Individualized and inverse optimized needle configuration for combined intracavitary-interstitial brachytherapy in locally advanced cervical cancer

ABSTRACT

Objectives: The aim of this study is to address the limitation of combined intracavitary-interstitial (IC/IS) brachytherapy (BT) in locally advanced cervical cancer using standardized applicators and to determine the optimal dose distribution in patients with challenging tumors, innovative methods of customizing and optimizing the IS needle configuration for combined IC/IS BT are proposed and investigated.

Materials and Methods: A software module that could customize the IS needle configuration and subsequently generate the digital model of guiding template for three-dimensional printing was developed and integrated into our in-house treatment planning system for BT. The inverse optimization method based on the technique of mixed-integer linear programming was introduced to determine the needle tracks out of a candidate pool and dwell times at corresponding locations to best meet dose objectives. A treatment planning study was conducted to evaluate the feasibility and performance of the proposed methods.

Results: The workflow for combined IC/IS BT with customized and inverse optimized IS needle configuration was presented. Dosimetric results of the treatment planning study showed that sufficient target coverage could be obtained with the customized IS needle configuration for challenging cases. The proposed dose-based optimization method for IS needle configuration was feasible and effective. Improved target coverage and organ-at-risk sparing were achieved using the inverse planning method.

Conclusions: Using the proposed methods of customizing and optimizing the IS needle configuration, the limitation in the standardized design of combined IC/IS applicators can be addressed, and sufficient target coverage is obtained in cervical cancer patients with unfavorable tumor topography and/or extra lateral expansion.

KEY WORDS: Applicators, cervical cancer, combined intracavitary-interstitial brachytherapy, individualized design, inverse treatment planning

INTRODUCTION

External beam radiation therapy (EBRT) to the pelvis with concurrent cisplatin chemotherapy followed by brachytherapy (BT) boost to the cervix is the standard treatment approach for patients with locally advanced cervical cancer. BT is an essential component of the treatment and has an important impact on clinical outcomes. For patients with moderate parametrial involvement and/or insufficient treatment response after EBRT, combined intracavitary-interstitial (IC/IS) BT techniques are developed and proved to be preferable to classical IC BT. The advantages of combined IC/IS BT in target coverage and organ-at-risk (OAR) sparing are gained by introducing additional IS needles to the conventional IC applicators. Recent studies have shown that three-dimensional (3D) image-based virtual preplanning for combined IC/IS BT in locally advanced cervical cancer is clinically feasible and effective, in which both the improved dosimetric result and promising clinical outcome can be obtained.

However, the commercial combined IC/IS applicators are available with a few standard designs of the
needle guiding template. Combined IC/IS BT with customized IS needle implant cannot be performed with these commercial products until now. For example, the most widely used Utrecht applicator is basically a modified classical tandem and ovoid applicator with additional IS needles implanted in a fixed pattern. The ovoids are used as the template for IS needle placement and guidance. As a commercial product, the Utrecht applicator is only available in certain standard sizes, with fixed number and insertion positions of IS needles. Therefore, optimal IS needle implant for a specific patient is limited by the standardized design.

3D printing technology provides a versatile method for obtaining a high degree of individualization. It has been successfully applied in the field of $^{125}$I seed BT, which is employed to make customized guiding template for seed implantation.$^{[10]}$ In this study, we present our methodology and workflow of customizing the needle configuration for combined IC/IS BT utilizing the virtual model and 3D printing technique. Software module for customizing is developed and integrated into our in-house developed treatment planning system (TPS), designating the insertion positions and directions of IS needles in the preplanning process and subsequently generating the virtual model of the guiding template. The 3D printer provides the possibility of constructing the virtual model of the guiding template rapidly and accurately. With the proposed methodology and workflow, combined IC/IS BT with customized IS needle implant becomes possible and will be performed smoothly and accurately.

With the possibility of customizing the IS needle implant in combined IC/IS BT, determining the needle configuration that could achieve the optimal dosimetric result becomes a challenging problem. Needle configuration in terms of the insertion position and direction can be determined according to the patient’s anatomy and tumor topography. However, it is strongly dependent on the subjective judgment and experience of the planner. The resulting dose distribution does not necessarily meet the clinical dose requirements for the target and OARs. When the dosimetric result is considered, the trial-and-error approach could be used to solve this problem. However, it is almost impossible to find the optimal configuration of IS needles in the large space of possible solutions. The trial-and-error method is time-consuming, and the optimality of the result cannot be guaranteed.

To obtain the needle configuration that can lead to the optimal dosimetric result, a dose-based inverse planning method allowing to simultaneously optimize the potential needle configuration and dwell time is introduced. The optimization problem is formulated as a process of finding a set of needle tracks out of a candidate pool of possible ones and determining the dwell times at corresponding locations to best meet the dose objectives. The optimization algorithm is based on the technique of mixed-integer linear programming (MILP) and is solved using a deterministic method. A treatment planning study is conducted to evaluate the feasibility and performance of the proposed inverse optimization method.

**MATERIALS AND METHODS**

**Software module development**

A software module was developed and integrated into our in-house developed TPS for BT with the capability of rendering the computer-aided design (CAD) models of the applicator and IS needle in the two-dimensional (2D) and 3D views of computed tomography (CT) and magnetic resonance imaging (MRI) images, rigid registration of the CAD model of applicator to its appearance in CT/MRI images, implantation of the virtual IS needles, customization of the configuration of IS needles, and generation of a 3D digital model of the template for needle immobilization and guidance. The presented software module for customizing the IS needle configuration and BT TPS with functionalities of data import/export, image segmentation, catheter reconstruction, dose calculation (based on TG-43 formalism), plan optimization, and evaluation were developed in C++ under Visual Studio 2010 for research purpose only. In this study, the most commonly used Utrecht applicator exemplified the combined IC/IS applicators. The proposed methodology and workflow of customizing the needle configuration can be extended to the scenarios of using other combined IC/IS applicators.

The 3D models of tandem and ovoid applicator [Figure 1a] and IS needles were created in advance using the CAD software from SolidWorks (Dassault Systèmes SolidWorks Corp., MA). The detailed dimensions of the CAD model were determined according to the product specifications from venders and precise measurements of the clinically used applicator and IS needle. The rigid registration between the CAD model of the applicator and its appearance in CT/MRI images was achieved using fiducial point-based registration algorithm. The landmarks in the CAD model were the three tip points of the tandem and ovoid tubes, and the corresponding fiducial points in CT/MRI images were manually identified by the planner.

As the core functionality, the developed software module enables the virtual implantation of IS needles through the guiding template with independently adjustable insertion position, depth, and direction [Figure 1b]. The potential

![Figure 1: (a) Three-dimensional computer-aided design model of the tandem and ovoid applicator created in advance. (b) Virtually implanting the interstitial needles through the ovoid templates according to tumor topography](image-url)
dwell locations in the virtual needles can be automatically generated when the needles are designated. Afterward, dose calculation and forward and inverse plan optimization can be performed. Therefore, customizing the needle configuration can be performed according to not only the anatomy of the patient and topography of the target but also the feedback of the resulting dose distribution. When needle configuration is determined, the needle channels are subtracted from the structure volume of the ovoid template. Then, 3D digital models of the ovoid template with designed empty guiding holes are created and prepared for exporting to 3D printer in the standard tessellation language (STL) format.

Implementation procedure
A customized needle guiding template for combined IC/IS BT is generated by the following process:

a. Load the preplanning CT/MRI images of the patient with the tandem and ovoid applicator in situ and the contours of targets and OARs into our in-house developed TPS
b. Import the CAD model of the implanted applicator, and identify three landmarks in the CT/MRI images. Then, rigid registration between the CAD model and its appearance in the CT/MRI images is accomplished automatically
c. Inspect the registration result in 2D and 3D views of the CT/MRI images. Manual refinement is performed if necessary
d. Implant IS needles through the ovoid template virtually according to the patient’s anatomy and tumor topography. Adjust the insertion position, depth, and direction of each needle interactively with consideration of the resulting dose distribution
e. Confirm the configuration of IS needles until the dosimetric result is clinically acceptable. The design of the customized ovoid template in STL format is directly exported to the 3D printer. A biocompatible material is used for 3D printing. After the assembly test, the ovoid templates are sterilized and ready for the definitive implant.

Dose‑based inverse optimization of needle configuration
In the process of inverse treatment planning for BT, initially, the catheters of the applicator and IS needles are digitized to determine the potential dwell positions. Then, the times spent at each dwell location are optimized to achieve the dose-based objectives as much as possible. Hence, determining the needle configuration is combined with dwell time optimization, and dose-based inverse optimization of the needle configuration should be performed simultaneously with that of dwell time. In this study, the optimization problem is formulated as a process of selecting a small set of needles from a pool of predefined ones and determining the corresponding dwell times to best meet the clinical dose prescriptions and constraints. The introduced optimization algorithm is based on the MILP technique, in which binary and positive float variables are employed to represent candidates for needle tracks and dwell times. A binary (0–1) variable is assigned to each predefined needle track, allocating the value 1 if the corresponding needle track remains in the final needle configuration and 0 if otherwise. The predefined needle tracks include not only parallel virtual needles with different insertion positions in the ovoid templates but also oblique ones with different angles in the same insertion position. The possible insertion positions in the ovoid templates are similar to the insertion pattern of the Utrecht applicator, but the lateral insertion points are arranged in two lines with three points for each line. The predefined needle tracks comprise those that are parallel to the tandem in every possible insertion point and additional oblique ones in the most lateral insertion points (three points in each ovoid template). Tilt angles between the oblique needle tracks and vertical plane through the central tandem are 5°, 10°, 15°, and 20°. Hence, there are a total of 40 possible needle tracks in the candidate pool for needle configuration optimization, in which the potential needle tracks with different tilt angles in the same insertion points could not be simultaneously selected.

The constraint for needle track selection, which enforces at most one needle track with a specific tilt angle at each insertion point to be selected, can be represented by:

$$\sum_{k \in K_p} b_k \leq 1$$  \hspace{1cm} (1)

Where \( P \) indicates the set of possible insertion points with oblique needle tracks inserted through and \( K_p \) is the corresponding set of possible needle tracks through the insertion point \( p, p \in P \). The limit to the number of selected needle tracks in the optimization result is obtained by:

$$\sum_{k \in K} b_k \leq N$$  \hspace{1cm} (2)

Where \( K \) is the set of all possible needle tracks in the candidate pool and \( N \) is the upper bound on the number of finally selected needle tracks.

Clinical dose objectives are provided in the dose calculation points within each anatomical structure. At each calculation point \( i \), the delivered dose \( D_i \) is calculated as:

$$D_i = \sum_{j \in J} d_{ij} t_{ij}$$  \hspace{1cm} (3)

Where \( d_{ij} \) represents the dose rate at calculation point \( i \) from the source dwell position \( j, j \in J \) is the set of all possible dwell positions in the channels of applicator and catheters of IS needles.

Linear penalty function is employed to translate the degree of fulfillment with the clinical dose objective to a quantitative value. The penalty value that penalizes the violation of upper or lower dose limits for dose calculation point \( i \) in specific structure \( s \) is defined as:

$$w_i = \begin{cases} P_{UL_s} (D_i - DU_s) & \text{if } D_i > DU_s \\ P_{LU_s} (DL_s - D_i) & \text{if } D_i < DL_s \\ 0 & \text{if } DL_s \leq D_i \leq DU_s \end{cases}$$  \hspace{1cm} (4)
Where $DU_s$ and $DL_s$ are the upper and lower bounds of dose range for structure $s$, $PU_s$ and $PL_s$ represent the increasing rates of penalty value when the dose go above or below the range.

$I_s$ denotes the set of dose calculation points in structure $s$ and $S$ denotes the set of anatomical structures involved in the optimization problem. $NC_s$ is the number of dose calculation points in the structure $s$. Objective function for the optimization problem is defined as the sum of normalized penalty functions for involved structures. Then, the optimization problem is formulated as follows:

\[
\text{Minimize} \quad \sum_{s \in S} \sum_{i \in I_s} w_i^s \frac{d_{s,i} - DU_s}{NC_s} \quad (5)
\]

Subject to

\[
w_i^s \geq PU_s \left( \sum_{j \in J_k} d_{s,j} - DU_s \right) \quad \forall s \in S \quad \forall i \in I_s \quad (6)
\]

\[
w_i^s \geq PL_s \left( DL_s - \sum_{j \in J_k} d_{s,j} \right) \quad \forall s \in S \quad \forall i \in I_s \quad (7)
\]

\[
w_i^s \geq 0 \quad \forall s \in S \quad \forall i \in I_s \quad (8)
\]

\[
t_j \geq 0 \quad \forall j \in J_k \quad (9)
\]

\[
t_j \leq b_k T^a_{\max} \quad \forall k \in K \quad \forall j \in J_k \quad (10)
\]

\[
t_j \leq T^a_{\max} \quad \forall j \in J_s \quad (11)
\]

\[
t_{j_2} \leq (1 + \delta) t_{j_1} \quad \forall j_1 \in J \quad \forall j_2 \in \tau(j_1) \quad (12)
\]

\[
b_k \in \{0, 1\} \quad \forall k \in K \quad (13)
\]

\[
\sum_{k \in K} b_k \leq 1 \quad \forall p \in P \quad (14)
\]

\[
\sum_{k \in K} b_k \leq N \quad (15)
\]

Where $J_s$ and $J_k$ are the sets of possible dwell positions in the applicator’s channels and needle track $k$, respectively. $T^a_{\max}$ and $T^p_{\max}$ denote the maximum dwell times for each dwell position in the applicator’s channels and needle tracks, respectively. In this optimization model, $T^a_{\max}$ is the standard dwell time for an IC BT plan (20 s for a source activity of 370 GBq with prescription of 7 Gy). To avoid undesired high dose regions in the adjacent normal tissue and OARs, parameter $T^a_{\max}$ is set at 20% of $T^a_{\max}$ (4 s for this optimization model) according to the guidelines from the American Brachytherapy Society. When the possible needle track $k$ is not selected, binary variable $b_k$ is zero, then corresponding dwell times within that catheterer can only be zero according to constraint Eq. (10). If the $b_k = 1$, Eq. (10) implements the upper limit of dwell times within catheter $k$. The constraints Eq. (6), (7), and (8) with the objective Eq. (5) make $w_i^s$ equal to the definition in Eq. (3) and (4); thus, the objective function for dose points is a piecewise linear function. Additional constraint Eq. (12) limits the relative difference in the dwell time between adjacent dwell positions, $\tau(j_i)$ is the set of dwell positions adjacent to the dwell position $j_i$, within the same catheter, and parameter $\delta$ is the maximum allowable relative difference ($\delta = 0.5$) in this optimization model.

The optimization problem is modeled as a MILP problem because the used objective and constraints are linear functions. When the needle configuration is fixed, this optimization model reduces to a linear programming (LP) problem. Then, the optimization model is similar to the ones used in the inverse planning by simulated annealing and hybrid inverse treatment planning and optimization algorithms which are the most widely used inverse treatment planning algorithms for BT.

Branch-and-cut (BC) algorithm, which is an exact optimization algorithm combining branch-and-bound and cutting planes, is employed to mathematically solve this MILP problem. The basic idea of BC algorithm is to take a LP relaxation of the problem, solve the relaxation, and either improve the relaxation by adding additional valid constraints (cutting planes) or split the problem into two or more subproblems and repeat the process. Due to the inherent characteristic of a deterministic method, BC will search the solution space in a systematic manner and will not be trapped in the local minima. For the LP problem, primal and dual simplex algorithms are used to find out the optimal solution. In this study, we modeled the optimization problem with Optimization Programming Language and solved it with CPLEX optimizer on the platform of IBM ILOG CPLEX Optimization Studio version 12.8.0 academic edition (IBM, Armonk, NY, USA).

The advanced and sophisticated algorithmic features, such as problem preprocessing and probing, variable selection, node and neighborhood heuristics, solution polishing, and parallel computation, have been adopted in the CPLEX MIP solver thus, the large and difficult MILP problem can be solved efficiently. All computations to solve the MILP or LP problem were performed on a workstation using an Intel Xeon E5-2620 v3 CPU with 2.4 GHz (6 cores) and 32 GB RAM.

**Treatment planning study for method evaluation**

To evaluate the feasibility and performance of the proposed optimization algorithm, three patients with locally advanced cervical cancer (distal parametrial infiltration, The International Federation of Gynecology and Obstetrics Stage IV A) were enrolled to perform the treatment planning study. Due to the limited resources for combined IC/IS BT in our institution, these patients received standard IC BT, followed by stereotactic body radiation therapy in clinical practice, to achieve sufficient dose overage of target volume. Utilizing the in-house developed software module and proposed dose-based inverse optimization method, virtual plans for combined IC/IS BT were designed based on the planning CT images of the clinically implemented IC BT. Virtual IS needles through the digital models of the ovoid template were introduced into the treatment planning. Treatment plans were created.
with the needle configuration identical to that of Utrecht combined IC/IS applicator (Utrecht Plan) and the customized needle configuration (Customized Plan) according to the topography of the target and OARs. Using the dose-based inverse planning method based on MILP technique, combined IC/IS BT plans (MILP Plan) consisting of the optimal needle configuration and dwell times were also generated for the three patients. Planning aims in terms of cumulative dose of EBRT and combined IC/IS BT expressed as equivalent dose in 2 Gy fractions (EQD\(^2\)) were ≥85 Gy in 90% of the high-risk clinical target volumes (HR-CTV) (D90), ≤85 Gy in the most irradiated 2 cm\(^3\) (D2cc) of the bladder, and ≤70 Gy in D2cc of the rectum, sigmoid, and small bowel. EQD\(^2\) was calculated using \(\alpha/\beta = 3\) for OARs and \(\alpha/\beta = 10\) for tumor according to the GYN GEC-ESTRO recommendations. The initial EBRT dose was 45 Gy/25 fractions (EQD\(^2\) = 44.3 Gy, \(\alpha/\beta = 10\)) delivered with Volumetric Modulated Arc Therapy. The combined IC/IS BT plans were designed employing the high-dose-rate (HDR) BT with 4 fractions, 1 fraction per week. The planning goals of HR-CTV and OARs per fraction were calculated and presented in [Table 1] with the parameters used for the dose-based inverse optimization. The needle insertion depths were determined by the shape and size of the target, and all possible dwell positions within the contours of HR-CVT were activated for optimization.

For each case involved in the planning study, inverse optimized plans with different IS needle configurations were generated and compared in terms of target coverage and OAR sparing. The optimization time for MILP Plans was recorded. Dosimetric parameters used for comparison included D90, D100, V100, and V200 of the HR-CTV, D90, and sparing factor (defined as the ratio between D2cc OAR and D90 h-CTV) for each OAR.

**RESULTS**

The virtual needle configuration of the Utrecht Plan was set exactly following the design of Utrecht combined IC/IS applicator in terms of the insertion positions and angulations through the ovoid templates. The possible insertion points in which the needle tracks could penetrate into the target were selected to implant the virtual needles. Finally, eight virtual needles with an average insertion depth of 2.9 cm (2.2–3.8 cm) were adopted in the treatment planning for each case. Then, the inverse optimization of dwell times was performed using the LP model with the optimization parameters as presented in Table 1

### Table 1: Planning goals for brachytherapy per fraction and optimization parameters used for dose-based inverse planning

| Structure   | Planning goal (physical dose) | Optimization parameters |
|-------------|-------------------------------|-------------------------|
| HR-CTV      | \(D_{2cc} \geq 7.13\) Gy     | 20.0                    | 2                      | 7.0                    | 10                     |
| Bladder     | \(D_{2cc} \leq 5.88\) Gy     | 5.5                     | 5                      | 0                      | 0                      |
| Rectum      | \(D_{2cc} \leq 5.48\) Gy     | 4.5                     | 6                      | 0                      | 0                      |
| Sigmoid     | \(D_{2cc} \leq 5.48\) Gy     | 4.5                     | 5                      | 0                      | 0                      |
| Small bowel | \(D_{2cc} \leq 5.48\) Gy     | 4.5                     | 5                      | 0                      | 0                      |

HR-CTV=High-risk clinical target volumes

Specific needle configurations were manually customized for each case to achieve sufficient dose coverage for the target while meeting the constraints for OARs. Compared with the needle configuration of the Utrecht Plan, additional oblique needle tracks were introduced, and the insertion points for partial needles were adjusted according to the tumor topography and relation to OARs. There were 8, 7, and 8 implanted virtual needles for Case 1, 2, and 3, respectively. Subsequently, clinically acceptable plans were generated by the LP model for all three cases. The Customized Plans for Case 1 and 3 were generated with only one loop of optimization using the initial parameters presented in Table 1. With a few loops of adjustments of the optimization parameters, an acceptable plan for Case 2 was generated.

Utilizing the proposed MILP model, the needle configuration and corresponding dwell times were optimized according to the dosimetric objectives as presented in Table 1. The upper bound of allowed needles was set the same as number of needles used in the Customized Plan for each case. Optimization parameters were also identical to that used for the Customized Plan. Optimization times of the MILP Plan for each case were 48.3 min, 40.5 min, and 45.6 min, respectively, and the resulting values of objective function decreased by 26.4%, 19.8%, and 25.5%, respectively, compared with those of the Customized Plan.

Comparisons of the dosimetric parameters [Table 2] for treatment plans with different needle configurations showed that the Customized Plan and MILP Plan had more sufficient target coverage compared to the Utrecht Plan. The average increments in D90 HR-CTV of the Customized Plan and MILP Plan over the Utrecht Plan in the entire BT were 1.86 Gy\(_{\text{equivalent}}^{}\) and 2.38 Gy\(_{\text{equivalent}}^{}\), respectively. It was also found that most of the OARs D2cc indices and sparing factors for the Customized Plan and MILP Plan were lower than those for the Utrecht Plan.
Table 2: Comparisons of dose-volume histogram parameters derived from brachytherapy plans with different needle configurations for each case

| Case number | DVH parameters | Utrecht plan | Customized plan | MILP plan |
|-------------|----------------|--------------|-----------------|-----------|
| Case 1      | HR-CTV D90 (Gy) | 6.80         | 7.07            | 7.28      |
|             | HR-CTV D100 (Gy)| 4.14         | 4.96            | 5.72      |
|             | HR-CTV V100 (%) | 88.1         | 90.9            | 93.5      |
|             | HR-CTV V200 (%) | 19.1         | 14.9            | 19.3      |
|             | Bladder D2cc (Gy) | 5.63        | 5.77            | 5.86      |
|             | Bladder sparing factor | 0.83     | 0.82            | 0.78      |
|             | Rectum D2cc (Gy) | 3.49         | 3.68            | 3.56      |
|             | Rectum sparing factor | 0.51     | 0.52            | 0.49      |
|             | Sigmoid D2cc (Gy) | 3.90         | 4.08            | 4.06      |
|             | Sigmoid sparing factor | 0.57    | 0.58            | 0.56      |
|             | Small bowel D2cc (Gy) | 4.40       | 4.51            | 4.44      |
|             | Small bowel sparing factor | 0.65    | 0.64            | 0.61      |
| Case 2      | HR-CTV D90 (Gy) | 6.68         | 7.18            | 7.21      |
|             | HR-CTV D100 (Gy)| 4.10         | 5.29            | 5.52      |
|             | HR-CTV V100 (%) | 84.1         | 91.9            | 92.1      |
|             | HR-CTV V200 (%) | 18.2         | 22.3            | 21.6      |
|             | Bladder D2cc (Gy) | 5.38         | 5.15            | 5.23      |
|             | Bladder sparing factor | 0.81     | 0.72            | 0.73      |
|             | Rectum D2cc (Gy) | 4.12         | 4.02            | 3.96      |
|             | Rectum sparing factor | 0.62     | 0.56            | 0.55      |
|             | Sigmoid D2cc (Gy) | 3.95         | 4.18            | 4.16      |
|             | Sigmoid sparing factor | 0.59    | 0.58            | 0.58      |
|             | Small bowel D2cc (Gy) | 3.74       | 3.68            | 3.80      |
|             | Small bowel sparing factor | 0.56    | 0.52            | 0.53      |
| Case 3      | HR-CTV D90 (Gy) | 6.30         | 7.12            | 7.30      |
|             | HR-CTV D100 (Gy)| 4.03         | 5.10            | 5.80      |
|             | HR-CTV V100 (%) | 82.3         | 91.2            | 93.8      |
|             | HR-CTV V200 (%) | 16.3         | 19.9            | 18.4      |
|             | Bladder D2cc (Gy) | 5.54         | 5.80            | 5.32      |
|             | Bladder sparing factor | 0.88     | 0.82            | 0.73      |
|             | Rectum D2cc (Gy) | 4.05         | 4.21            | 3.95      |
|             | Rectum sparing factor | 0.64     | 0.59            | 0.54      |
|             | Sigmoid D2cc (Gy) | 4.12         | 4.26            | 4.05      |
|             | Sigmoid sparing factor | 0.65    | 0.60            | 0.55      |
|             | Small bowel D2cc (Gy) | 3.96       | 3.87            | 3.68      |
|             | Small bowel sparing factor | 0.63    | 0.54            | 0.50      |

The dose values were all physical dose for each BT fraction. Sparing factor was defined as D2cc for a certain OAR divided by D90 of HR-CTV.

DVH=Dose-volume histogram, HR-CTV=High-risk clinical target volumes, OAR=Organ-at-risk, MILP=Mixed-integer linear programming, BT=Brachytherapy.

Plan. Effective OAR protection could be achieved with the customized and inverse optimized needle configurations. [Figure 2] showed dose-volume histograms of the treatment plans with different needle configurations for representative Case 1. It could be observed that the quality of BT plan was significantly improved with the customized or inverse optimized needle configuration. Although the OAR sparing was comparable between the Customized Plan and MILP Plan, the target coverage of the MILP Plan was superior to that of the Customized Plan. The treatment plans with highest quality were generated using the MILP based optimization method.

DISCUSSION

Several studies have demonstrated that combined IC/IS BT for locally advanced cervical cancer is beneficial in cases of large residual tumor and/or moderate parametrial involvement. [4,5,15]

However, the current application of combined IC/IS BT is limited by the standardized design of commercially available applicators, such as the combined IC/IS Utrecht and Vienna applicators. Only parallel IS needles in the fixed insertion positions can be implanted with these commercial applicators. In patients with unfavorable tumor topography and/or extra lateral expansion, the universal needle template cannot allow the optimal implantation of IS needles to obtain sufficient target coverage without exceeding OAR tolerance. Even with the sophisticated plan optimization approaches, the ability to compensate for inadequacies of needle insertion by optimization of the source dwell times is limited. Due to the inherent characteristics of BT, optimal placement of the source channels is still the precondition for the success of combined IC/IS BT. Therefore, individualizing the needle configuration according to the specific anatomy of each patient would be the ultimate method to obtain optimal dose distribution. With the methodology and workflow presented in this study, an individualized design of the needle configuration for combined IC/IS BT can be achieved during the preplanning process. Theoretically, this would introduce a high degree of freedom of the source dwell positions into the treatment planning, consequently resulting in better target coverage and OAR sparing. The proposed methodology and workflow address the limitation of combined IC/IS BT using the standardized applicators and have the potential to be adopted as the routine combined IC/IS BT technique for the patients with locally advanced cervical cancer, especially for those with large tumor and/or extreme involvement of the parametrium.

To make full use of the degrees of freedom derived from individualized needle configuration, an inverse treatment planning approach based on the MILP technique to optimize both the needle configuration and dwell time was proposed and validated in this study. Compared with the planner’s subjective judgment or trial-and-error approach, dose-based inverse planning is a more intuitive and efficient method to
determine the optimal needle configuration. Moreover, better dosimetric result is also expected with the inverse planning method. MILP technique was employed in the optimization of beam orientation for EBRT and catheter placement for prostate BT in previous studies. With extensions and modifications of the algorithms proposed previously, we modeled the dose-based inverse planning for combined IC/IS BT in cervical cancer as a MILP problem, in which the IS needle configuration and dwell time could be simultaneously optimized. Because the formulated MILP problem is solved with the deterministic optimization method, the mathematical optimality of the solution can be guaranteed; then, the optimal dose distribution can be obtained. The drawback of MILP based inverse planning approach is computationally expensive, and hence, it is considered not suitable for clinical use. However, the computational performance of MILP solver is improved dramatically by the incorporation of many advanced algorithms and techniques and improvements in computer hardware. It is shown in our study that the optimization time of solving the formulated MILP problem by CPLEX optimizer is clinically acceptable for treatment preplanning.

After individualized design or dose-based inverse planning of the needle tracks using the proposed techniques, 3D design data of the corresponding ovoid templates can be generated automatically and exported to a 3D printer in the universal STL format. The ovoid templates can be printed using biocompatible 3D printing materials. Afterward, the applicator needs to be sterilized for definitive implantation. It should be noted that the 3D printed ovoid templates are only used as guidance for the commercially available IS needles. There is no direct contact between the radioactive source and 3D printed ovoid templates. Thus, additional considerations of the compatibility with the clinically used transfer tube and radioactive source are not needed.

This study mainly focuses on the development of the software module and inverse planning approach, which is entirely technical and methodologic. Further systematic investigation and evaluation of the individualized and optimized applicator for combined IC/IS BT are necessary, including studies on manufacturing accuracy and efficiency, clinical feasibility, and safety. Accuracy of the 3D printing technique adopted to produce the ovoid templates should be investigated in a future study. Moreover, there is a wide range of currently available commercial 3D printing materials. To be suitable for clinical BT, the 3D printing materials need to be biocompatible, sterilizable, and free of CT/MRI scanning artifacts and distortions and have similar dose attenuation properties as those of water (for TPS using the AAPM TG 43 formalism). Thus, the suitability of the used 3D printing material for clinical application needs to be evaluated in subsequent studies.

CONCLUSIONS

We proposed a methodology and workflow for the individualized design of the IS needle configuration for combined IC/IS BT in locally advanced cervical cancer. A software module was developed and integrated into our in-house developed TPS for BT, virtually designating the needle configuration and generating the guiding template. Using the proposed method, the limitation of the standardized design of commercially available combined IC/IS applicator can be addressed, and sufficient target coverage, while respecting the OAR constraints, is obtained in patients with unfavorable tumor topography and/or extra lateral expansion. Furthermore, a dose-based inverse optimization method for the needle configuration for combined IC/IS BT was introduced. The optimization problem was formulated as a MILP problem and solved with a deterministic method. A treatment planning study demonstrated that the introduced optimization method is feasible and suitable for clinical application, and the needle configuration with improved dosimetric results can be obtained using this optimization method.

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Conflicts of interest

There are no conflicts of interest.

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