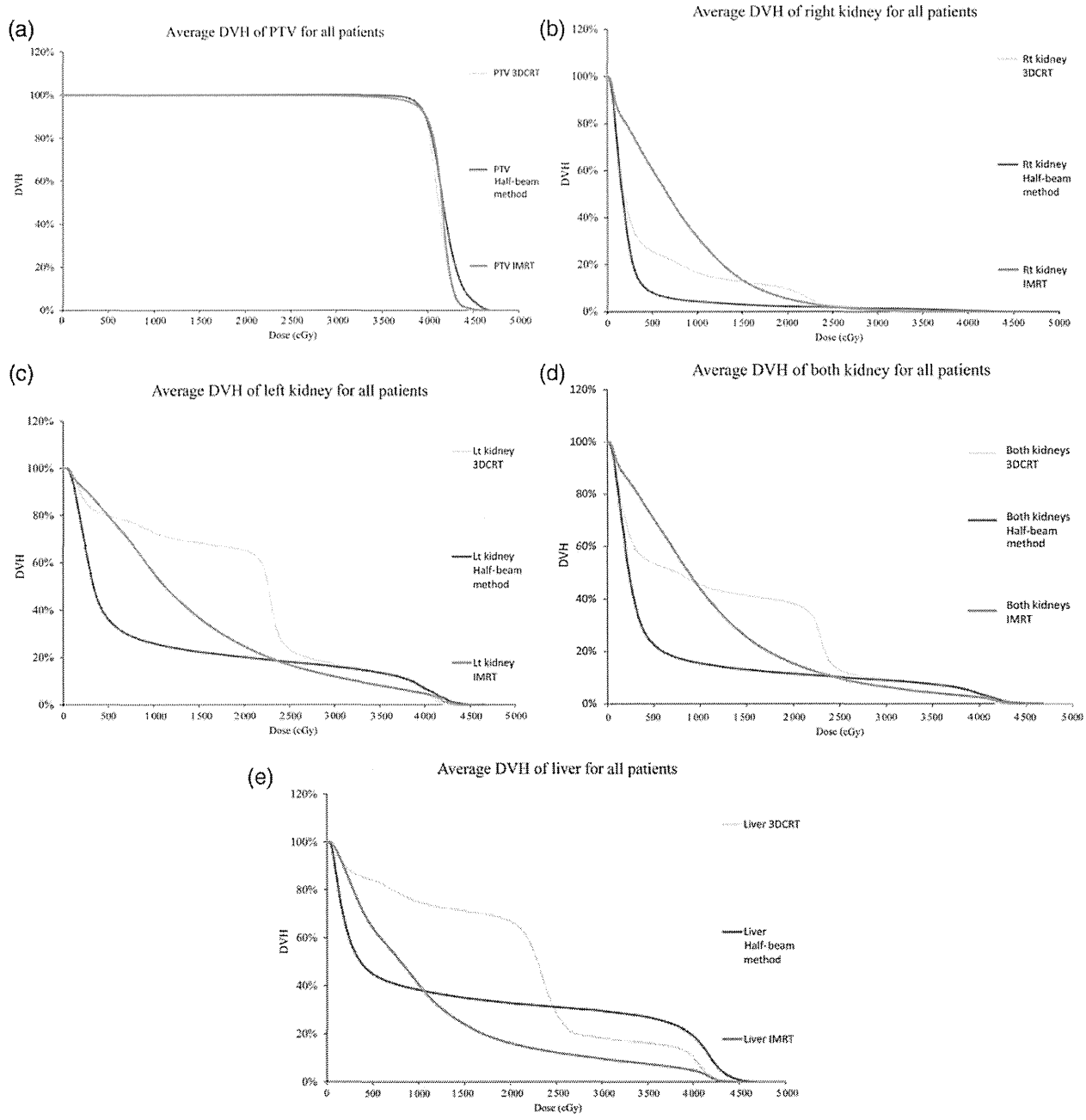

Fig. 1. Average DVH comparing 3DCRT, the half-beam method and IMRT. (a) DVH of PTV, (b) DVH of the right kidney, (c) DVH of the left kidney, (d) DVH of both kidneys, and (e) DVH of the liver.

Table 1. Mean doses and gEUDs of right, left and both kidneys and liver according to 3DCRT, the half-beam method and IMRT

	3DCRT (mean)	Half-beam method (mean)	IMRT (mean)	*P* value IMRT vs half-beam method	*P* value half-beam method vs 3DCRT	*P* value IMRT vs 3DCRT
Rt kidney						
mean dose (cGy)	519	283	835	<0.0001*	0.021	0.0012*
gEUD (cGy)	622	344	913	<0.0001*	0.0192	0.0043*
Lt kidney						
mean dose (cGy)	2117	1100	1520	0.0175	0.0003*	0.023
gEUD (cGy)	2224	1357	1637	0.2025	0.0017*	0.0192
Both kidneys						
mean dose (cGy)	1335	700	1184	0.0002*	<0.0001*	0.2025
gEUD (cGy)	1559	937	1311	0.0034*	0.0002*	0.0915
Liver						
mean dose (cGy)	2115	1520	1135	0.0007*	0.0003*	<0.0001*
gEUD (cGy)	2656	2746	1976	<0.0001*	0.2856	<0.0001*

*$P < 0.0167$ considered to have a significant difference.

the half-beam method with statistical significance. The mean dose for IMRT was 835 cGy, for 3DCRT was 519 cGy ($P = 0.0012$) and for the half-beam method was 283 cGy ($P < 0.0001$). The gEUD for IMRT was 913 cGy, for 3DCRT was 622 cGy ($P = 0.0043$) and for the half-beam method was 344 cGy ($P < 0.0001$).

Similarly, in the dose range <25 Gy, an increasing volume of the left kidney was irradiated using the half-beam method, IMRT, and 3DCRT (in that order). In the higher dose range (>25 Gy), the DVHs of the three plans showed no difference. The resulting mean dose and the gEUD for 3DCRT was higher than for IMRT and the half-beam method, with the difference between the half-beam method and 3DCRT reaching statistical significance. The mean dose for 3DCRT was 2117 cGy, for IMRT was 1520 cGy ($P = 0.023$) and for the half-beam method was 1100 cGy ($P = 0.0003$). The gEUD for 3DCRT was 2224 cGy, for IMRT was 1637 cGy ($P = 0.0192$) and for the half-beam method was 1357 cGy ($P = 0.0017$).

Regarding the DVHs for both kidneys, in the low dose range (<10 Gy) an increasing volume of both kidneys was irradiated using the half-beam method, 3DCRT and IMRT (in that order), while in the moderate dose range (between 10 Gy and 25 Gy) an increasing volume of both kidneys was irradiated using the half-beam method, IMRT and 3DCRT (in that order); for >25 Gy the DVHs of the three plans converged with one another. The resulting mean dose and the gEUD for both kidneys using 3DCRT and IMRT was higher than using the half-beam method with statistical significance. The mean dose for the half-beam method was 700 cGy, for 3DCRT was 1335 cGy ($P < 0.0001$) and for IMRT was 1184 cGy ($P = 0.0002$). The gEUD using the half-beam method was 937 cGy, using 3DCRT was 1559 cGy ($P = 0.0002$) and using IMRT was 1311 cGy ($P = 0.0034$).

In the DVHs of the liver, a larger volume was irradiated using 3DCRT in the dose range <25 Gy, while the half-beam method irradiated a larger volume of the liver in the higher dose range. Although the mean dose of the liver was largest using 3DCRT (the mean dose using 3DCRT was 2115 cGy, using the half-beam method was 1520 cGy ($P = 0.0003$) and using IMRT was 1135 cGy ($P < 0.0001$)), the gEUD was largest using the half-beam method because the half-beam method exposed a larger volume of the liver in the dose range >25 Gy (the gEUD using the half-beam method was 2746 cGy, using 3DCRT was 2656 cGy ($P = 0.2856$) and using IMRT was 1976 cGy ($P < 0.0001$)).

DISCUSSION

In radiotherapy for gastric lymphoma, cases with a small overlap between the left kidney and the PTV are easy for radiotherapy planning, but for cases with a large overlap between them, OAR dose reduction is very difficult. We conducted this study to compare dose distributions for 3DCRT, the half-beam method and IMRT to establish the benefits of each radiation method in difficult cases where there is a large overlap between the left kidney and the PTV. The half-beam method and IMRT showed a great advantage over 3DCRT in reducing the doses to the left kidney and liver.

This planning study revealed that the half-beam method and IMRT were appropriate treatment plans for cases with a large overlap between the left kidney and the PTV in terms of reducing the doses to the left kidney and liver. The half-beam method irradiated the bilateral kidneys with the lowest dose, which may be quite important for the possible future administration of chemotherapy. However, the half-beam method had a disadvantage in that the high-dose region

of the liver was larger. Meanwhile, IMRT had a tendency for the mean dose to the kidney being larger than for the half-beam method. The tolerance dose of the kidneys is lower than that of the liver; therefore, the half-beam method seems to be preferable to IMRT. However, the dose distribution for IMRT can be altered by changing the setting of the priority parameters of the OARs during planning; thus, it was difficult to decide whether IMRT or the half-beam method was more suitable. It seems advisable to make plans both using the half-beam method and IMRT and then to compare them with respect to the DVHs to decide which plan will be more suitable. Lately, localized DLBCL has sometimes been treated by R-CHOP alone; therefore, these difficult cases could be candidates for immune-chemotherapy alone. In the QUANTEC, the tolerance dose for both kidneys is reported to be ~15–18 Gy in mean dose, and the tolerance dose for the normal liver is reported to be ~30–32 Gy in mean dose [8]. However, there have been some reports showing that late renal toxicity occurs even under 15–18 Gy in long-term follow-up study of patients undergoing total-body irradiation (TBI) [16, 17, 18]. Cheng *et al.* reported that the dose associated with a 5% risk of kidney toxicity is 9.8 Gy [17]. Patients of primary gastric lymphoma (PGL) have good prognosis; thus, they would be long-time survivors. Therefore, from the standpoint of keeping adequate renal functions in the long term, the dose to the kidneys should be kept even lower than 15–18 Gy. Further study of the DVHs of the kidney and liver associated with long-term adequate kidney and liver functions is needed. It would also be beneficial to investigate whether the half-beam method or IMRT are more suitable for treatment of PGL patients.

CONCLUSION

This study shows an advantage for the half-beam method and IMRT over 3DCRT in the treatment of post-chemotherapy gastric DLBCL in cases where there is a large overlap between the kidney and the PTV.

CONFLICT OF INTEREST

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RESEARCH ARTICLE Open Access

CT based three dimensional dose-volume evaluations for high-dose rate intracavitary brachytherapy for cervical cancer

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Abstract

Background: In this study, high risk clinical target volumes (HR-CTVs) according to GEC-ESTRO guideline were contoured retrospectively based on CT images taken at the time of high-dose rate intracavitary brachytherapy (HDR-ICBT) and correlation between clinical outcome and dose of HR-CTV were analyzed.

Methods: Our study population consists of 51 patients with cervical cancer (Stages IB-IVA) treated with 50 Gy external beam radiotherapy (EBRT) using central shield combined with 2–5 times of 6 Gy HDR-ICBT with or without weekly cisplatin. Dose calculation was based on Manchester system and prescribed dose of 6 Gy were delivered for point A. CT images taken at the time of each HDR-ICBT were reviewed and HR-CTVs were contoured. Doses were converted to the equivalent dose in 2 Gy (EQD_2) by applying the linear quadratic model ($\alpha/\beta = 10$ Gy).

Results: Three-year overall survival, Progression-free survival, and local control rate was 82.4%, 85.3% and 91.7%, respectively. Median cumulative dose of HR-CTV D_{90} was 65.0 Gy (52.7-101.7 Gy). Median length from tandem to the most lateral edge of HR-CTV at the first ICBT was 29.2 mm (range, 18.0-51.9 mm). On univariate analysis, both LCR and PFS was significantly favorable in those patients D_{90} for HR-CTV was 60 Gy or greater ($p = 0.001$ and 0.03, respectively). PFS was significantly favorable in those patients maximum length from tandem to edge of HR-CTV at first ICBT was shorter than 3.5 cm ($p = 0.042$).

Conclusion: Volume-dose showed a relationship to the clinical outcome in CT based brachytherapy for cervical carcinoma.

Keywords: Brachytherapy, Image-based gynecological brachytherapy, Cervical cancer, IGBT, CT-based gynecological brachytherapy

Background

Standard therapy for patients with locally advanced cervical cancer is combination of external beam radiotherapy (EBRT) and brachytherapy with concurrent chemotherapy [1-5]. Intracavitary brachytherapy employing intrauterine (tandem) and vaginal (ovoid) sources based on Manchester principles, has been the standard for many decades [6,7]. Manchester system is point-based (i.e. two-dimensional) and uses orthogonal x-ray images for calculation and prescription of treatment doses. This concept neglects each tumor size or shape because prescribed dose is delivered to a fixed reference points. Therefore while excellent long-term tumor control rates can be obtained for patients with small tumors, for larger tumors relapse rate are high [8,9]. Over the decades, GEC-ESTRO [10,11] and ABS [12] proposed the concept of 3D image-based brachytherapy (IGBT) for the cervical cancer. Recently improved clinical outcomes are reported using IGBT for the advanced cervical carcinomas [13-19]. GEC-ESTRO working group recommend using MRI for determining high-risk clinical target volume (HR-CTV) and intermediate-risk CTV (IR-CTV) because MRI is superior to CT for delineating the normal anatomy of the female pelvis and for identifying cervical carcinoma extension [19-22]. However, practically majority

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of institutions do not have access to an MRI unit every time of brachytherapy treatment. In many circumstances CT scanners are often more widely available than MRI, therefore Viswanathan et al. developed guidelines for standard contouring of HR-CTV based on CT images [23]. From 2008 we introduced CT imaging in gynecological brachytherapy but continued to use Manchester system for dose calculation. In this study, we analyzed correlations between clinical outcome and dose of HR-CTV contoured based on CT images.

Methods

Patients included in current study are females with cervical carcinoma treated by primary radiation therapy including brachytherapy with or without concurrent chemotherapy from April 2008 to December 2010. As mentioned above, our department introduced CT imaging in the process of high-dose rate intracavitary brachytherapy (HDR-ICBT) for cervical cancer from 2008. Sixty two patients were identified who had CT image after insertion of brachytherapy applicator and 9 patients were excluded because of having distant disease beyond pelvis and another 2 patients were excluded because they were treated by combination of ICBT and interstitial brachytherapy (ISBT). Therefore current study consisted of 51 patients. All patients underwent pelvic examination, cystoscopy, pyeloureterography, chest X-ray/CT, pelvic CT/magnetic resonance image (MRI), and blood test. Maximum tumor diameters were measured based on the CT/MRI findings. All biopsy specimens were diagnosed in Department of Pathology of our hospital.

Treatment

Principles of management of the cervical cancer in this institute were described elsewhere [24]. The treatment policy for locally advanced cervical cancer is concurrent chemoradiation therapy (cCRT) with chemotherapy regimen of weekly cisplatin (40 mg/m^2/week) or cisplatin (50 mg/m^2/3 weeks) plus oral S-1 (80–120 mg/body/day). Concurrent chemoradiotherapy was not performed in the patients with insufficient renal function (serum creatinine > 1.5 mg/dl) and aged over 75 years. Supportive treatments such as blood transfusions were encouraged during radiotherapy.

Radiotherapy

EBRT was delivered by 3D conformal technique with linear accelerator (Clinac iX, Varian Medical System, Palo Alto, CA) using 15 MV photon beam. Treatment planning was based on CT images of 3 mm slice thickness taken by Aquilion LB CT scanner (Toshiba Medical Systems, Japan). The common EBRT portals included whole uterus, as well as parametrium, upper part of vagina down to the level of lower border of obturator foramens, and the draining pelvic lymph nodes up to the level of the common iliac (L4/5 junction). The nodal CTV included internal (obturator and hypogastric), external, and common iliac lymph nodes as well as presacral lymph nodes down to the level of S3. If the primary lesion involved lower third of vagina or there were clinically palpable metastatic inguinal nodes, inguinal regions were also included in EBRT fields. The initial 20–40 Gy was delivered to the whole pelvis with a 4-field box and then pelvic irradiation with a 4 cm-width of central shield (CS) being ensued reducing organ at risk (OAR) exposure. The initiation of CS was depend upon tumor shrinkage. Every week tumor response was accessed by attending radiation oncologist by physical examination. For early responding tumor width of which was smaller than 4 cm after having received 20 Gy of EBRT, CS was initiated. For late responding tumor width of which was larger than 4 cm at 20 Gy, EBRT was continued until tumor width became smaller than 4 cm. For tumors in which response of radiation was unfavorable, CS did not introduced. Total pelvic side wall dose was 50 Gy in 25 fractions. After the CS was inserted, HDR-ICBT was performed in 1–2 sessions/week, but EBRT and HDR-ICBT were not carried out on the same day. All brachytherapy was carried out by ^{192}Ir remote after loading system (RALS, MicroSelectron HDR™, Nucletron, Veennendaal, The Netherlands). ICBT with tandem + ovoid applicators without shielding was performed with a prescribed dose of 6 Gy in point A using Manchester method. A tandem-cylinder was used in the cases with a vaginal involvement exceeding more than one-third of total vaginal length. At each brachytherapy session, CT image of 3 mm slice thickness was taken by a large bore CT simulator (Aquilion™, Toshiba, Tokyo, Japan) situated in operating room with the patient lying in lithotomy position with the applicators in place. Before the acquisition of CT, bladder was filled with 100 ml of saline. Emptiness of rectum was checked at the time of gynecological examination before insertion of the applicators. For dose calculation of ICBT, Oncentra® (Nucletron, Veennendaal, The Netherlands) was used. HR-CTV was determined based on CT images according to Viswanathan's contouring guidelines [23]. Rectum and bladder were contoured as OARs. Dose constraints for OARs were determined as followed; D_{2cc} bladder < 90 Gy EQD_2, D_{2cc} rectum < 75 Gy EQD_2. In order to fulfill these dose constraints for OARs, tumors with insufficient response after EBRT and required 50 Gy of EBRT without CS generally could only afford two times of brachytherapy sessions while tumors with sufficient response and started CS only after 20 Gy of EBRT could undergo four or even five times of brachytherapy sessions. The workload with using CT-based IGBT required only additional several minutes for contouring targets and OARs compared with conventional X-ray based 2D planning.

Follow-up

All patients were evaluated weekly for toxicity during radiotherapy through physical examination and blood

tests. CT and/or MRI scans and cytology were performed 1–3 months after radiotherapy, and physical examination and blood tests were performed regularly every 1–6 months.

Statistical analysis

Overall survival rate was estimated from the start of radiation therapy to the date of death or of the last follow-up. Progression-free survival rate was estimated to the date of any disease relapse considered as an event. Patients without relapse who died of another disease or still alive were censored at the time of death or last follow-up. Local control rate which includes central and parametrium relapses was considered as an event, and censored at the time of death, non-local relapse, or last follow-up. Overall survival, Progression-free survival, and local control rate were calculated by the Kaplan-Meier method.

For adding dose of EBRT and HDR-ICBT, the equivalent dose in 2 Gy fractions (EQD_2) [11] according to LQ model [25] was calculated by the following formula:

$$EQD_2 = \frac{Nd\left(1+\frac{d}{\alpha/\beta}\right)}{1+\frac{2}{\alpha/\beta}}$$

The parameter N indicates the number of fractions and d the dose per fraction. For calculating tumor doses, α/β was assumed as 10 Gy. Because after insertion of CS most of the primary disease did not receive EBRT, EQD_2 of EBRT before the initiation of CS was added to the EQD_2 of HDR-ICBT. As calculation of HDR-ICBT was based on CT taken by each brachytherapy session, EQD_2 at every fraction was calculated and added together.

The survival curves were compared by the log-rank test. For univariate analysis, all of the variables were dichotomized at the median. Statistical significance was set to less than 0.05 as usual. All of the statistical analyses were performed using SPSS Statistics version 18.0 (SAS Institute, Tokyo, Japan).

This retrospective study was approved by the institutional review board of the National Cancer Center.

Results

Among 51 patients included in this study, 42 patients were alive at the time of the analysis and 39 were alive without disease recurrence (December 2012). The pretreatment characteristics of the 51 patients are summarized in Table 1. Treatment details were summarized in Table 2. Among 30 patients who received concurrent chemotherapy, 9 patients received cisplatin plus S-1. The median value of EQD_2 for FIGO I/II/III/IVA was 64.55 Gy, 64.97 Gy, 64.68 Gy, and 63.35 Gy, respectively. The median follow-up length of living entire patients was 39.2 months (range, 24.3-52.0 months). Three-year Overall survival, Progression-free survival and local control rate were 82.4%, 85.3% and 91.7%, respectively (Figure 1). At the time of analysis 39 patients were alive without disease recurrence, while 5 patients died because of cancer and 4 due to other reasons without any evidence of cervical cancer. Eight out of 51 patients (15.7%) experienced persistent disease or disease recurrence after definitive radiotherapy (one, two, three, and two patients in FIGO I/II/III/IVA, respectively). Two patients recurred at only local site, 2 both local and distance simultaneously, and 4 distant only. No one experienced regional lymph node recurrence. Among seven FIGO stage IVA patients, one patient experienced local recurrence and eventually died of disease, one experienced single lung metastasis which was successfully salvaged by six cycles of carboplatin and paclitaxel followed by stereotactic radiation therapy for lung metastasis, and one elderly patient died from chronic kidney dysfunction without any evidence of disease recurrence. Figure 2 shows example of patient who experienced local recurrence. Tumor extended to pelvic wall at diagnosis (Figure 2a). The right lateral part of HR-CTV was not covered by isodose line of 60 Gy equivalent dose in 2 Gy per fraction (EQD_2, Figure 2b). In axial MR image 3 months after completion of treatment (Figure 2c), the persistent disease was found in the area not sufficiently treated by brachytherapy. On univariate analysis, both local control rate and Progression-free survival was significantly favorable in those patients with D_{90} for HR-CTV equal to or greater than 60 Gy (Figure 3; $p = 0.001$ and 0.03, respectively). The number of patients with HR-CTV $D_{90} < 60$ Gy and ≥ 60 Gy was 12 and 39, respectively. Median volume of

Table 1 Patients characteristics (n = 51)

Characteristics		No. of patients
Age	Median (range)	62 (28-90)
FIGO stage	I/II/III/IVA	10/15/19/7
Vaginal invasion	Yes	19
	No	32
Parametrium invasion	Yes	33
	No	18
Corpus invasion	Yes	15
	No	36
Pyometra	Yes	6
	No	45
Pelvic LN metastasis	Yes	11
	No	40
Pathology	Scc	48
	Adeno	3
Initial tumor size (cm)		4.5 (1.8-7.7)
Pre treatment Scc (mg/dl)		7.0 (0.9-94.2)

LN lymph node.

Table 2 Treatment details

EBRT* central pelvic dose (Gy)	Median (range)	30 (20-50)
HDR-ICBT† dose for point A	Median (range)	24 (12-30)
Applicor type	Tandem + ovoid	42
	Tandem + cylinder	9
Concurrent chemotheraphy	Yes	30
	No	21
TTT†† (days)	Median (range)	42 (36-67)
Volume of HR-CTV at first ICBT (ml)	Median (range)	23.3 (8.3-100.8)
Maximum diameter of HR-CTV at first ICBT (mm)	Median (range)	46.9 (32.2-77.5)
Maximum length from tandem to edge of HR-CTV at first ICBT (mm)	Median (range)	29.2 (18.0-51.9)
EQD_2^{II} of point A	Median (range)	62 (52-72.3)
EQD_2^{II} of HR-CTV D_{90}^{**}	Media (range)	65.0 (52.7-101.7)

*EBRT: external beam radiation therapy.
†HDR-ICBT: high-dose rate intracavitary brachytherapy.
††TTT: total treatment time.
II EDQ_2: equivalent dose in 2 Gy fractions.
**HR-CTV D_{90}: dose covering 90% of the HR-CTV.

HR-CTV at the first application of brachytherapy in each group was 31.8 ml and 21.1 ml, respectively and patients with HR-CTV $D_{90} < 60$ Gy had statistically larger volume compared with that of patients with HR-CTV $D_{90} \geq 60$ Gy ($p = 0.022$). Three-year local control rate and Progression-free survival for those whose HR-CTV $D_{90} < 60$ Gy was 72.9% and 64.3% whereas that of patients with HR-CTV $D_{90} \geq 60$ Gy was 97.3% and 91.5%, respectively. Progression-free survival was significantly favorable in those patients when the maximum length from tandem to the margin of HR-CTV at first ICBT was shorter than 3.5 cm ($p = 0.042$).

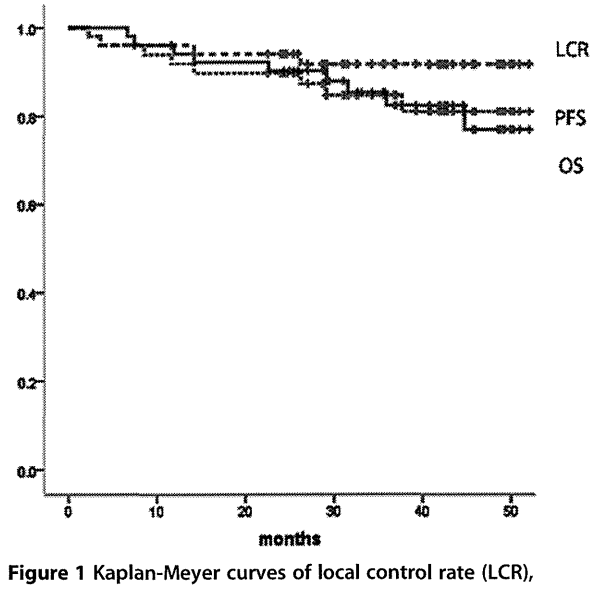

Figure 1 Kaplan-Meyer curves of local control rate (LCR), progression survival (PFS), and overall survival (OS).

Treatment related toxicities

One patient experienced sigmoid colon perforation 1 month after completion of radiotherapy which required colostomy. Because cumulative dose for sigmoid colon D_{2cc} was only 43.8 Gy (EQD_2, $\alpha/\beta = 3$ Gy) and development of the perforation was rather too early, it was implausible that radiation played a major role developing this severe morbidity. Two patients developed grade 2 proctitis and none experienced greater than grade 2 cystitis or vaginitis.

Discussion

In the current study, definitive radiotherapy using traditional Manchester method with or without concurrent chemotherapy for cervical carcinoma resulted in favorable local control with only 4 local recurrences (7.8%).

Since the introduction of the concept of IGBT [10-12], several improved clinical results have been reported [13-18]. It is recommended in GEC-ESTRO working group that MRI should be used to determine IR-CTV and HR-CTV because of its superiority of tissue discrimination over CT image [20-22,25]. However, it is even now hard for most of brachytherapy suits to prepare MRI instruments for the use of every brachytherapy procedure for cervical cancer. As an alternative and practical solution, Viswanathan et al. proposed a guideline to contour HR-CTV based on CT images [23]. Current study was to the best of our knowledge first report which validated this CT based HR-CTV contouring guideline in clinical practice. Schmid et al. reported interesting study concerning the feasibility of transrectal ultrasonography for identifying HR-CTV in comparison with MRI [26]. However authors still believe utilizing CT for brachytherapy is the most realistic solution for

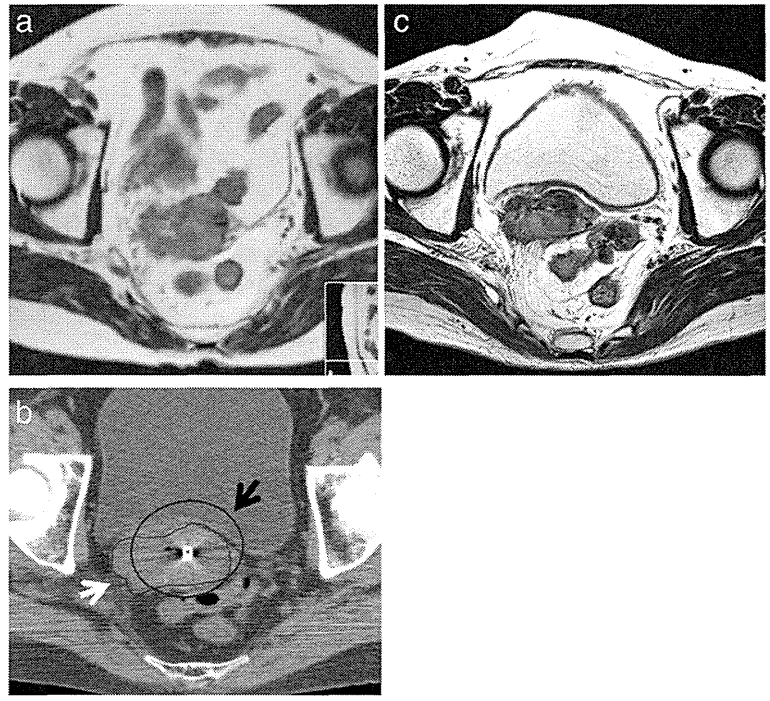

Figure 2 Representative images of patient who experienced local relapse. a. Axial MR T2 weighted image before treatment. Tumor extends to right pelvic wall. **b**. Axial CT image at the first session of intracavitary brachytherapy (ICBT). Tumor still extends to right pelvic wall after 40 Gy of whole pelvic EBRT. Black arrow represents isodose line of 60 Gy (EQD_2) and white arrow HR-CTV at the time of brachytherapy. **c**. Axial MR T2 weighted image 3 months after completion of chemoradiotherapy. Persistent disease was found in right parametrium.

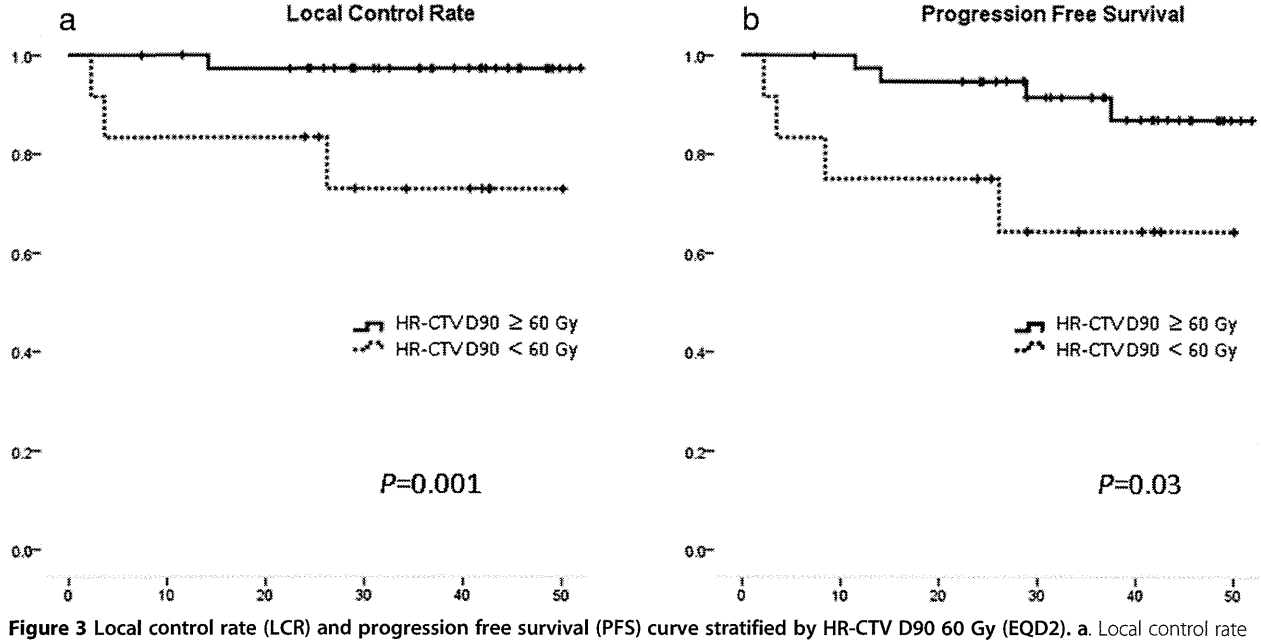

Figure 3 Local control rate (LCR) and progression free survival (PFS) curve stratified by HR-CTV D90 60 Gy (EQD2). a. Local control rate (LCR) stratified by HR-CTV D_{90} 60 Gy (EQD_2). **b**. Progression free survival (PFS) stratified by HR-CTV D_{90} 60 Gy (EQD_2).

the future evolution of image-guided brachytherapy for cervical cancer because of its prevalence and reproducibility.

Dimopoulos et al. analyzed the relationships between dose-volume histogram (DVH) and local control using MRI-based IGBT for cervical cancer and found out that the D_{90} for HR-CTV greater than 87 Gy resulted in excellent local control [13]. In current study, the cut-off value of D_{90} was 60 Gy and it was much lower than what Dimopoulos et al. pointed out. It has been known that Japanese centers use lower cumulative dose schedules with shorter overall treatment time (OTT) than those of US and Europe [27,28]. Recently Toita et al. showed the efficacy of Japanese schedule in a series of multicenter prospective trials in which Stage I and II with small (<4 cm) tumor diameter can be effectively treated by BED 62 Gy_{10} (JAROG0401/JROSG04-2) [29] and Stage III/IVA by BED 62–65 Gy_{10} at point A (JCOG1066) [30]. Therefore it is reasonable that in current study the cut-off value is much lower than Vienna group. In addition 60 Gy could be used as a target dose for HR-CTV D_{90} in institutions which perform IGBT with Japanese schedule. However further evidence must be accumulated in order to validate the value of HR-CTV $D_{90} \geq 60$ Gy in Japanese schedule.

In current study it was revealed that PFS was significantly favorable if the maximum length from tandem to the margin of HR-CTV at the first ICBT was shorter than 3.5 cm. Therefore if the maximum distance between uterine cavity and margin of HR-CTV is longer than 3.5 cm at the first session of brachytherapy, application of image-guided brachytherapy or combined intracavitary/interstitial brachytherapy [16,31-33] would improve clinical results.

From current study, it was demonstrated that favorable local control could be achieved for tumors with HR-CTV $D_{90} \geq 60$ Gy using conventional Manchester method. However for tumors with delayed response after EBRT and HR-CTV D_{90} could only be under 60 Gy by Manchester method, further treatment improvement is warranted. In this context, maximum length from tandem to the rim of HR-CTV ≥ 3.5 cm could be used as a cut-off point where ISBT would play an important role. Currently in our institution tumors of which maximum length from tandem to the rim of HR-CTV is longer than 3.5 cm at the time of brachytherapy are treated by the combination of ICBT and ISBT or ISBT alone. Improvement of clinical results after the introduction of the combination of ICBT and ISBT compared with conventional technique will be reported elsewhere.

This study has several limitations. This is a result from single retrospective study with a limited follow-up period and HR-CTV was determined based on CT images rather than MR images. Viswanathan et al. compared CT based and MRI based CTV and concluded that the width of CT based CTV was larger than that of MRI [23]. Therefore HR-CTV contoured based on CT in this study may overestimate the tumor volume in lateral direction. This may be part of the reason of lower cut-off value of HR-CTV D_{90} in this study. However it will take long before MRI will be available in majority of brachytherapy suit. At present as current standard for IGBT is based on MRI, IGBT is not so popular after its introduction in the treatment of cervical cancer brachytherapy because MRI itself is not prevalent yet. Therefore it is worth accumulating evidence that IGBT based on CT image could also achieve favorable clinical results if used properly.

Conclusions

Dose-volume relationship was found in CT-based intracavitary brachytherapy for cervical carcinoma in Japanese schedule. Further improvement could be expected for cervical cancers with insufficient response after EBRT. For such tumor, ISBT would play an important role and should be investigated.

Abbreviations

EBRT: External beam radiotherapy; HR-CTV: High-risk clinical target volume; IR-CTV: Intermediate-risk clinical target volume; HDR-ICBT: High-dose rate intracavitary brachytherapy; ISBT: Interstitial brachytherapy; cCRT: Concurrent chemoradiation therapy; CS: Central shield; OAR: Organ at risk; EQD_2: The equivalent dose in 2 Gy fractions.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

NM, AW, SN, HO, and JI have made substantial contributions to conception and design. NM and JI have been involved in drafting the manuscript or revising it critically for important intellectual content. MM, MS, KI, YI, and TK participated in acquisition and interpretation of data. All authors read and approved the final manuscript.

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Vaginal tolerance of CT based image-guided high-dose rate interstitial brachytherapy for gynecological malignancies

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Abstract

Background: Purpose of this study was to identify predictors of vaginal ulcer after CT based three-dimensional image-guided high-dose-rate interstitial brachytherapy (HDR-ISBT) for gynecologic malignancies.

Methods: Records were reviewed for 44 female (14 with primary disease and 30 with recurrence) with gynecological malignancies treated with HDR-ISBT with or without external beam radiation therapy. The HDR-ISBT applicator insertion was performed with image guidance by trans-rectal ultrasound and CT.

Results: The median clinical target volume was 35.5 ml (2.4-142.1 ml) and the median delivered dose in equivalent dose in 2 Gy fractions (EQD_2) for target volume D_{90} was 67.7 Gy (48.8-94.2 Gy, doses of external-beam radiation therapy and brachytherapy were combined). For re-irradiation patients, median EQD_2 of D_{2cc} for rectum and bladder, $D_{0.5cc}$, D_{1cc}, D_{2cc}, D_{4cc}, D_{6cc} and D_{8cc} for vaginal wall was 91.1 Gy, 100.9 Gy, 260.3 Gy, 212.3 Gy, 170.1 Gy, 117.1 Gy, 105.2 Gy, and 94.7 Gy, respectively. For those without prior radiation therapy, median EQD_2 of D_{2cc} for rectum and bladder, $D_{0.5cc}$, D_{1cc}, D_{2cc}, D_{4cc}, D_{6cc} and D_{8cc} for vaginal wall was 56.3 Gy, 54.3 Gy, 147.4 Gy, 126.2 Gy, 108.0 Gy, 103.5 Gy, 94.7 Gy, and 80.7 Gy, respectively. Among five patients with vaginal ulcer, three had prior pelvic radiation therapy in their initial treatment and three consequently suffered from fistula formation. On univariate analysis, re-irradiation and vaginal wall D_{2cc} in EQD_2 was the clinical predictors of vaginal ulcer ($p = 0.035$ and $p = 0.025$, respectively). The ROC analysis revealed that vaginal wall D_{2cc} is the best predictor of vaginal ulcer. The 2-year incidence rates of vaginal ulcer in the patients with vaginal wall D_{2cc} in EQD_2 equal to or less than 145 Gy and over 145 Gy were 3.7% and 23.5%, respectively, with a statistically significant difference ($p = 0.026$).

Conclusions: Re-irradiation and vaginal D_{2cc} is a significant predictor of vaginal ulcer after HDR-ISBT for gynecologic malignancies. Three-dimensional image-guided treatment planning should be performed to ensure adequate target coverage while minimizing vaginal D_{2cc} in order to avoid vagina ulcer.

Keywords: Gynecologic brachytherapy, High-dose-rate brachytherapy, Interstitial brachytherapy, Vaginal ulcer

Introduction

High-dose rate intracavitary brachytherapy (HDR-ICBT) is an established method in the management of gynecological malignancies, especially in cervical cancer. However, in patients with a narrow vagina, short uterine cavity, distal vaginal extension, and bulky tumors in which the optimal dose distribution cannot be obtained by intracavitary brachytherapy (ICBT), interstitial brachytherapy (ISBT) is employed. Also in patients with bulky postoperative central pelvic recurrence, ISBT has proven to be effective [1-5]. With the advent of image-guided brachytherapy it has become possible to assess the dose volume histogram (DVH) in brachytherapy. Several studies have validated the D_{2cc} as a predictor of rectal and bladder toxicities for ICBT [6] or for ISBT [7]. D_{2cc} of the rectum and bladder have been introduced into daily clinical practice of gynecological image-guided brachytherapy. However in ICRU 38 vagina was not recognized as organ at risk

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during brachytherapy tough it is adjacent to target volume and radioactive sources [8].

The purpose of this study was to retrospectively analyze the incidence of vaginal morbidities after HDR-ISBT for gynecological cancers and to find clinical and dosimetric factors which affect the incidence of the vaginal morbidities.

Methods

The inclusion criteria of this single institutional retrospective study were patients with gynecological malignancies who were treated by HDR-ISBT with or without external beam radiation therapy (EBRT) with a follow-up length exceeding 6 months or more. Patients with distant metastasis outside of pelvis were excluded from current study. HDR-ISBT was applied for both primary and salvage intents. Patients with superficial vaginal disease with thickness less than 5 mm were treated with HDR-ICBT and did not treated by HDR-ISBT; therefore these patients were not included in this analysis. Also HDR-ISBT was not applied for those patients who had distant metastasis or for those patients with far advanced tumors which had not responded to EBRT performed before HDR-ISBT. These patients were treated with EBRT alone. One patient who succumbed to progressive cancer in 5.5 months after ISBT was also excluded in this analysis. The medical records of all patients with gynecological malignancies treated with HDR-ISBT at the National Cancer Center Hospital, Tokyo, Japan, between 2008 and 2011 were retrieved and 44 patients were included in this study.

In the patients without prior pelvic irradiation, pelvic EBRT was delivered before HDR-ISBT. The common EBRT portals were whole pelvic irradiation including gross tumor volume (GTV) with adequate margin as well as the pelvic lymph nodes basin up to the level of the common iliac (L4/5 junction). If the tumor involved the lower third of the vagina, or there were clinically palpable inguinal nodes, inguinal regions were also included in the EBRT portals. The initial 20-40 Gy was delivered to the whole pelvis with a 4-fields box technique and then pelvic irradiation was administered with a central shield being employed to reduce exposure of organs at risk (OAR). The total dose delivered to the pelvic side wall was up to 50 Gy in a conventional fractionation. In patients with a history of prior pelvic radiation therapy or in feeble elderly patients, no EBRT or smaller EBRT fields with a reduced total dose were employed. HDR-ISBT was basically performed after the central shield was inserted. However for those patients treated without EBRT, HDR-ISBT was applied as solitary radiotherapy modality. The detailed procedure of gynecological HDR-ISBT was described elsewhere [9]. In brief, transperineal needle applicator insertion was performed under either general or local anesthesia with the patients in lithotomy position and guided by trans-rectal ultrasound (TRUS) or CT which can be taken with the patients lying in lithotomy position with the applicators in place. For advanced large disease, a Syed-Neblett perineal template (Best Medical International, Inc., Springfield, VA) was used in order to sufficiently cover lateral disease extent. For rather localized small disease, with limited parametrial and/or paracolpial invasion, free-hand needle applicator insertion with or without a vaginal applicator was used with fewer needles inserted compared to the Syed-Neblett perineal template. Treatment planning was performed with brachytherapy planning system (Oncentra® Nucletron, Veenendaal, The Netherlands) using CT images taken by the large bore CT simulator (Aquilion LG®, Toshiba, Tokyo, Japan), which allows imaging of the patients in lithotomy position. Although different applicator was used throughout the patients, the calculation method applied was the same. The clinical target volume (CTV) was defined based on the CT image obtained after needle insertion, as well as physical examination immediately before needle insertion, the intra-operative TRUS image and the most recent MRI were also taken into account. Reference points were set on the surface of CTV and prescribed dose was delivered to those points. HDR-ISRT treatment plan was calculated initially by geometrical optimization or volume optimization and then manual graphical modification was followed to enclose the CTV by the prescription dose while minimizing high dose to OAR. The median HDR-ISBT dose was 24 Gy (range, 18-54 Gy), and median HDR-ISBT dose per fraction was 6 Gy (range, 4-6 Gy). HDR-ISBT was performed twice daily with each fraction 6 hours apart. HDR-ISBT was performed with MicroSelectron HDR (Nucletron, Veenendaal, The Netherlands) using Ir-192.

At the discretion of the attending physician, weekly CDDP 40 mg/m^2 was used in 10 patients concurrently with EBRT. In general, patients with bulky disease, good performance status and adequate organ function were selected for the candidate for the administration of concurrent chemoradiation. Patients were seen in follow up 1 week after HDR-ISBT for a skin check, then every 1-2 months for 2 years, every 3-4 months for 5 years, and every 6-12 months thereafter.

When adding doses of EBRT, HDR-ISBT, and HDR-ICBT, we used the equivalent dose in 2 Gy fractions (EQD_2) according to the LQ model [10,11]. For re-irradiated patients, prior central pelvic EBRT doses were also added to EQD_2 for OARs. For those who had prior HDR-ICBT without DVH parameters of OARs because of lack of three dimensional dose calculations, it was difficult to estimate EQD_2 for OARs. Therefore, prescribed dose for tumor in EQD_2 ($\alpha/\beta = 10$) was converted to EQD_2 for late responding tissue ($\alpha/\beta = 3$) and added

together. Time interval between prior RT and the current RT was not taken into consideration in this analysis.

Rectum and bladder were contoured as a whole organ. Vaginal wall was extracted with a thickness of 4 mm on all CT images according to the Vienna group [12]. As for rectum and bladder, dosimetric parameter of D_{2cc} was used because these values have been validated by several studies [6-8]. On the other hand, there is no validated parameter for vaginal dose; therefore $D_{0.5cc}$, D_{1cc}, D_{4cc}, D_{6cc}, and D_{8cc} were calculated along with D_{2cc} for vaginal wall dose volume parameters.

Late vaginal morbidities were retrospectively evaluated according to LENT-SOMA scales [13]. Because morbidity scores were evaluated retrospectively in this study, we focused on only vaginal ulcer which could be regarded as one of the severest symptoms and could be retrieved accurately from medical records.

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. In addition, calculation of the area under the curve (AUC) of receiver operating characteristics (ROC) was used to determine the most predictive dosimetric parameter of vaginal ulcer. The predictive values of parameters were evaluated based on the AUC. The optimal threshold for each parameter was defined as the point yielding the minimal value for $(1 - \text{sensitivity})^2 + (1 - \text{specificity})^2$, which is the point on the ROC curve closest to the upper left-hand corner [14]. The obtained cutoff point was used for dividing patients into two groups and the incidences of vaginal ulcer were calculated by Kaplan-Meier method with the difference evaluated by log-lank test. All statistical analyses were performed using SPSS Statistics version 18.0 (SAS Institute, Tokyo, Japan).

This retrospective study was approved by the institutional review board of the National Cancer Center.

Results

There were 44 patients who met the eligibility criteria and 36 patients were alive at the time of the analysis (May 2012). The median follow-up length of living patients was 18.3 months (range, 7.6-39.5 months). The pretreatment characteristics of the 44 patients included in this study are summarized in Table 1. Median age was 56 years (range, 25-89 years). HDR-ISBT was applied as the primary therapy in 14 patients (31.8%) and as the salvage therapy in 30 patients (68.2%). Eight patients (18.2%) had previously received pelvic irradiation, in the form of EBRT and/or ICBT. Twenty four patients were treated with Syed-Neblett perineal template, 17 with free-hand with vaginal applicator and three with free-hand without vaginal applicator. Treatment details are summarized in Table 2. Ten patients underwent concurrent chemotherapy. In most cases HDR-ISBT dose per fraction was 6 Gy. Median total EQD_2 of CTV D_{90} was 67.7 Gy. Median EQD_2 of D_{2cc} for rectum and bladder was 60.8 Gy and 58.1 Gy, respectively. Median EQD_2 of $D_{0.5cc}$, D_{1cc}, D_{2cc}, D_{4cc}, D_{6cc}, and D_{8cc} for vaginal wall were 210.7 Gy, 167.3 Gy, 131.5 Gy, 111.6 Gy, 100.0 Gy, and 83.2 Gy, respectively. Table 3 shows EQD_2 of rectum, bladder and vaginal wall for the patients with or without prior pelvic radiation therapy. For re-irradiation patients, median EQD_2 of D_{2cc} for rectum and bladder, $D_{0.5cc}$, D_{1cc}, D_{2cc}, D_{4cc}, D_{6cc} and D_{8cc} for vaginal wall was 91.1 Gy, 100.9 Gy, 260.3 Gy, 212.3 Gy, 170.1 Gy, 117.1 Gy, 105.2 Gy, and 94.7 Gy, respectively. For those without prior radiation therapy, median EQD_2 of D_{2cc} for rectum and bladder, $D_{0.5cc}$, D_{1cc}, D_{2cc}, D_{4cc}, D_{6cc} and D_{8cc} for vaginal wall was 56.3 Gy, 54.3 Gy, 147.4 Gy, 126.2 Gy, 108.0 Gy, 103.5 Gy, 94.7 Gy, and 80.7 Gy, respectively (Table 3). In EQD_2 of D_{2cc} for rectum, bladder and vaginal wall the difference was statistically significant ($p < 0.001$, $p < 0.001$, and $p = 0.001$, respectively).

As for late morbidities of vagina, five patients experienced vaginal ulcer after HDR-ISBT. All of vaginal ulcer occurred within two years after completion of the HDR-ISBT. Patient characteristics and objective/management

Table 1 Patients characteristics (n = 44)

		Patients (n)
Median age (years, range)		56 (25-89)
Primary site	Cervix	24 (54.6%)
	Vagina	12 (27.3%)
	Corpus	5 (11.3%)
	Ovary	2 (4.5%)
	Vulva	1 (2.3%)
Primary therapy		14 (31.8%)
	Cervical cancer	4 (9.1%)
	Vaginal cancer	10 (22.7%)
Salvage therapy		30 (68.2%)
	Post ope regidual tumor	5 (11.4%)
	Post ope recurrent tumor	21 (47.7%)
	Post RT recurrent tumor	4 (9.1%)
Histology	Scc	25 (56.8%)
	Adeno	16 (36.4%)
	Others	3 (6.8%)
Prior pelvic RT*	Yes	8 (18.2%)
	No	36 (81.8%)
Median tumor size (cm, range)		3.6 (1.0-8.0)
Pelvic LN† metastais	Yes	11 (25%)
	No	33 (75%)

*RT radiation therapy.
†LN lymph node.

Table 2 Treatment details (n = 44)

	Median range
Central pelvic dose of EBRT* (Gy)	30 (0-50)
No. of needles used in HDR-ISBT†	15 (5-29)
HDR-ISBT† fractions	4 (3-9)
HDR-ISBT† dose per fraction (Gy)	6 (4-6)
CTV†† (ml)	35.1 (2.4-142.1)
CTV†† D_{90} in EQD_2‖ (Gy)	67.7 (48.8-94.2)
Rectum D_{2cc}¶ in EQD_2‖ (Gy)	60.8 (30.5-114.3)
Bladder D_{2cc}¶ in EQD_2‖ (Gy)	58.1 (7.3-120.3)
Vaginal wall $D_{0.5cc}$¶ in EQD_2‖ (Gy)	210.7 (51.5-468.1)
Vaginal wall D_{1cc}¶ in EQD_2‖ (Gy)	167.3 (49.9-352.1)
Vaginal wall D_{2cc}¶ in EQD_2‖ (Gy)	131.5 (43.7-294.4)
Vaginal wall D_{4cc}¶ in EQD_2‖ (Gy)	111.6 (34.0-200.8)
Vaginal wall D_{6cc}¶ in EQD_2‖ (Gy)	100.0 (20.4-173.7)
Vaginal wall D_{8cc}¶ in EQD_2‖ (Gy)	83.2 (10.3-144.4)
Concurrent chemotherapy	
Yes	10 patients
No	34 patients

*EBRT: external beam radiation therapy.
†HDR-ISBT: high-dose-rate interstitial brachytherapy.
††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.

Table 3 DVH parameters for bladder and vaginal wall with or withour prior radiation therapy

	Prior pelvic RT[J] (+) (n = 8)	Prior pelvic RT[J] (-) (n = 36)	*p* value
eMedian rectum D_{2cc}† (EQD_2*, Gy, range)	91.1 (71.0-114.3)	56.3 (30.5-82.7)	< 0.001*
Median bladder D_{2cc}† (EQD2*, Gy, range)	100.9 (69.7-120.3)	54.3 (7.3-82.7)	< 0.001*
Median vaginal wall $D_{0.5cc}$† (EQD2*, Gy, range)	260.3 (59.9-349.3)	147.4 (47.9-267.3)	0.109
Median vaginal wall D_{1cc}† (EQD2*, Gy, range)	212.3 (58.2-277.5)	126.2(33.6-182.7)	0.013
Median vaginal wall D_{2cc}† (EQD2*, Gy, range)	170.1 (56.6-247.5)	108.0 (31.7-150.9)	0.001*
Median vaginal wall D_{4cc}† (EQD2*, Gy, range)	117.1 (34.0-200.8)	103.5 (39.1-139.4)	0.139
Median vaginal wall D_{6cc}† (EQD2*, Gy, range)	105.2 (33.0-173.7)	94.7 (20.4-138.7)	0.097
Median vaginal wall D_{8cc}† (EQD2*, Gy, range)	94.7 (32.4-144.4)	80.7 (10.3-130.4)	0.105

[J]RT: radiation therapy.
*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.

scores of vaginal ulcer according to LENT-SOMA are summarized in Table 4. Two patients had superficial and > 1 cm^2 vaginal ulcer and three had vaginal fistula (two vesicovaginal fistulae and one vesicovaginorectal fistula). Three out of the five patients had prior pelvic irradiation and the interval between prior pelvic irradiation and secondary pelvic irradiation was 15, 27, and 40 months, respectively. All of the three patients with vaginal fistula received hyperbaric oxygen therapy without success. Two underwent surgical intervention (one total cystectomy for massive hematuria and one nephrostomy) for their vesicovaginal fistula, while one was followed up conservatively with a persistent vesicovaginal fistula. The other two patients with grade 2 vaginal ulcer were treated conservatively. The overall 2-year actuarial incidence of vaginal ulcer was 11.4%; 37.5% for re-irradiation patients and 5.6% for those without prior radiation therapy (Figure 1a). Comparison of dose-volume parameters of the vaginal wall is shown in Table 5 for the patient with and without vaginal ulcer. It was shown that the incidence of vaginal ulcer in the patients with prior pelvic irradiation was statistically higher than that of the patients without prior pelvic irradiation ($p = 0.035$). It was also shown that the mean EQD_2 of vaginal wall D_{2cc} of patients with or without vaginal ulcer was statistically different ($p = 0.025$). There was no relationship between administration of concurrent chemotherapy and manifestation of vaginal ulcer ($p = 0.256$), number of needles used in HDR-ISBT ($p = 0.293$) nor bladder D_{2cc} EQD_2 ($p = 0.091$). The ROC analysis revealed that vaginal wall D_{2cc} was the best dosimetric parameter predicting the incidence of vaginal ulcer and the cutoff value of 145 Gy in vaginal wall D_{2cc} provided the lowest p value in log-rank test (Table 6). Figure 1b shows Kaplan-Meyer curve for the incidence of vaginal ulcer stratified by vaginal wall D_{2cc} 145 Gy in EQD_2. The 2-year incidence rates of vaginal ulcer in the patients with vaginal wall D_{2cc} equal to or less than 145 Gy in EQD_2 and over 145 Gy were 3.7% and 23.5%, respectively, with a statistically significant difference ($p = 0.026$).

Discussion

Although the Manchester method of ICBT for the cervical cancer was developed to avoid the occurrence of radiation induced vaginal ulcer and necrosis, vaginal ulcer is now very rarely encountered because vaginal wall is relatively radioresistant and typical ICBT delivers radiation dose less than the tolerance of the relatively radioresistant vaginal wall. In a retrospective study of cervical cancer patients using EBRT and the film based low-dose rate (LDR) brachytherapy, Samuel et al. showed that vaginal tolerance dose was above 150 Gy [15]. In recent advancement of image guided brachytherapy (IGBT), rectum and bladder doses were recommended to be

Table 4 Patient characteristics who developed vaginal ulcer

Patient no.	Age at HDR-ISBT*	Primary site	Prior pelvic RT	Interval between prior RT and HDR-ISBT* (mo)	HDR-ISBT* with/without EBRT††	Total vaginal wall $D_{0.5cc}^{\#}/D_{1cc}^{\#}/D_{2cc}^{\#}$ in $EQD_2^{\#\#}$ (Gy)	LENT SOMA¶ objective score	LENT SOMA¶ management score
1	40	Cervix	WPRT† 45 Gy/25fr + EBRT†† boost 15 Gy/5fr	27	HDR-ISBT* 36 Gy/9fr	272.1/202.6/169.1	4	4
2	51	Cervix	None	None	WPRT† 30 Gy/15fr + CS‖ 20 Gy/10fr + HDR-ISBT* 24 Gy/4fr	215.2/171.8/145.4	4	3
3	64	Corpus	None	None	WPRT† 30 Gy/15fr + HDR-ISBT* 30 Gy/5fr	196.6/141.5/109.1	2	1
4	64	Cervix	WPRT† 40 Gy/20fr + CS 10 Gy/5 + HDR-ICBT 18 Gy/3fr	40	HDR-ISBT* 48 Gy/8fr	465.4/352.1/294.4	2	1
5	67	Cervix	WPRT† 50 Gy/50fr + HDR-ICBT 12 Gy/3fr	15	HDR-ISBT* 42 Gy/7fr	234.0/211.1/193.5	4	3

*HDR-ISBT: high-dose-rate interstitial brachytherapy.
†WPRT: whole pelvis radiation therapy.
††EBRT: external beam radiation therapy.
‖CS: radiation therapy with center shielding.
¶LENT-SOMA: Late Effects of Normal Tissues - Subjective, Objective, Management, Analytic.
#D0.5cc, D1cc, D2cc: most exposed 0.5, 1 and 2 cm3 of tissue.
##EQD2: equivalent dose in 2 Gy fractions.

reported in the treatment of ICBT for cervical cancer but vagina was not mentioned as OAR [9]. In the GEC-ESTRO working group (II) or American Brachytherapy Society guidelines, vagina was taken into consideration for OAR but it was stated that the vaginal dose volume parameters still need to be defined [16,17]. Dimopoulos et al. reported clinical result of primary vaginal cancer treated with IGBT and they experienced two vaginal fistulae and one periurethral necrosis. However they did not specify DVH parameters of vaginal wall with vaginal complication [18]. Lee et al. reported in detail the toxicity analysis of CT based HDR-ISBT for gynecologic malignancies. They reported that D_{2cc} for the rectum was a reliable predictor of late rectal complication; however because of limited number of events it was not able to explore the DHV parameters for vaginal complication [5]. Recently, Vienna group tried to find out DVH parameters that correlate with vaginal late morbidities but vaginal D_{2cc} did not relate with the vaginal morbidities [12]. The calculation method was the same as

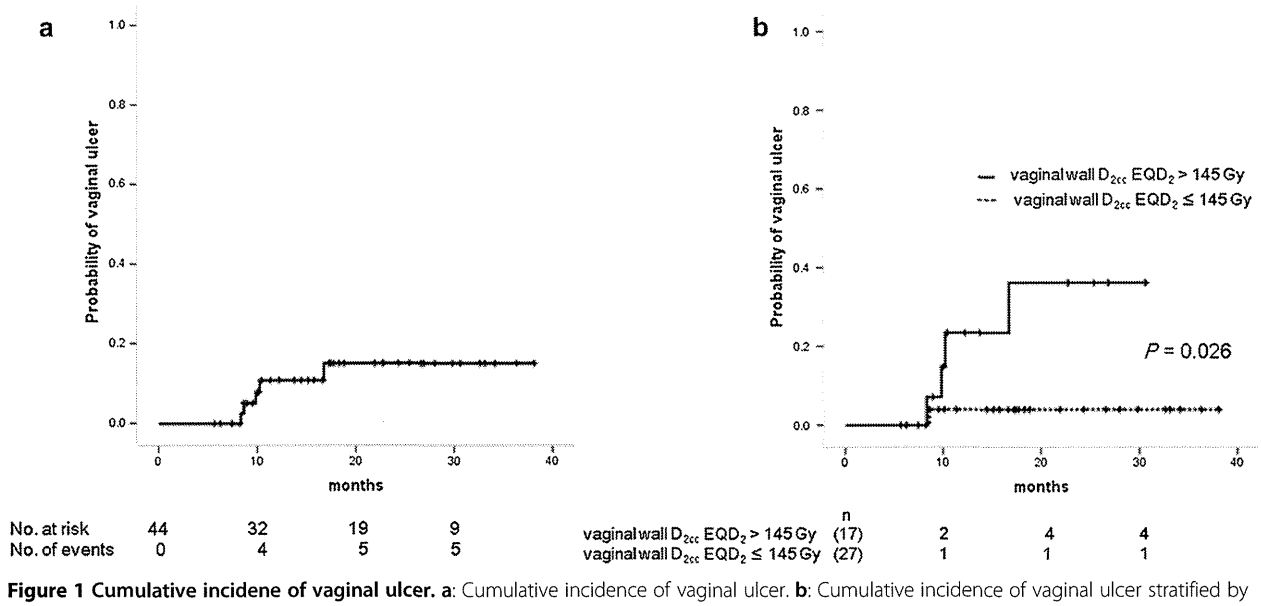

Figure 1 Cumulative incidene of vaginal ulcer. a: Cumulative incidence of vaginal ulcer. **b**: Cumulative incidence of vaginal ulcer stratified by vaginal wall D_{2cc} 145 Gy in EQD_2.