

Model assessment of individual tumor control rate and adverse effects in comparing locally advanced cervical cancer treatment using intracavitary with and without interstitial brachytherapy

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Abstract

Purpose: This study assessed the modeled probability of tumor control and organ at risk toxicities in locally advanced cervical cancer in patients treated by external beam radiation plus brachytherapy using intracavitary combined with interstitial brachytherapy (IC/IS) vs. intracavitary brachytherapy (IC) alone.

Material and methods: Twenty cervical cancer patients with a mean HR-CTV volume of 47.4 cm³ and a mean width of 54 mm were planned with both IC/IS and IC brachytherapy alone. A probit model was utilized to model 3-year (3-yr) local control rate (LC), 3-yr cancer specific survival rate (CSS), and the adverse effect (AE) of the organ at risk by using a modeled data set from multiple institutions. Modeling results were used to estimate the LC, CSS, and AE of the treatments in this study.

Results: Using the IC/IS technique, an EQD₂ increase of 12.3 Gy to D₉₀ (from 76.1 Gy to 88.3 Gy) of HR-CTV is expected to increase 3-yr LC and 3-yr CSS by 12.5%, and 11.0%, respectively. Comparing IC/IS to IC alone, the expected G2⁺ AE were 7.7% vs. 7.9% for the bladder, and 5.9% vs. 6.8% for the rectum.

Conclusions: The IC/IS technique improved dose coverage to the HR-CTV without significantly increasing dose to 2 cm³ of the organ at risk (OAR) surrounding it. With different regimens of EBRT combined with BT, IC/IS can be used to increase the probability of LC and CSS, or decrease the risk of AE.

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Key words: cervical cancer, brachytherapy, tumor control, adverse effect.

Purpose

External beam radiotherapy (EBRT) with concurrent cisplatin followed by intracavitary brachytherapy (IC BT) has been the standard treatment for locally advanced cervical cancer patients. The evolution of brachytherapy (BT) from 2D to 3D has changed the treatment technique from prescription to Point-A, based on 2D radiographs, to a technique using a 3D target volume prescription based on CT/MRI images. To adapt to the shape change of the target volume at the time of implant, image guided adaptive brachytherapy (IGABT) was introduced [1]. Specifically, this requires the use of 3D imaging with the applicator *in situ* at the time of BT. The GEC-ESTRO [2] guidelines for contouring of the high risk clinical target volume (HR-CTV), intermediate risk clinical target volume (IR-CTV), and organs at risk (OAR), as well as dose

volume parameters for treatment of locally advanced cervix cancer with IGABT were used.

Evaluation of plan results using dose volume histogram (DVH) parameters requires computerized treatment planning. This development modified the standard loading pattern to conform the target shape or to avoid dose to OAR [3], and facilitated the development of inverse planning processes in gynecologic cases [4,5,6]. For bulky and asymmetrical tumors with residual parametrial involvement at the time of BT, the use of intracavitary combined with interstitial brachytherapy (IC/IS BT) [7,8,9] has offered another option to improve the dose coverage for locally advanced cervical cancer. However, its implementation has not been widespread and the clinical results in terms of using IC/IS are yet to be determined.

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We have been routinely using IC/IS with IGABT in the treatment of locally advanced cervical cancer patients with bulky tumors and residual parametrial involvement. This study aims to investigate and assess the clinical advantage of using IC/IS over IC alone in the treatment of locally advanced cervical cancer.

Material and methods

Twenty patients who underwent CT-guided HDR intracavitary combined with interstitial brachytherapy (IC/IS BT) for cervical cancers (CC) were selected in this retrospective study. Among them, nine were stage IIB and eleven were stage IIIB. Dose was prescribed at 45-54 Gy in 25-28 fractions (four 45 Gy, thirteen 50 Gy, two 50.4 Gy, and one 54 Gy) with external beam radiotherapy (EBRT) plus 24-30 Gy (one 3 x 8 Gy, two 4 x 7 Gy, and seventeen 5 x 6 Gy) with IC/IS implant.

Nucletron Utrecht applicators (Nucletron, an Elekta company, Elekta AB, Stockholm, Sweden) were used in each implant. The Utrecht applicator is composed of one tandem and two ovoids. Each ovoid has five holes into which needles can be inserted to function as an IC/IS implant. Table 1 summarizes the patient characteristics and the technical data of the IC/IS implants in this study. There were 248 needle inserts performed within a total of

96 implants. On average, each implant had 1.0 inserts via the right ovoid and 1.2 inserts via the left ovoid. The average depth of needle insertion was 3.2 cm and 3.0 cm for the right and left ovoids, respectively.

High risk clinical target volume (HR-CTV), intermediate risk clinical target volume (IR-CTV), bladder, rectum, and sigmoid were contoured following the GYN GEC-ESTRO recommendations [2], and the guidelines of CT to MRI target delineation published by Viswanathan *et al.* [10]. The tumor (HR-CTV) volume and tumor width reported in Table 1 were defined from the CT image of the first BT treatment. Treatment planning was performed with each fraction using the Oncentra® (Nucletron, an Elekta company, Elekta AB, Stockholm, Sweden) treatment planning system. Dose in each BT treatment was prescribed to HR-CTV, with the goal dose being an equivalent dose in 2 Gy fractions (EQD₂) of 85 Gy, using an α/β -ratio of 10 Gy. Optimization was performed manually by limiting the dose constraints of EQD₂ = 90 Gy to 2 cm³ of bladder, and EQD₂ = 75 Gy to both the rectum and sigmoid using an α/β -ratio of 3 Gy. Dose calculation and reporting were based on the total EQD₂ of EBRT + BT using an α/β ratio of 10 Gy for the tumor and an α/β -ratio of 3 Gy for the organs at risk (OAR), and a repair half time of 1.5 h.

To compare the difference of the planning results between combined IC/IS implants and IC alone in locally advanced CC, all the original plans (the IC/IS - MO sub-group) were re-optimized by an inverse planning process using a simulated annealing (IPSA) algorithm (the IC/IS - IPSA sub-group). The inverse planning process kept the OAR dose similar to the original plan by MO while maximizing the coverage to HR-CTV and IR-CTV with the prescription dose. A 2.5 mm step size was applied for the dwell positions. To prevent small hot spots around an individual dwell positions, a value of 0.3 DTDC (dwell time deviation constraint) was applied to restrict dwell time deviation in each catheter [11]. After optimization was done for an IC/IS plan, the same dose constraints in the IPSA were used to optimize another IC plan (the IC - IPSA sub-group) by inactivating the dwell positions in each interstitial needle. Both IC alone and IC/IS plans using IPSA were finalized by minor manual adjustment of the dwell times to optimize the coverage without increasing the dose to OARs. The purpose of this optimization workflow is to standardize the study. The IPSA method was not clinically utilized in our department.

Plans were compared between IC/IS and IC techniques using the summed EQD₂ dose to 90% volume (D₉₀) of the HR-CTV, and EQD₂ dose to 2 cm³ volume of the bladder (B_{2cc}), rectum (R_{2cc}), and sigmoid (S_{2cc}). In order to estimate the individual tumor control (TC) and OAR toxicity in this study, long term outcomes based on IGABT technique published by different institutions [12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22] were utilized to model the three-year local tumor control rate (3-yr LC) and three-year cancer specific survival rate (3-yr CSS). To reduce the variation within the data set, IGABT technique was used as inclusion criteria and data from more than 30% of patients who were stage IIA or less was excluded [12, 13, 22]. At the time of this study, only Georg *et al.* had published large volume-based data modeling the Grade 1-4 toxicity

Table 1. Patient characteristics regarding clinical stage at diagnosis, tumor size at brachytherapy (BT), and the IC/IS implant data in this study

Patient characteristics	Mean \pm SD or n (%)
Diagnosis	
Stage IIB	9 (45)
Stage IIIB	11 (55)
Tumor size	
Volume	47.4 \pm 19.6 cm ³
Width (W)	5.4 \pm 0.7 cm
W \geq 5 cm	16 (80)
W < 5 cm	4 (20)
IC/IS Implant	
Implant no.	96
Needle no.	248
Needle _{Rt}	1.0 (0, 2.3)*
Needle _{Lt}	1.2 (0.8, 2.3)*
Depth _{Rt}	3.2 \pm 1 cm
Depth _{Lt}	3 \pm 0.9 cm
Dwell time% @IC	57 (45.78)
Dwell time% @IS	33 (12.55)

*Median (range)

IC/IS – intracavitary combined with interstitial brachytherapy

of the bladder and rectum [23,24]. Since the number of the reported AE was low, their data was reproduced without further modeling to estimate the Grade 2 and above adverse effect (AE) for each patient in our study.

Probit model

The long-term outcomes from multiple institutions used in this modeling were summarized in Table 2. The binary outcomes were recorded and displayed as a proportion of the patients that had LC and CSS reported. The proportion data from each institute's report was considered as a quantal data such that the entire data set consists of dose (EQD₂ to D₉₀ of HR-CTV) and the proportion responding in terms of LC and CSS. A probit model was utilized to examine their association. Probit analysis is a type of regression technique used to analyze binomial response variables. It transforms the sigmoid dose-response curve to a straight line that can then be analyzed by regression either through least squares (LS) or maximum likelihood (ML). In this study, we utilized the ML method. Proportion data do not have a uniform variance, i.e., as the proportion (*p*) changes (with changing dose), the variance changes. The probit method of linear regression adjusts for this non-constant variance through the application of weights [25]. The variances of the probit regression line can be used to estimate the precision in probit calculation. The 95% confidence interval (CI)

of the probit at each dose level, which was derived from the variance of the probit was calculated and reported. A likelihood-ratio (LR) test was assessed by reporting a χ^2 value. Large χ^2 lead to a small p-value indicating a good model fit. In addition to the variance of the regression line reported by the 95% CI and LR test, the area under the curve (AUC) of the receiver operating characteristic (ROC) was used as another figure of merit for comparing alternative model [26].

Modeled outcome assessment between IC/IS and IC technique

The probit link function is based on the normal cumulative distribution function (CDF). The normal CDF derived after probit analysis was used to assess and predict the individual probability of an outcome from the EQD₂ of the HR-CTV using both IC and IC/IS techniques. Evaluated outcomes included the 3-yr LC and 3-yr CSS modeled from the multi-institution data set with above method. The EQD₂ to 2 cm³ of bladder and rectum calculated from both IC/IS, and IC plans were used to evaluate the AE of bladder and rectum. They were estimated using the regression curved modeled in Georg's paper [24].

Statistical analysis

Descriptive summaries of patient and clinical characteristics are presented. Continuous scale variables are pre-

Table 2. Clinical outcomes of locally advanced cervical cancer treated with radiation therapy reported from eight institutions

Factor	GRC [14]	Vien. [15]	STIC [16]	ChiMai [17]	Utrecht [18]	Aarhus [19]	UPMC [20]	UCSD [21]
Period	06-11	01-08	05-07	08-11	06-08	05-11	07-13	07-14
Imaging	CT/MRI	MRI	CT	CT/MRI	MRI	MRI	MRI	CT/MRI
Patients no	225	156	117	47	46	140	128	76
IIB/ > IIB	110/36	88/41	77/29	32/15	22/10	79/41	75/21	23/26
W (> 5; < 5) (cm)	– ^{&}	103;53	4.9	–	4	6	5	–
Volume (cm ³)	–	–	35.2	–	52/63	–	31.8	–
IC; IC/IS	–	–	–; 0	–	–	80; 60	121; 7	70; 0
D ₉₀ (Gy ₁₀)	80.4 (77.9) ⁵ (80/71.6)	93 (96;91)	73.1	93	84 (84/76)	91	83.2	86.3
3-yr LC (%)	86.4 (81.9) ⁵ (85.5/71)	95 (96/86) (98;92)	70	98 (97/100)	93	91	91.6	94
3-yr CSS (%)	76.1 (74.5) ⁵ (71/83.6)	74 (84/52) (83;70)	60	85.1 (87.5/80)	74 (69/50)	87	85.4	70
D-B _{2cc} (Gy ₃)	71.1	86	69.5	88.2	83	69/79	76.5	75.3
D-R _{2cc} (Gy ₃)	62.1	65	61	69.6	66	62/68	55.9	67.5
D-S _{2cc} (Gy ₃)	60.0	64	58.1	72	61	62/73	65.0	66.2
3-yr > G2* (%)	4 ² ; 2.7 ³	2 ² ; 3.2 ³	2.6 ^{1,2,3}	2 ² ; 2.1 ³	2.2 ² ; 8.7 ³	1 ² ; 3 ³	1 ^{2,3}	1.5 ³

*Grade 3 & 4 toxicity, 1. Gynecologic; 2. Urinary; 3. Gastrointestinal; ⁵value in parenthesis excludes stage bellow IIB; [&]data not available; [#]value in italic font denotes patient number; the 1st number in (/) denotes value for stage IIB, 2nd number denotes value for stage > IIB; the 1st number in (;) denotes value for W < 5 cm, the 2nd number denotes value for W > 5 cm; IC/IS – intracavitary combined with interstitial brachytherapy; D₉₀ – dose to 90% volume of the HRCTV; LC – local control rate; CSS – cancer specific survival rate; D-B_{2cc} – dose to 2 cm³ of the bladder; D-R_{2cc} – dose to 2 cm³ of the rectum; D-S_{2cc} – dose to 2 cm³ of the sigmoid; Gy₁₀ – equivalent dose in 2 Gy fractions an α/β ratio of 10 Gy; Gy₃ – equivalent dose in 2 Gy fractions an α/β ratio of 3 Gy

sented as mean (standard deviation) or median (range), as appropriate, while categorical scale variables are presented as frequency count and percentages. A Wilcoxon signed-rank test was used to compare the difference of EQD₂, 3-yr LC, 3-yr CSS, and AEs between implant techniques. *P*-value < 0.05 was considered a statistically significant difference.

Results

Modeling of treatment outcome

The reported mean D₉₀ ranges from EQD₂ = 73.1 Gy to 93 Gy, which resulted in 3-yr LC and 3-yr CSS rates of 70% to 98% and 60% to 87.6%, respectively. The fitted curves shown in the left panel of Figure 1 have ED₅₀ values (expected dose with 50% probability) of EQD₂ = 58.5 Gy and 58.9 Gy for 3-yr LC and 3-yr CSS, respectively. In addition to ED₅₀, the corresponding ED₆₀, ED₇₀, ED₈₀, ED₉₀, and ED₉₉ in 2 Gy fraction equivalent doses with 95% confident interval (95%CI) were summarized in Table 3.

Here ED_{level} denotes the expected dose to achieve the specified local control level. Chi-square values were 71.73 (*p* < 0.0001) and 29.85 (*p* < 0.0001) for LC and CSS, respectively, after LR test. LR test showed good fits of the models for both 3-yr LC and 3-yr-CSS. The AUC values were 0.67 and 0.54 in the model of 3-yr LC and 3-yr CSS, respectively. When comparing the two models, which have the same modeling quantitative data (D₉₀) but have different end points, the LC model showed a better prediction power than the CSS model. The right panel of Figure 1 reproduced the side effect data published in Georg’s paper [24]. Their modeled values of ED₅, ED₁₀, and ED₂₀ along with the 95% PI were listed in Table 4 for reference. The bladder and rectum dose constraints suggested by GEC-ESTRO and ABS (90 Gy for bladder and 70-75 Gy for rectum) are located between 5-10% Grade 2 adverse effect in their model, which is clinically acceptable. The regression using the same probit method has goodness of fit values of 0.702 (*p* = 0.4) and 1.27 (*p* = 0.26) for bladder and rectum, respectively.

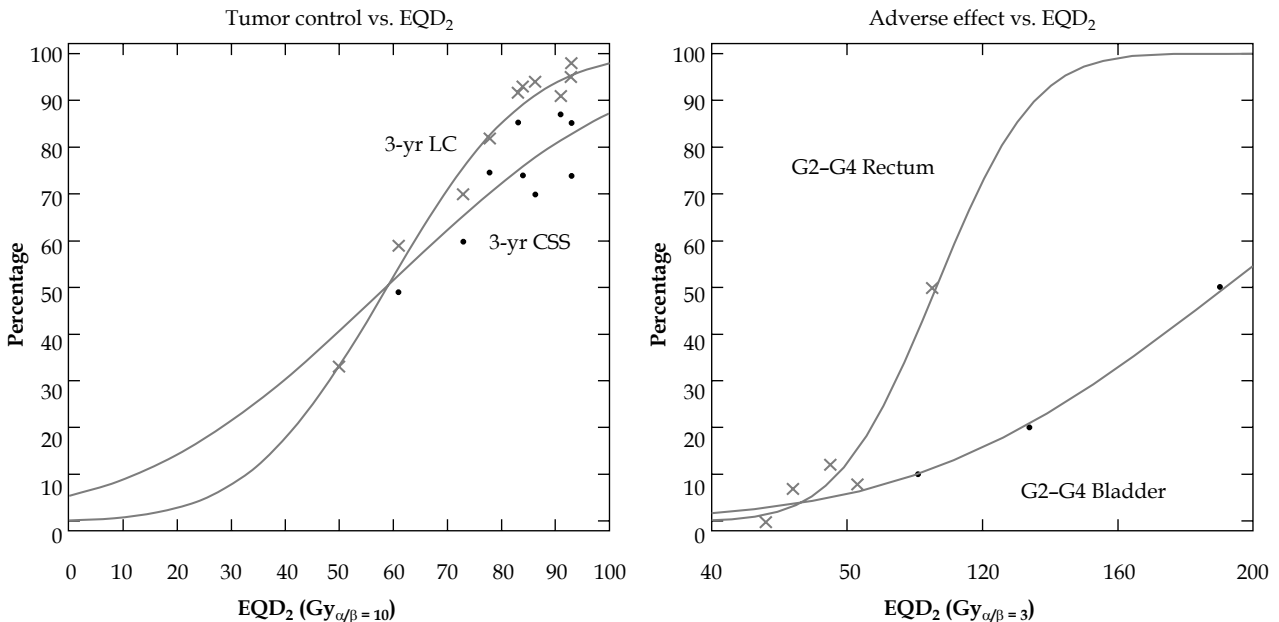


Fig. 1. Dose effect curves depicting 3-yr probability of LC and CSS (left panel: × - data points for LC model; • - data points for CSS model) and Grade 2 (G2) - Grade 4 (G4) risk of rectum and bladder (right panel: × - data points for rectum AE model; • - data points for bladder AE model)

Table 3. Modeled dose values ED_{level} with 95% CI (range in parenthesis) of expected 3-yr level% LC and 3-yr level% CSS

ED _{level} (95% CI)	ED ₅₀	ED ₆₀	ED ₇₀	ED ₈₀	ED ₉₀	ED ₉₉
3-yr LC* (n = 903)	58.8 (51.6-63.4)	64.0 (58.3-67.7)	69.5 (65.3-72.4)	76.0 (73.1-78.2)	84.9 (82.7-87.8)	106.3 (100.9-114.7)
3-yr-CSS*	58.6 (44.4-65.6)	67.8 (58.4-72.6)	77.6 (72.8-81.0)	89.2 (85.7-94.5)	105.1 (98.6-118.5)	143.1 (126.9-177.5)
3-yr LC [‡] (n = 225)	41 (-41-56.7)	49.4 (-14-62)	58.4 (14.6-67.9)	68.9 (47-76)	83.5 (76.5-103)	118.2 (100.5-221)
3-yr LC [#] (n = 77)	61 (22-70)		72 (57-82)	80 (71-97)	92 (82-131)	
3-yr LC [#] w > 5 (n = 31)	68 (30-78)		77 (67-118)	83 (74-137)	91 (80-228)	

*Current study; [‡]Dimopoulos’s study [32]; [#]GRC’s study [14]; ED_{level} - expected dose with level% probability (of LC or CSS); ED₅₀ - expected dose with 50% probability; ED₆₀ - expected dose with 60% probability; ED₇₀ - expected dose with 70% probability; ED₈₀ - expected dose with 80% probability; ED₉₀ - expected dose with 90% probability; ED₉₉ - expected dose with 99% probability; CSS - cancer specific survival rate; LC - local control rate; GRC - Gustave Roussy Cancer campus

Dosimetric comparison between IC/IS and IC technique

Figure 2 displays the distribution of EQD₂ to D₉₀ of HR-CTV and the EQD₂ to 2 cm³ of various OARs using different combinations of EBRT and BT. The median D₉₀ to HR-CTV were 88.3 Gy and 76.1 Gy for the IC/IS and IC techniques, respectively. There was a significant difference in D₉₀ of HR-CTV (*p* < 0.001) when comparing the IC/IS to the IC group. The higher coverage in the IC/IS group only slightly increased the median EQD₂ to by 3 Gy to the sigmoid (73.9 Gy vs. 70.2 Gy), but yielded a 2 Gy reduction for the rectum (71.3 Gy vs. 73.2 Gy) and 1 Gy reduction (89.6 Gy vs. 90.6 Gy) for the bladder.

Modeled outcome assessment between IC/IS and IC technique

Comparing IC/IS and IC alone, the 12.2 Gy (1.01 Gy, 21.5 Gy) increase to D₉₀ of HR-CTV in 2 Gy fraction equivalents is expected to increase 3-yr LC and 3-yr CSS by 12.5% (0%, 20%), and 11% (0.1%, 17.6%), respectively. The expected median (range) of Grade 2 and above AE of the OARs using IC/IS was 7.7% (5%, 10%) and 6.3% (2%, 23%) for bladder and rectum, respectively. The assessed AE for the bladder was the same between IC/IS and IC techniques. The IC/IS technique decreased assessed AE in the rectum by 1%. The individual biological model assessments were demonstrated with boxplot distributions in lower left panel (AE) and left panel (LC and CSS) of Figure 2. Compared with IC alone, the IC/IS technique had higher means and narrower ranges in both the 3-yr LC and 3-yr CSS. The 1-3 Gy difference in EQD₂ between different techniques transforms to 0.2-2% AE differences in the range of the results presented in this study.

Table 4. Probability of Grade 2 and above adverse effect according to dose levels reproduced from the study by Georg *et al.* [24]

Dose volume	Probability of EQD ₂ for G2-G4 side effects (Gy) for the incident rate shown (95% CI)		
	5%	10%	20%
R _{2cc}	67 (30-79)	78 (66-110)	90 (78-171)
B _{2cc}	70 (0-95)	101 (29-137)	134 (110-371)

EQD₂ – equivalent dose in 2 Gy fractions, R_{2cc} – 2 cm³ of the rectum, B_{2cc} – 2 cm³ of the bladder

Discussion

Interpretation of clinical outcome is complicated and requires data from several clinical trials. If sufficient clinically similar trials were available, results which usually demonstrate the efficacy of a treatment using odds ratio (OR) or relative risk (RR), could be pooled into a meta-analysis to assess the heterogeneity between trials. This could also be used to determine the influence of selected variables (the independent variables) on the effect size (the dependent variable) by using an appropriate meta-regression model [27]. More importantly, the cumulated OR (or RR) determined by meta-analysis concludes a precise measurement of treatment effect. Except the EMBRACE trial, which aims to recruit 600 patients to study the efficacy of the treatment in CC patients utilizing IGABT, no other ongoing trial is available [28]. However, the preliminary outcome of using IGABT from different reports is encouraging in terms of reducing toxicity and increasing local control. Both Dimopoulos and Castelnau-Marchand modeled their LC based on the EQD₂ to D₉₀ of the HR-CTV. Their results were listed in Table 3

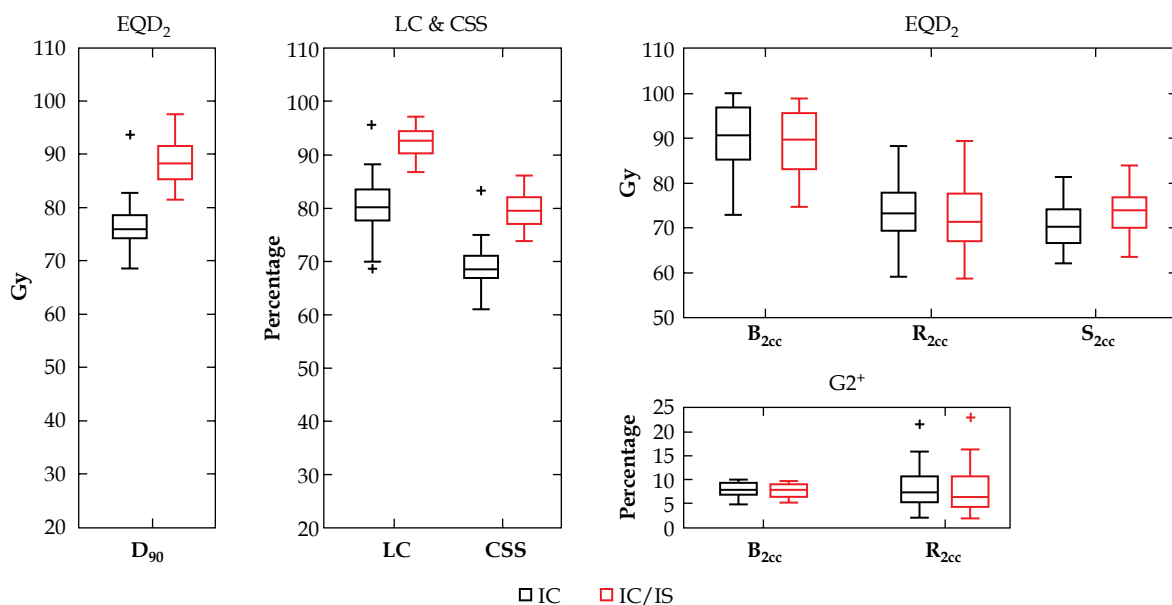


Fig. 2. Left panel: boxplot displaying the D₉₀ distribution (left) and the distribution of the estimated LC, and CSS (right) from the treatment with different combinations of EBRT and BT techniques (IC and IC/IS); right panels: boxplot displaying the EQD₂ distribution (up) of the OARs and the estimated Grade 2 and above (G2⁺) AEs (down) from the treatment with different combination of EBRT and BT techniques (IC and IC/IS)

for comparison. The 95% CI in their reports were large, which could be due to the sample size. Peduzzi's Monte Carlo study suggested a minimum number of 10 events per variable (EPV) to prevent unstable modeling results [29]. The range of data available has great impact on the estimated dose response model [30]. Specifically, the lack of data at the lower dose range can result in a major difference below the ED_{50} position. Treatment outcome also correlates to clinical prognostic factors, such as: stage, histology, volume, hypoxic status, HPP (human papilloma virus pathobiology), age, etc. Other technical factors, which contribute to model variation include delineation of target, imaging modality, and implant technique. Due to the insufficient information available in the literature, this study did not account for the potential uncertainty of the dose response model due to factors other than D_{90} to HR-CTV. It was the major limitation of this study.

The total extent to which models are carried out highly influences the rate of well-predicted absences and the AUC scores [31]. To expand the number of points in the dose range of 50 Gy to 70 Gy, two additional points (not shown in Table 2) were incorporated in the modeling. The 50 Gy point was read from Figure 2 (33% LC, estimated to be three patients and was included in LC model only) in the Dimopoulos' paper [32]. Another 61 Gy vs. 56%/50% (3-yr LC/3-yr CSS) point was adopted from Christi Hospital, which reported 36 CC patients who were not able to be treated with BT [33]. These additional points, which were considered as low or no BT dose contribution, yielded a model that allows for better prediction at a dose range of 50 Gy to 65 Gy. Due to the dose constraints to OARs, it is difficult to deliver a dose higher than 70 Gy without brachytherapy in CC patients. In two survey reports conducted by Han *et al.* [34] and Gill *et al.* [35], the 3-yr CSS of cervix patients treated with brachytherapy vs. no brachytherapy, and with brachytherapy vs. with SBRT/IMRT were 68% vs. 55% and 65% vs. 45%, respectively. An ED_{50} between 55-60 Gy for both 3-yr LC and 3-yr CSS is comparable to these clinical results.

The hypothesis in this study was that LC and CSS can be improved by using IC/IS BT for locally advanced CC patients, who normally have a larger tumor at the time of BT and/or higher clinical stage. Several groups have studied the dosimetric differences between using IC/IS and using IC alone using different IC/IS applicators with different study designs. The Netherland Utrecht Medical center used the same Utrecht applicator to study the dosimetric gain of using IC/IS (only in the 2nd fraction of PDR BT) when compared to IC alone in 20 patients [36]. There was an EQD_2 of 4.4 Gy difference in their study. The mean HR-CTV volume at the time BT using IC/IS was 52 cm³. In terms of the number of needles applied and the depth of the needle insert, there were 54 needles (in 20 implants) and a mean of 25 mm in depth. The mean fraction of the dwell time from the IS component was 19%. Aarhus University Hospital used the tandem and ring applicator in 24 patients who had a mean HR-CTV volume of 46 cm³ [37]. The mean number of needles implanted was 5.3 and the mean implanted depth was 30 mm. Combined with EBRT dose of 45-50 Gy to pelvis in 25-30 fractions, the dosimetric benefit was from 85.1 Gy to an

EQD_2 of 89.5 Gy. In a historical comparison between IC alone (HR-CTV volume of 33 cm³) and IC/IS using tandem and ring (HR-CTV volume of 44 cm³) conducted by the Vienna group [7], the D_{90} to the HR-CTV increased from an EQD_2 of 87 Gy to 96 Gy. This difference could be larger if the IC/IS patient group re-optimized with IC only. A multicenter study [38] compared the optimized IC/IS plan vs. optimized IC plan in three CC patients and showed 11.7 Gy, 14.8 Gy and 12.9 Gy increase to D_{90} of the HR-CTV. The dosimetric benefit of IC/IS over IC should therefore depend on the tumor size, tumor shape, and the OARs surrounding it.

The dosimetric benefit of using the IC/IS technique for locally advanced CC in this study was statistically significant. It demonstrated an increased EQD_2 of 12.3 Gy when compared to using IC alone. The implantation of the IC/IS technique in this study did not limit the fraction of the dwell time from the interstitial component to be less than 20% in any single implant as the implantation done by Aarhus University [37] and the Vienna group [7] did. During IPSA optimization, a DTDC (dwell time deviation constraint) value of 0.3 was applied to reduce the deviation between neighboring dwell positions, which decreased the hot spots and heterogeneity of the dose along the implanted needles. The median fraction value of the dwell time from the interstitial component was 33%. This could be the reason why this study has higher D_{90} increase compared to the results from the other groups [7,36,37].

IC/IS technique geometrically expands the implant dimension compared to IC alone, which is beneficial for larger tumors. According to Dimopoulos's study [32], tumor width > 5 cm has slightly less LC than width < 5 cm. In a later study by the same group [15], they found that improved LC in tumors > 5 cm seems to be associated with an increase in 3-yr CSS from 57%/40% in 1993-1997/1998-2000 to 70% in 2001-2008, whereas no change was detectable in tumors < 5 cm. Rijkmans *et al.* showed a 3-yr LC rate of 85.9%, 89.6%, and 62.4% for tumor size (at diagnosis) of less than 4 cm, 4-6 cm, and greater than 6 cm, respectively [39]. Therefore, a bulkier tumor could receive a better dose coverage using IC/IS technique compared to IC alone, which leads to higher LC and CSS. Tumor stage is a prognostic factor of LC and CSS and is as important as dose coverage. Our modeling results showed that dose is a good predictor of 3-yr LC and 3-yr-CSS for locally advanced CC including stage II and higher stage. However, the larger variation of stage with outcome, as shown in Table 3, implies that the model may work better for stage II but is not as reliable for higher stage. Modeling including both dose and stage as independent explanatory variables is warranted in the future when more outcome data are available.

In addition to increasing the LC and CSS, the evolution of BT from x-ray based implants to IGABT, and of plan evaluation from anatomical points to DVH parameters, has greatly reduced the toxicity of the adjacent OARs. Lindegaard *et al.* [19] compared 99 patients treated with X-ray based implants to 140 different patients treated with IGABT: the 3-yr CSS increased from 68% to 87%; the Grade 3 and above combined urological and gastrointestinal AE were 10% vs. 4%; the Grade 2 and

above combined AE were 53% vs. 35%. In Kang's study [22], the LC was 97% in the 3D group and was 91% in the 2D group. For tumor diameter > 4 cm, the difference of the LC was 98% vs. 81%. Late rectal bleeding (LRB) between the 2D and 3D groups was similar, however, severe LRB rate was significantly lower in the 3D group. Our study design was to keep similar dose to the OARs (at reasonable level according to GESTRO's constraints) and optimize the dose coverage to HR-CTV. Our results showed minimal dosimetric difference to OAR between IC/IS and IC alone. An insignificant impact on the AE of bladder and rectum was expected because the OARs dose between IC/IS and IC were kept the same. Of note, AEs in our study were assessed using a model from a single institution, and therefore there is potential for higher variation. On the contrary, IC/IS can be utilized to reduce dose to the OARs, especially in the situation when they are closely surrounding the target. If using IC/IS aims at reducing dose to OARs to demonstrate a large difference in dose to OARs between IC/IS and IC alone, a different model with data compiled from multiple institutions is necessary. In conclusion, clinical outcomes of locally advanced cervical cancer patients from multiple institutions were used to model and predict the individual LC, CSS, and AE of OARs with combined EBRT and BT using IC/IS or IC alone. The IC/IS technique improved dose coverage to the HR-CTV without significantly increasing dose to 2 cm³ of the OARs surrounding it. This technique potentially can reduce dose to the surrounding OARs at the same time. With different regimens of EBRT combined with BT, IC/IS can be used to increase the probability of LC and CSS, or decrease the risk of AE.

Disclosure

Authors report no conflict of interest.

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