Original paper

Predictive value of Excel forms based on an automatic calculation of dose equivalent in 2 Gy per fraction in adaptive brachytherapy for cervical cancer

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Abstract

Purpose: External beam radiotherapy (EBRT) combined with brachytherapy (BT) is the standard mode of radical radiotherapy for locally advanced cervical cancer. The cumulative equivalent doses in 2 Gy per fraction (EQD_2) is an important basis for estimating the probability of local control of tumors and monitoring the occurrence of side effects in normal tissues. The purpose of this study was to explore the predictive value of Excel forms based on an automatic calculation in radical adaptive BT for cervical cancer.

Material and methods: A retrospective analysis of 119 patients suffering from cervical cancer, treated with radical radiotherapy. All patients were treated with EBRT and adaptive BT. EBRT prescribed dose was 42.0-50.4 Gy in 21-28 fractions. BT nominal prescribed dose was 28 Gy in 4 fractions, separated by one week. Total EQD_2 prediction at nth (n = 1-3) BT ($TEPB_n$) or actual cumulative EQD_2 ($ACEQD_2$) can be calculated automatically by inputting the physical dose based on an in-house designed application. The relationship between $TEPB_n$ and $ACEQD_2$ was evaluated, and the predictive value of Excel forms based on the automatic calculation was analyzed.

Results: For the volume of high-risk clinical target, there was a significant decrease between BT1 and BT2. Similarly, for the volume of intermediate-risk clinical target, there was a significant decrease between BT2 and BT3. The sensitivity ranges of $TEPB_1$, $TEPB_2$, and $TEPB_3$ prediction were 74.5-91.3%, 83.7-95.7%, and 92.9-99.1%, respectively, and the specificity ranges were 46.7-80.0%, 53.3-90.5%, and 66.7-90.5%, respectively.

Conclusions: The in-house designed application has the function of quickly reading dose-volume histogram (DVH) parameters from the treatment planning system, which allows for balance between the total dose to target volumes and organs at risk (OARs). Excel forms based on EQD_2 automatic calculation presents high predictive accuracy.

J Contemp Brachytherapy 2020; 12, 5: 454–461
DOI: https://doi.org/10.5114/jcb.2020.100378

Key words: cervical cancer, high-dose-rate, adaptive brachytherapy, EQD_2, dose prediction.

Purpose

External beam radiotherapy (EBRT) combined with brachytherapy (BT) is the standard mode of radical radiotherapy for locally advanced cervical cancer, and is recommended by the NCCN guidelines for cervical cancer [1]. Because of the significant tumor shrinkage during BT [2,3,4] and the large interfraction variance in organs at risk (OARs) [5,6,7], image-guided adaptive BT is the recommended treatment modality [8,9]. Several studies have shown that high-risk clinical target volume (HR-CTV) D_{90} (dose to 90% of target volume) and intermediate-risk clinical target volume (IR-CTV) D_{90} have a significant correlation with the treatment outcome in BT of cervical cancer [10,11,12,13]. Similarly, for OARs, the dose-volume histogram (DVH) parameters, especially the minimum doses to the most irradiated 2 cm^3 portions (D_{2cc}), are also associated with the probability of late side effects [14]. In most treatment planning systems, doses can be shown only in the form of physical doses and cannot be directly converted into equivalent doses in 2 Gy per fraction (EQD_2). Oncentra (Nucletron BV, an Elekta company, The Netherlands) treatment planning system provides a tool named "preset DVH table", which uses a table to display the presented DVH

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Received: 21.12.2019
Accepted: 02.08.2020
Published: 30.10.2020

parameters. However, these parameters are displayed in physical dose, not bioequivalent dose. They cannot be copied due to the permission restrictions of treatment planning system. Although, an Excel forms for automatically calculating EQD_2 can be easily compiled or obtained, DVH parameters need to be stored one by one, which consumes manpower and increases treatment planning time. Furthermore, in the first BT fractions, it is difficult to balance the cumulative doses of targets and OARs due to unavailability of the doses of both the targets and OARs in the subsequent BT. The purpose of this study was to introduce a home-made application for fast input of DVH parameters and to explore the predictive value of Excel forms based on automatic calculation of EQD_2 in adaptive BT for cervical cancer.

Material and methods

Patient population and treatment

Between April 2016 and June 2018, a total of 163 patients with biopsy-confirmed locally advanced cervical cancer received EBRT and computed tomography (CT)- or magnetic resonance imaging (MRI)-based adaptive BT. Of these, 44 patients were excluded for the following reasons: incomplete information (n = 3), recurrent tumors (n = 24), previous BT (n = 13), or incomplete treatment (n = 4). A total of 119 patients (median age, 53 years; range, 30-79 years) were retrospectively analyzed in the study. Patients and treatments characteristics are shown in Table 1.

EBRT and BT procedure

For EBRT, the median fraction dose was 1.8 Gy (range, 1.8-2.0 Gy), and the median total dose was 45 Gy (range, 42-50.4 Gy). For high-dose-rate (HDR) BT, the nominal prescribed dose was 28 Gy in 4 fractions, separated by one week. Utrecht interstitial Fletcher CT/MR applicator, interstitial ring CT/MR applicator, multichannel cylinder applicator, and 3D-printed template were selected to fit the morphology and topography of the tumor [15,16,17]. MicroSelectron (v.3, Nucletron, Veenendaal, The Netherlands) HDR afterloading system was used for the patients' treatment. Oncentra (v.4.3, Nucletron, Veenendaal, The Netherlands) treatment planning system was applied to produce and optimize the treatment plan. The total dose for combined EBRT and BT was normalized to EQD_2 using α/β = 10 Gy for tumor tissue and α/β = 3 Gy for normal tissue. The planning aims dose (soft constraints) and limits dose (hard constraints) together constituted two levels for dose constraint. The planning aim dose (total EBRT and BT) for HR-CTV and IR-CTV was $D_{90} \geq 85\ Gy_{EQD2,10}$ and $65\ Gy_{EQD2,10}$, respectively, whereas planning aim dose for OARs was $D_{2cc} < 70\ Gy_{EQD2,3}$ for rectum, sigmoid, and bowel and $< 85\ Gy_{EQD2,3}$ for bladder. The limit dose for HR-CTV and IR-CTV was $D_{90} \geq 80\ Gy_{EQD2,10}$ and $60\ Gy_{EQD2,10}$, respectively, whereas limit dose for OARs was $D_{2cc} < 75\ Gy_{EQD2,3}$ for rectum, sigmoid, and bowel and $< 90\ Gy_{EQD2,3}$ for bladder.

In order to evaluate the treatment plan and balance the doses between targets and OARs, we compiled an Excel form for each patient, called "patient's Excel form". When a DVH parameter is entered, it automatically calculates and accumulates EQD_2 from EBRT and BT. To quickly obtain the relevant DVH parameters from the treatment planning system and complete the patient's Excel form, we created an in-house designed application, which was composed of three files. The main program was compiled by Visual Basic (version 6.0, Microsoft, USA). Another file was GetWindowText.exe (version 3.06, Freeware), free for downloading from the Internet. The third file was an Excel form (named "calculation Excel form") called by the main program, which runs in the background to avoid confusion with the patient's Excel form. It uses an Excel function (LOOKUP) to automatically search the data required by the patient's Excel form, such as HR-CTV D_{90}, IR-CTV D_{90}, D_{2cc} for OARs, and other DVH parameters of interest. Data flow of this in-house designed application is shown in Figure 1.

In the first n fractions (n = 1-3), to predict the total EQD_2 at the nth BT ($TEPB_n$), we assumed that the dose of subsequent fraction(s) would be the same as that of current nth fraction and dose, until the previous fraction was summed up. The actual cumulative EQD_2 ($ACEQD_2$) was obtained at the fourth BT. For each BT, the fraction dose was controlled with $TEPB_n$ or $ACEQD_2$ from the Excel form based on the automatic calculation of EQD_2. There were two ways to address the contradiction between target dose and dose to OARs: to meet the dose requirements of target volumes and increase the dose constraints of OARs, or to meet the dose constraints of OARs and lower the dose to the target, leading to an insufficient

Table 1. Patient and treatment characteristics

Characteristic	No. of patients
Age (years)	
Median (range)	53 (30-79)
FIGO stage	
IB	9 (7.56%)
IIA	20 (16.81%)
IIB	62 (52.10%)
IIIA	5 (4.20%)
IIIB	19 (15.97%)
IVA	4 (3.36%)
Image modality	
CT	6 (5.04%)
MRI	113 (94.96%)
Changed applicator	
Yes	38 (31.93%)
No	81 (68.07%)

No. – number, FIGO – International Federation of Gynecology and Obstetrics, CT – computed tomography, MRI – magnetic resonance imaging

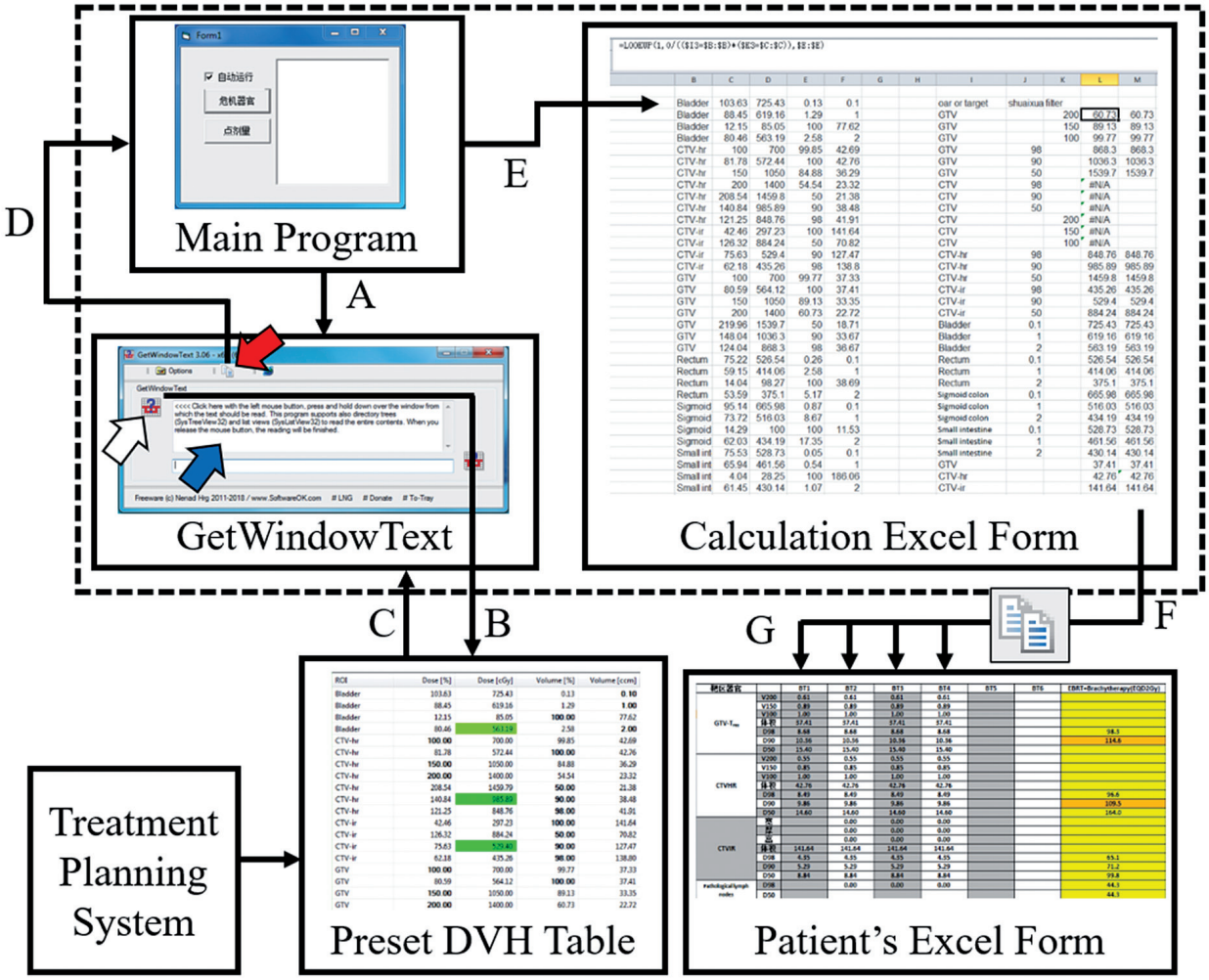

Fig. 1. Data flow of the in-house designed application (three files in the dotted box are in-house designed application). **A)** The main program opens the GetWindowText.exe program, **B)** click and drag the icon (white arrow) in the GetWindowText program to the preset DVH table in Oncentra treatment planning system, **C)** the text in preset DVH table is automatically loaded and displayed in the text box (blue arrow) of the GetWindowText.exe program, **D)** click the clipboard icon (red arrow) of the GetWindowText program, reads text in memory to the Clipboard, **E)** the main program automatically stores the contents of the clipboard in columns B to F of the calculation Excel form, **F)** the calculation Excel form automatically looks for the corresponding DVH parameters and stores them in the clipboard, **G)** paste the DVH parameter in the clipboard into the corresponding fraction of the patient's Excel form

dose. The choice or compromise depends on whether the target dose can be increased or the dose to OARs can be decreased in the subsequent fraction(s). It is an effective way to increase the target dose and/or decrease the dose to OAR by adjusting the type of applicator or increasing the number of interstitial needles. For patients with high-risk factors, the target doses should be increased under the premise of a controllable dose to OARs to achieve better clinical outcomes.

All the patients in this retrospective analysis read and wrote DVH parameters to patients' Excel forms with the in-house designed application. $TEPB_n$ was used to predict $ACEQD_2$, to balance the doses between targets and OARs, and to decide whether to increase the number of implantation needles or change the applicator. The data in this retrospective analysis were all from the actual delivered plan without any changes.

Statistical analysis

Receiver operating characteristic (ROC) curves were created to choose the optimal cut-off dose for predicting whether $ACEQD_2$ met the planning aim dose. Boxplots of $TEPB_n$ and $ACEQD_2$ (Figures 2-4) were generated using SPSS (version 23.0, IBM, USA) software. The volumes of HR-CTV and IR-CTV were compared between any two adjacent fractions, using two-tailed paired *t*-test. A *p*-value ≤ 0.05 was considered statistically significant.

Results

Interfractional target volume variations

The volume of HR-CTV decreased gradually during four BTs: 46.3 ±36.8 cc, 41.8 ±28.3 cc, 39.5 ±24.7 cc, and 38.3 ±26.1 cc. There was a significant decrease between

BT1 and BT2, with a *p*-value of 0.016. Similarly, the volume of IR-CTV also decreased gradually: 126.2 ±67.4 cc, 120.1 ±53.1 cc, 112.8 ±46.4 cc, and 112.4 ±48.5 cc. There was a significant decrease between BT2 and BT3, with a *p*-value of 0.001.

Prediction accuracy of TEPB$_n$

Boxplots of TEPB$_n$ and ACEQD$_2$ are shown in Figure 2. For the ACEQD$_2$ of HR-CTV D$_{90}$, 109 patients (91.6%) achieved the planning aim dose, and for the ACEQD$_2$ of IR-CTV D$_{90}$, 98 patients (82.4%) achieved the planning aim dose. The boxplots of TEPB$_n$ and ACEQD$_2$ for patients in whom the ACEQD$_2$ of HR-CTV D$_{90}$ or IR-CTV D$_{90}$ achieved and did not achieve the planning aim dose are shown in Figure 3. The choice of applicator type depends on the individual anatomy and tumor spread at the time of BT. However, there are many difficulties in the selection of applicators, which need to be changed between fractions. If the applicator in the previous BT session is not optimal, a different applicator has to be used in the subsequent fraction(s). For example, instead of ring applicator, Utrecht applicator can be used or vice versa. Of the 119 patients, the applicator was changed in 38 (31.9%) cases: the applicator was changed after the first BT in 25 patients, after the second BT in 16 patients, and after the third BT in 14 patients. Distribution of changes in applicator with patients' numbers is shown in Table 2. For the patients in whom different applicators were used, the boxplots of dose increase caused by changing the applicator are shown in Figure 4. The cut-off value was set to the planning aim dose, and the

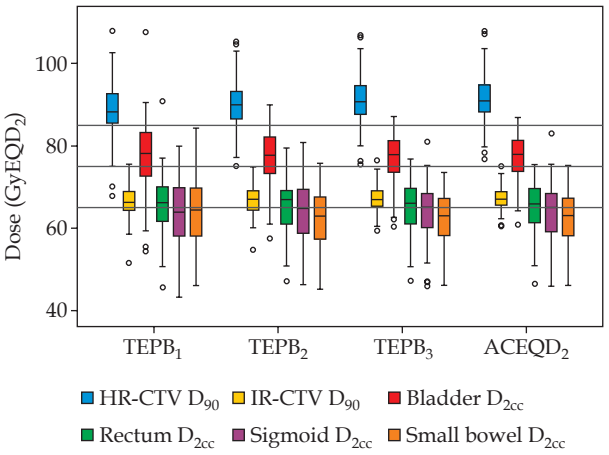

Fig. 2. Boxplots of TEPB$_n$ and ACEQD$_2$. The thin horizontal lines indicate 85, 75, and 65 Gy EQD$_2$

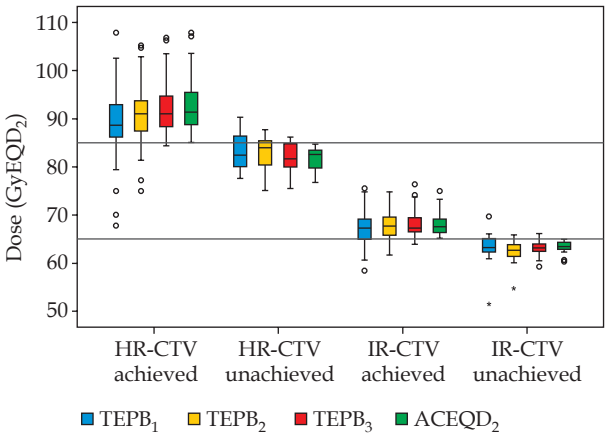

Fig. 3. Boxplots of TEPB$_n$ and ACEQD$_2$ for subgroup. Boxplots of TEPB$_n$ and ACEQD$_2$ for the patients in whom the ACEQD$_2$ of HR-CTV D$_{90}$ or IR-CTV D$_{90}$ achieved and did not achieve the planning aim dose. Thin horizontal lines indicate 65 and 85 Gy EQD$_2$

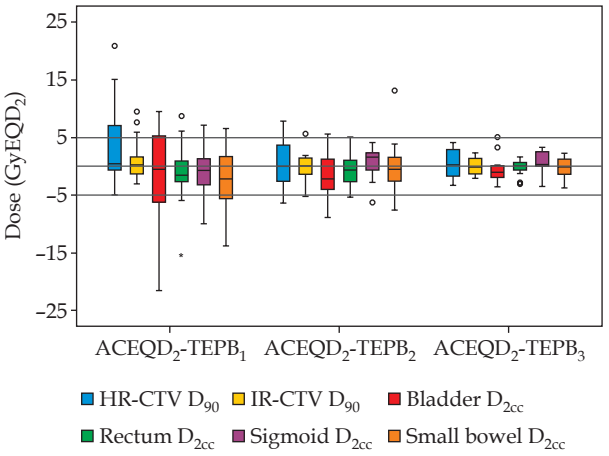

Fig. 4. Boxplots of dose alterations caused by changing the applicator. Thin horizontal lines indicate 5, 0, and –5 Gy EQD$_2$

Table 2. Distribution of change in applicator

Change in applicator	Number of patients (%)		
	Fraction 1 to 2	Fraction 2 to 3	Fraction 3 to 4
TO IC/IS to TR IC/IS	12 (10.1%)	5 (4.2%)	4 (3.4%)
TR IC/IS to TO IC/IS	4 (3.4%)	3 (2.5%)	3 (2.5%)
TO IC/IS to 3D PCI	3 (2.5%)	1 (0.8%)	1 (0.8%)
Miscellaneous*	6 (5.0%)	7 (5.9%)	6 (5.0%)

*TO – tandem and ovoids, IC/IS – intracavitary and interstitial, TR – tandem and ring, 3D PCI – 3D printing cylinder-based interstitial, *the number of patients of change in applicator between fractions was two or less*

Table 3. Patient distribution was used to determine whether TEPBn predicts and ACEQD2 achieves the planning aim dose according to cut-off (planning aim dose)

	HR-CTV D_{90}	IR-CTV D_{90}	Bladder D_{2cc}	Rectum D_{2cc}	Sigmoid D_{2cc}	Bowel D_{2cc}
$TEPB_1$						
TP	90 (75.6%)	73 (61.3%)	105 (88.2%)	84 (70.6%)	91 (76.5%)	86 (72.3%)
FP	3 (2.5%)	6 (5.0%)	2 (1.7%)	4 (3.4%)	3 (2.5%)	8 (6.7%)
FN	19 (16.0%)	25 (21.0%)	10 (8.4%)	15 (12.6%)	13 (10.9%)	18 (15.1%)
TN	7 (5.9%)	15 (12.6%)	2 (1.7%)	16 (13.4%)	12 (10.1%)	7 (5.9%)
Sensitivity	82.6%	74.5%	91.3%	84.8%	87.5%	82.7%
Specificity	70.0%	71.4%	50.0%	80.0%	80.0%	46.7%
$TEPB_2$						
TP	95 (79.8%)	82 (68.9%)	110 (92.4%)	89 (74.8%)	95 (79.8%)	98 (82.4%)
FP	4 (3.4%)	2 (1.7%)	1 (0.8%)	5 (4.2%)	5 (4.2%)	7 (5.9%)
FN	14 (11.8%)	16 (13.4%)	5 (4.2%)	10 (8.4%)	9 (7.6%)	6 (5.0%)
TN	6 (5.0%)	19 (16.0%)	3 (2.5%)	15 (12.6%)	10 (8.4%)	8 (6.7%)
Sensitivity	87.2%	83.7%	95.7%	89.9%	91.3%	94.2%
Specificity	60.0%	90.5%	75.0%	75.0%	66.7%	53.3%
$TEPB_3$						
TP	108 (90.8%)	92 (77.3%)	113 (95.0%)	92 (77.3%)	103 (86.6%)	98 (82.4%)
FP	2 (1.7%)	2 (1.7%)	1 (0.8%)	3 (2.5%)	5 (4.2%)	5 (4.2%)
FN	1 (0.8%)	6 (5.0%)	2 (1.7%)	7 (5.9%)	1 (0.8%)	6 (5.0%)
TN	8 (6.7%)	19 (16.0%)	3 (2.5%)	17 (14.3%)	10 (8.4%)	10 (8.4%)
Sensitivity	99.1%	93.9%	98.3%	92.9%	99.0%	94.2%
Specificity	80.0%	90.5%	75.0%	85.0%	66.7%	66.7%

D_{90} – dose to 90% of the target volume, D_{2cc} – minimal dose to the most irradiated 2 cc of an OAR, $TEPB_n$ – total EQD_2 prediction at nth BT, TP – true positive (both $TEPB_n$ and ACEQD achieved the planning aim), FP – false positive ($TEPB_n$ achieved the planning aim, but ACEQD did not), FN – false negative ($TEPB_n$ did not achieve the planning aim, but ACEQD did), TN – true negative (neither $TEPB_n$ nor ACEQD achieved the planning aim)

result of $TEPB_n$ in predicting whether $ACEQD_2$ achieves the planning aim dose is shown in Table 3. To obtain the accuracy and optimal cut-off (see Table 4) of $TEPB_n$ prediction, we analyzed the ROC curve of each parameter.

Discussion

Radical radiotherapy for locally advanced cervical cancer includes EBRT followed by BT. Because of the implantation of applicator in BT, the patient positioning for EBRT is different from that for BT, especially the changes in tumors and OARs around the applicator. During BT, the changes in tumor and OARs are also significant. In order to accurately identify the most exposed volume of OARs in BT, manually contour on EBRT CT images is a suitable method, but it is very inconvenient and difficult [18]. It is difficult to track and accumulate the doses of EBRT and BT using rigid registration. Even if deformable registration is used, it is limited to BT different fractions. Currently, there is a lack of straightforward metrics to evaluate deformable image registration errors between EBRT and BT [19,20,21]. In this study, EQD_2 was directly mathematically accumulated, which is a general method recommended by the GEC-ESTRO, and a conservative superposition method for evaluating OARs [22]. Although this method based on assumption of static hotspot is a little different from the actual absorbed dose, it has been widely used [23,24].

In our study, the volumes of HR-CTV and IR-CTV for the four fractions gradually decreased. The results are consistent with those of other studies [2,7]. This is also one of the important bases for the recommendation of adaptive BT for cervical cancer. Even a small reduction in the target volume can help the target to receive a higher dose due to high-dose gradient in BT. Therefore, if the target dose in previous fraction is slightly insufficient, there is no need for serious concerns. Even if there are no changes in the applicator, a higher dose is expected since the target is closer to the high absorbed dose region.

According to current studies, HR-CTV D_{90} and IR-CTV D_{90} are highly correlated with probability of local

Table 4. The area under curve value and the optimal cut-off of receiver operating characteristic curves for parameters

Parameters	Area under curve	*p*-value	95% confidence interval	Optimal cut-off ($Gy_{EQD2,\alpha/\beta}$)
HR-CTV D_{90}				
$TEPB_1$	0.818	0.001	0.702-0.934	86.8
$TEPB_2$	0.899	0.000	0.835-0.962	86.0
$TEPB_3$	0.987	0.000	0.967-1.000	86.2
IR-CTV D_{90}				
$TEPB_1$	0.819	0.000	0.729-0.909	65.7
$TEPB_2$	0.948	0.000	0.908-0.987	65.7
$TEPB_3$	0.980	0.000	0.958-1.000	65.1
Bladder D_{2cc}				
$TEPB_1$	0.864	0.014	0.618-1.000	78.7
$TEPB_2$	0.909	0.006	0.783-1.000	81.4
$TEPB_3$	0.976	0.001	0.932-1.000	83.2
Rectum D_{2cc}				
$TEPB_1$	0.852	0.000	0.757-0.946	70.1
$TEPB_2$	0.920	0.000	0.861-0.980	68.3
$TEPB_3$	0.961	0.000	0.922-0.999	69.2
Sigmoid D_{2cc}				
$TEPB_1$	0.916	0.000	0.854-0.978	69.7
$TEPB_2$	0.932	0.000	0.880-0.985	69.2
$TEPB_3$	0.988	0.000	0.972-1.000	69.2
Bowel D_{2cc}				
$TEPB_1$	0.755	0.001	0.639-0.872	65.2
$TEPB_2$	0.885	0.000	0.797-0.973	65.2
$TEPB_3$	0.942	0.000	0.899-0.984	68.6

D_{2cc} – minimal dose to the most irradiated 2 cc of an OAR, $TEPB_n$ – total EQD_2 prediction at nth BT

control of cervical cancer. Dimopoulos *et al*. reported that to achieve 90% of local control probability, HR-CTV D_{90} and IR-CTV D_{90} were 86 $Gy_{EQD2,10}$ and 71 $Gy_{EQD2,10}$, respectively [11]. Mazeron *et al*. reported that the thresholds to achieve 90% of local control probability were 85 $Gy_{EQD2,10}$ to HR-CTV D_{90} and 75 $Gy_{EQD2,10}$ to IR-CTV D_{90} [10]. A meta-analysis by Mazeron *et al*. showed that HR-CTV D_{90} warranting 90% of local control probability was 81.4 $Gy_{EQD2,10}$ and for IR-CTV D_{90}, the dose of 60 $Gy_{EQD2,10}$ was associated with 79.4% of local control probability [12]. Recently, an updated meta-analysis encompassing 2,893 patients demonstrated that a tumor control probability of > 90% can be expected at doses > 84 $Gy_{EQD2,10}$ and 69 $Gy_{EQD2,10}$ for HR-CTV D_{90} and IR-CTV D_{90}, respectively [13]. The doses of D_{2cc} in OARs were also highly correlated with side effects [14]. Based on significant dose-effect relationship, the planning aims dose and the limits of the prescribed doses were obtained by referring to other studies [25,26].

In general, the area under the curve (AUC) was between 0 and 1. The closer the AUC to 1, the more accurate the prediction. A comprehensive judgment based on the AUC can avoid the bias caused by only considering the sensitivity or specificity. From our results, $TEPB_n$ exhibited high accuracy in predicting whether $ACEQD_2$ meets the planning aim dose. Among the six predictive parameters for $TEPB_1$, there was one (16.7%) parameter, for which the AUC value of ROC curve was greater than 0.9, whereas for $TEPB_2$ and $TEPB_3$, there were four (66.7%) and six (100%), respectively. As shown in Table 3, the range of false negative cases was 1-25 (0.8-21.0%), which indicates that in some patients in previous fractions of

predictive dose, the planning aim dose was not achieved, but $ACEQD_2$ reached the planning aim dose. This result is due to our positive adjustment, when $TEPB_n$ did not achieve the planning aim dose, including changed applicator [27], interstitial needles' optimization [15,28,29,30], or/and optimized bladder volume [31,32]. We also found that the false negative values gradually decreased with BT, from 10-25 (8.4-21.0%) of $TEPB_1$ to 1-7 (0.8-5.9%) of $TEPB_2$ and to 1-5 (0.8-4.2%) of $TEPB_3$. These findings show that in the operation of dosage adjustment, we must be early and accurate. If $TEPB_3$ does not achieve the planning aim dose, the probability of $ACEQD_2$ achieving the planning aim dose is very low.

Usually, if there is no change in the applicator type, tandem length, ovoid/ring size, etc., the dose parameters between interfraction maintain a high consistency, unless there is a significant change in the tumor size or organ filling. In other words, the sensitivity, specificity, and prediction accuracy of $TEPB_n$ would be very high. In this study, about 68% of the patients used the same applicator in all fractions. This determined that $TEPB_n$ had high accuracy in predicting $ACEQD_2$.

In addition, we found that the AUC value of ROC curve for small intestine D_{2cc} was lesser than that of other parameters. This result is due to a high interfraction variation in tumors and OARs in BT, especially in the small intestine, which has higher internal motion than other OARs. Moreover, the dose balance between the bladder and small intestine can be adjusted by bladder filling, due to adjacent relationship between the bladder and small intestine. Study from Mahantshetty *et al*. [31] demonstrated that the higher bladder volume, the lesser dose to small intestine, whereas bladder filling had no significant impact on the dose to bladder, rectum, and sigmoid. Study from Yamashita *et al*. [32] confirmed that bladder filling preferentially protects the small bowel. This is one of the reasons why we used bladder filling as a control method for patients with high-dose to smaThe application of this in-house designed application only takes less than 10 seconds, four times mouse click, to obtain $TEPB_n$ or $ACEQD_2$. In the absence of such an application, DVH parameters need to be typed in the patient's Excel form one by one. Each dose evaluation takes about five to ten minutes. After any dose optimization, DVH parameters need to be retyped again one after the other, which takes another five to ten minutes. Generally, a clinical actually delivered plan needs to be evaluated several times before its confirmation. Therefore, this application played an important role in shortening the treatment planning time. Even in the department with limited BT applications, this application would be of great value, especially for busy departments.

The in-house designed application reduces time-cost during treatment planning. Therefore, the potential displacement of the applicator and danger caused by the prolongation of treatment planning have been decreased. However, our in-house designed application has some limitations. It does not replace Excel sheet tools (we call it patient's Excel form) used in most of departments. Moreover, this application is not yet integrated into the treatment planning system.

Conclusions

The in-house designed application has the function of quickly reading DVH parameters from the treatment planning system, which allows for a balance between the total dose to target volumes and OARs. Excel forms based on the automatic calculation of EQD_2 have high predictive accuracy. In case of unsatisfactory dose in the first fraction(s), the dose distribution can be improved by changing the applicator or increasing the number of interstitial needles.

Disclosure

The authors report no conflict of interest.

References

1. National Comprehensive Cancer Network. Cervical Cancer (Version 2.2019). www.nccn.org/professionals/physician_gls/pdf/cervical.pdf.
2. Schernberg A, Bockel S, Annede P et al. Tumor shrinkage during chemoradiation in locally advanced cervical cancer patients: prognostic significance, and impact for image-guided adaptive brachytherapy. *Int J Radiat Oncol Biol Phys* 2018; 102: 362-372.
3. Kirisits C, Pötter R, Lang S et al. Dose and volume parameters for MRI-based treatment planning in intracavitary brachytherapy for cervical cancer. *Int J Radiat Oncol Biol Phys* 2005; 62: 901-911.
4. Lin LL, Mutic S, Low DA et al. Adaptive brachytherapy treatment planning for cervical cancer using FDG-PET. *Int J Radiat Oncol Biol Phys* 2007; 67: 91-96.
5. Kobayashi K, Murakami N, Wakita A et al. Dosimetric variations due to interfraction organ deformation in cervical cancer brachytherapy. *Radiother Oncol* 2015; 117: 555-558.
6. Meerschaert R, Nalichowski A, Burmeister J et al. A comprehensive evaluation of adaptive daily planning for cervical cancer HDR brachytherapy. *J Appl Clin Med Phys* 2016; 17: 323-333.
7. Kirisits C, Lang S, Dimopoulos J et al. Uncertainties when using only one MRI-based treatment plan for subsequent high-dose-rate tandem and ring applications in brachytherapy of cervix cancer. *Radiother Oncol* 2006; 81: 269-275.
8. Pötter R, Georg P, Dimopoulos JC et al. Clinical outcome of protocol based image (MRI) guided adaptive brachytherapy combined with 3D conformal radiotherapy with or without chemotherapy in patients with locally advanced cervical cancer. *Radiother Oncol* 2011; 100: 116-123.
9. Viswanathan AN, Thomadsen B, American Brachytherapy Society Cervical Cancer Recommendations Committee et al. American Brachytherapy Society consensus guidelines for locally advanced carcinoma of the cervix. Part I: general principles. *Brachytherapy* 2012; 11: 33-46.
10. Mazeron R, Castelnau-Marchand P, Dumas I et al. Impact of treatment time and dose escalation on local control in locally advanced cervical cancer treated by chemoradiation and image-guided pulsed-dose rate adaptive brachytherapy. *Radiother Oncol* 2015; 114: 257-263.
11. Dimopoulos JC, Pötter R, Lang S et al. Dose-effect relationship for local control of cervical cancer by magnetic resonance image-guided brachytherapy. *Radiother Oncol* 2009; 93: 311-315.
12. Mazeron R, Castelnau-Marchand P, Escande A et al. Tumor dose-volume response in image-guided adaptive brachytherapy for cervical cancer: A meta-regression analysis. *Brachytherapy* 2016; 15: 537-542.

13. Tang X, Mu X, Zhao Z et al. Dose-effect response in image-guided adaptive brachytherapy for cervical cancer: A systematic review and meta-regression analysis. *Brachytherapy* 2020; 19: 438-446.
14. Georg P, Pötter R, Georg D et al. Dose effect relationship for late side effects of the rectum and urinary bladder in magnetic resonance image-guided adaptive cervix cancer brachytherapy. *Int J Radiat Oncol Biol Phys* 2012; 82: 653-657.
15. Nomden CN, de Leeuw AA, Moerland MA et al. Clinical use of the Utrecht applicator for combined intracavitary/interstitial brachytherapy treatment in locally advanced cervical cancer. *Int J Radiat Oncol Biol Phys* 2012; 82: 1424-1430.
16. Dumane VA, Yuan Y, Sheu RD et al. Computed tomography-based treatment planning for high-dose-rate brachytherapy using the tandem and ring applicator: influence of applicator choice on organ dose and inter-fraction adaptive planning. *J Contemp Brachytherapy* 2017; 9: 279-286.
17. Gebhardt BJ, Vargo JA, Kim H et al. Image-based multichannel vaginal cylinder brachytherapy for the definitive treatment of gynecologic malignancies in the vagina. *Gynecol Oncol* 2018; 150: 293-299.
18. Frohlich G, Vizkeleti J, Nguyen AN et al. Comparative analysis of image-guided adaptive interstitial brachytherapy and intensity-modulated arc therapy versus conventional treatment techniques in cervical cancer using biological dose summation. *J Contemp Brachytherapy* 2019; 11: 69-75.
19. Kim H, Huq MS, Houser C et al. Mapping of dose distribution from IMRT onto MRI-guided high dose rate brachytherapy using deformable image registration for cervical cancer treatments: preliminary study with commercially available software. *J Contemp Brachytherapy* 2014; 6: 178-184.
20. van Heerden LE, Visser J, Koedooder K et al. Role of deformable image registration for delivered dose accumulation of adaptive external beam radiation therapy and brachytherapy in cervical cancer. *J Contemp Brachytherapy* 2018; 10: 542-550.
21. Kadoya N, Miyasaka Y, Yamamoto T et al. Evaluation of rectum and bladder dose accumulation from external beam radiotherapy and brachytherapy for cervical cancer using two different deformable image registration techniques. *J Radiat Res* 2017; 58: 720-728.
22. Pötter R, Haie-Meder C, Van Limbergen E et al. Recommendations from gynaecological (GYN) GEC ESTRO working group (II): concepts and terms in 3D image-based treatment planning in cervix cancer brachytherapy-3D dose volume parameters and aspects of 3D image-based anatomy, radiation physics, radiobiology. *Radiother Oncol* 2006; 78: 67-77.
23. Mahantshetty U, Gudi S, Singh R et al. Indian Brachytherapy Society Guidelines for radiotherapeutic management of cervical cancer with special emphasis on high-dose-rate brachytherapy. *J Contemp Brachytherapy* 2019; 11: 293-306.
24. Kumar M, Thangaraj R, Alva RC et al. Impact of different dose prescription schedules on EQD_2 in high-dose-rate intracavitary brachytherapy of carcinoma cervix. *J Contemp Brachytherapy* 2019; 11: 189-193.
25. Pötter R, Tanderup K, Kirisits C et al. The EMBRACE II study: The outcome and prospect of two decades of evolution within the GEC-ESTRO GYN working group and the EMBRACE studies. *Clin Transl Radiat Oncol* 2018; 9: 48-60.
26. Majercakova K, Pötter R, Kirisits C et al. Evaluation of planning aims and dose prescription in image-guided adaptive brachytherapy and radiochemotherapy for cervical cancer: Vienna clinical experience in 225 patients from 1998 to 2008. *Acta Oncol* 2015; 54: 1551-1557.
27. Viswanathan AN, Beriwal S, De Los Santos JF et al. American Brachytherapy Society consensus guidelines for locally advanced carcinoma of the cervix. Part II: high-dose-rate brachytherapy. *Brachytherapy* 2012; 11: 47-52.
28. Kirisits C, Lang S, Dimopoulos J et al. The Vienna applicator for combined intracavitary and interstitial brachytherapy of cervical cancer: design, application, treatment planning, and dosimetric results. *Int J Radiat Oncol Biol Phys* 2006; 65: 624-630.
29. Otter S, Coates A, Franklin A et al. Improving dose delivery by adding interstitial catheters to fixed geometry applicators in high-dose-rate brachytherapy for cervical cancer. *Brachytherapy* 2018; 17: 580-586.
30. Zhao Z, Tang X, Mao Z et al. The design of an individualized cylindrical vaginal applicator with oblique guide holes using 3D modeling and printing technologies. *J Contemp Brachytherapy* 2019; 11: 479-487.
31. Mahantshetty U, Shetty S, Majumder D et al. Optimal bladder filling during high-dose-rate intracavitary brachytherapy for cervical cancer: a dosimetric study. *J Contemp Brachytherapy* 2017; 9: 112-117.
32. Yamashita H, Nakagawa K, Okuma K et al. Correlation between bladder volume and irradiated dose of small bowel in CT-based planning of intracavitary brachytherapy for cervical cancer. *Jpn J Clin Oncol* 2012; 42: 302-308.