UNIVERSITY OF CALIFORNIA, SAN DIEGO

Direction Modulated Brachytherapy High-Dose-Rate Treatment Of Cervical Cancer

A dissertation submitted in partial satisfaction of the requirements for the degree

Doctor of Philosophy

in

Electrical Engineering (Nanoscale Devices and Systems)

by

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2015

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DEDICATION

To my supervisors, family, friends, and colleagues,

I would like to take this opportunity to express my sincere thanks to all those who have supported me to complete this thesis. Without the help of you, this thesis could not have accomplished.

Special dedication to the GOD.

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LIST OF ABBREVIATIONS

AN - Attached Needle to a Ring Applicator

AP - Anterior-posterior

Conv. - Conventional

CT - Computed Tomography

HRCTV - High Risk Clinical Target Volume

DHI - Dose Heterogeneity Index

DMBT - Directional Modulated Brachytherapy

DVH - Dose Volume Histogram

EBRT - External Beam Radiation Therapy

ESTRO - European Society for Radiotherapy and Oncology

FN - Free Loaded Needle

GEC - Group of Europeen de Curietherapie

HDR - High Dose Rate

LDR - Low Dose Rate

MBDCA - Model Based Dose Calculation Algorithms

MCNP - Monte Carlo n Particle

MRI - Magnetic Resonance Imaging

OAR - Organs at Risk

PDR - Pulse Dose Rate

T&O - Tandem and Ovoids

T&R - Tandem and Ring

TG - Task Group

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Webster M, Devic S, Vuong T, Han D, Scanderbeg D, Choi D, Song B, Song WY. HDR Brachytherapy of Rectal Cancer Using a Novel Grooved-Shielding Applicator Design. Med Phys 2013;40(9):091704-1-091704-10.

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ABSTRACT OF THE DISSERTATION

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Professor Zhaowei Liu, Chair
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To achieve most effective cervical cancer breachytherapy treatment quality with image guided brachytherapy (IGBT), we propose a directional intensity modulate-available applicator. The direction modulate brachytherapy (DMBT) cervical cancer tandem applicator was designed to create non-isotropic dose distribution using tungsten alloy shielding in a tandem for an isotropic 192-Ir HDR radiation source.

Conventional tandem has 6 mm in outer diameter with 1 channel, however, the DMBT tandem has 6 channels, which is 1.3 mm in diameter, on a surface of the tungsten alloy shield. Prototypes of the DMBT tandem was manufactured to prove of compatibilities with conventional clinical treatment systems such as MR image test, 192-Ir afterloader source delivering test, and so on. The Monte Calro code was used to calculate the non-isotropic 192-Ir dose distributions and in-house developed brachytherapy planning platform were used for plan re-optimizaiton.

To evaluate a potential of the DMBT tandem, 3 different clinical treated patients group were re-optimized with DMBT tandem. The conventional tandem was replaced to the DMBT tandem for comparing differences while the ovoid or ring was kept in the same position. For comparing plan quality, HRCTV coverage was matched to each the clinical treated plans. The D2cc to OARs such as bladder, rectum, and sigmoid was recorded and compared.

The first group was 75 clinical cases, which treated with the conventional tandem and ovoids (T&O) applicator. In the second group, a patient case with 5 brachytherapy fractions course was evaluated. From the 3rd to 5th fraction, supplementary free loaded needles were used. To evaluate the DMBT tandem potential of covering irregular HRCTV growth patters, the clinical plans were compared with DMBT and ovoid (without supplement needles) plans. The last group was clinical treated patient cases treated with T&R with combined intracavitary-interstitial applicator with PDR brachytherapy afterloader. The free loaded needles and the attached to ring applicator needles were modified to investigate the DMBT tandem covering availability of an irregular growth pattern of the HRCTV.

Chapter 1

Introduction

1. 1. CERVICAL CANCER

A. Cervix

The cervix has a convex round surface in between uterine and vagina [1]. The cervix is surrounded with bladder, rectum, and sigmoid. Usually, cervix is 2-3 cm in length with a cylindrical shape. The cervix plays a major role in childbirth and the exocervix is exposed to the vagina. The external cervix os is connected into the endocervical cancel. For delivering, the cervix is dilated to accommodate a head of the detus. The squamocolumnar junction is located in the cervical os. In the cervical os, a transformation epithelium junction, a squamocolumnar junction, of a squamous epithelium and a mucus-secreting columnar epithelium is located [1,2]. The squamous epithelium is characteristic of exocervix, and the columnar epithelium is characteristic of endocervix. The squamocolumnar junction is a dynamic interface, which is dependent on hormonal stimulation, and most vulnerable to the development of a cancer. Usually, the epithelium may extend to the exocervix for younger ages women. However, the squamocolumnar junction maybe moves into the endocervical canal after menopaus.

B. Cervical Cancer

Unlike other cancers, the cervical cancer epidemiology was known and nearly always involves human papillomavirus (HPV) infection [1]. Even the cervical cancer

disease rate and survival rate is still getting better with a regular diagnosis and HPV vaccines, the cervical cancer is ranked to the third largest women cancer in United State [1,3].

For staging the cervical cancer, the historical the international federation of gynecology and obstetrics (FIGO) staging system is current standard (Figure 1-1,2) [1]. The FIGO Stage is based on the cervical cancer size and a degree of the cervical cancer invasion. The 5 FIGO stage steps, Stage 0 – Stage IV, were differentiated with the degree of invasion to the near cancer volume tissue. The Stage 0 is a pre-invasive cancer and does not counted for therapeutic statistics. From Stage I to Stage IV were invasive cancers. The Stage I is confined to the cervix. The Stage I has 2 subcategories, Stage Ia and Stage Ib, based on size of the growth cancer volume size. The Stage II is extends beyond the cervix, but is not extended onto the pelvic wall. The Stage II also has 2 subcategories with invasion to a parametrium. The Stage III is extended onto the pelvic wall. The Stage IV is extended onto the true pelvis or organs such as bladder and rectum. Each Stages, III and IV, also have 2 different subcategories.

For the cervical cancer staging, computer tomography (CT), magnetic resonance (MR), ultrasound, and positron emission tomography (PET), etc., images are utilized for improving the staging accuracy.

For clinical treatment of the cervical cancer, radical surgery, chemotherapy, and radiation therapy were considered. Each treatment method can be in company with another(s). The radiation therapy can be applied to most of cervical cancer FIGO stages, from Stage Ib – Stage IVa [1].

C. Cervical Cancer Statistics

The cervical cancer is the third most common cancer in woman cancer diseases [1]. Figure 1-3 shows statics of the cervical cancer rate verses ages [4]. From age 35 years old, the cervical cancer incidence rate is remarkably increased. As getting more ages, the squamocolumnar junction is move to endocervical canal with hormone and menopaus reason. In this reason, 99% of the cervical cancer cases were related to squamous cervical cancer [1,2,4]. Figure 1-4 shows a relation between cervical cancer distribution and the FIGO stage [4]. Most of cases, 70%, of all cervical cancer cases were Stage I-II [1,4]. Around 80% of all cases, Stage Ib – Stage IVa, can be treated with radiation therapy [1,4].

Table 1-1 shows a cervical cancer extension pattern to the cervix [4]. The cervical cancer pattern is not symmetric and the AP direction extension was 30.5% and the lateral direction extension was 47.5%.

1. 2. RADIATION THERAPY

A. Intensity Modulate Radiation Therapy and Image Guided Radiation Therapy

Since modern computer technology has been improved, better understanding of pelvic organ can be possible. Furthermore, MR images can make better soft tissue contrast than an X-ray based 2-dimension images. Combined ultrasound guided implementing system can also improve a cervical cancer modality and applicator implementing accuracy.

The improved image can make possible to delineate growth cancer volume and organs, such as bladder, rectum, and sigmoid. All of patient organs information was compressed on 2-dimension images plane, however, the 3-dimension images can gave realistic 3-dimension geometric information. For planning, delivering prescription dose to a cancer target with sparing healthy organs was possible with the 3-dimension image guided radiation therapy (IGRT) planning [13]. For generating conformal dose deliberation to a target cancer volume, intensity modulate-available radiation therapy (IMRT) applicator for sculpturing radiation helps better planning to satisfy IGRT.

B. Volumetric Dose Calculation

Unlike traditional 2-dimension image based planning system, such as point A system in cervical cancer brachytherapy using a tandem and ovoid cervical cancer treatment applicator, 3-dimension image based planning can make possible to calculate volumetric dose calculation. The organs and the target cancer volume modality can be defined on the 3-dimension volume imges. A mesh-grid is generated on the volume contouring and dose to each voxel can be calculated from each radiation source. With the dose information to the unit voxel, accumulated dose-volume histogram can be analyzed.

Recently, Dimopoulos et al. [7] studied an impact of IGRT to the cervical cancer brachytherapy. The group investigated clinical treated patients plans and recurrence rate and reported that 90% of target cancer volume coverage dose (D90) was affected on recurrence rate. If the D90 is greater than 87 Gy equivalent dose in 2 Gy (EQD2), the recurrence rate is less than 4%. However, the recurrence rate will be

increased to 20% when the EQD2 D90 is less than 87 Gy. Lindegaard et al. [5] and De Brabandere et al. [6] reported the importance of intensity modulation to meet the image guided target volume coverage. Lindegaard et al. reported that only 3 clinical cases were meet the D90 coverage overall 21 clinical cases with 2-dimension X-ray based planning, point A system. Utilizing intensity modulation of a radiation beam based on the cancer target volume modality on a 3-dimension volume image, 16 cases over 21 cases were meet D90 coverage.

C. Image Guided Brachytherapy and Guide Line

The brachytherapy followed by the external beam radiation therapy (EBRT) played major rule in the cervical cancer treatment [1, 8-12]. Traditionally, 2-dimension image based tandem and ovoids applicator generate pear shape iso-dose line for covering ‘point A’, which is 2 cm from the tandem and 2 cm from the ovoid. The point A system does not consider a shape, location, and size of a target cancer volume. Furthermore, surrounding healthy organs to the cancer volume, such as bladder, rectum, and sigmoid, were not considered. In this reason, recurrent rate [5-7] and healthy organ complications observed [18,19].

Adapting image guided brachytherapy (IGBT) using MR image, recent the Groupe Européen de Curiethérapie (GEC) and European Society for Radiotherapy and Oncology (ESTRO) formed a GYN working group to publish a series of guidelines for acceptable treatment practices [8-12]. For evaluating a plan with 3-dimension volume image, new protocols were suggested. For a cancer volume, growth tumor volume (GTV), clinical target volume (CTV), high risk CTV (HRCTV), intermediate CTV

(IRCTV) were defined and 90 % of CTV covering dose (D90) and 100 % of CTV covering dose (D100), 100% and 200 % prescription dose iso-dose covering CTV (V100 and V200) were recommended to calculate. For organs at risk (OARs) such as bladder, rectum, and sigmoid, 2cc organ volume dose (D2cc) were recommended to record.

1. 3. FIGURES AND TABLES

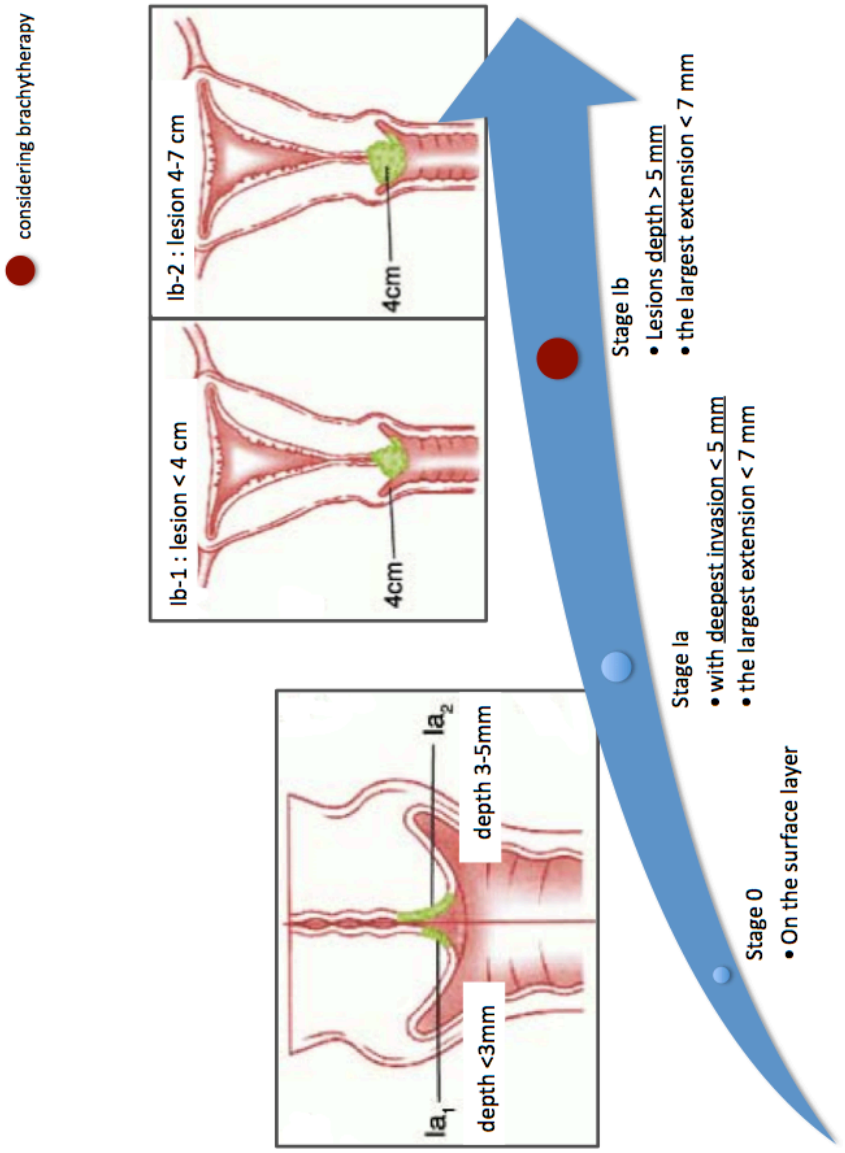

Figure 1-1. FIGO Stage 0 - Stage I. [1]

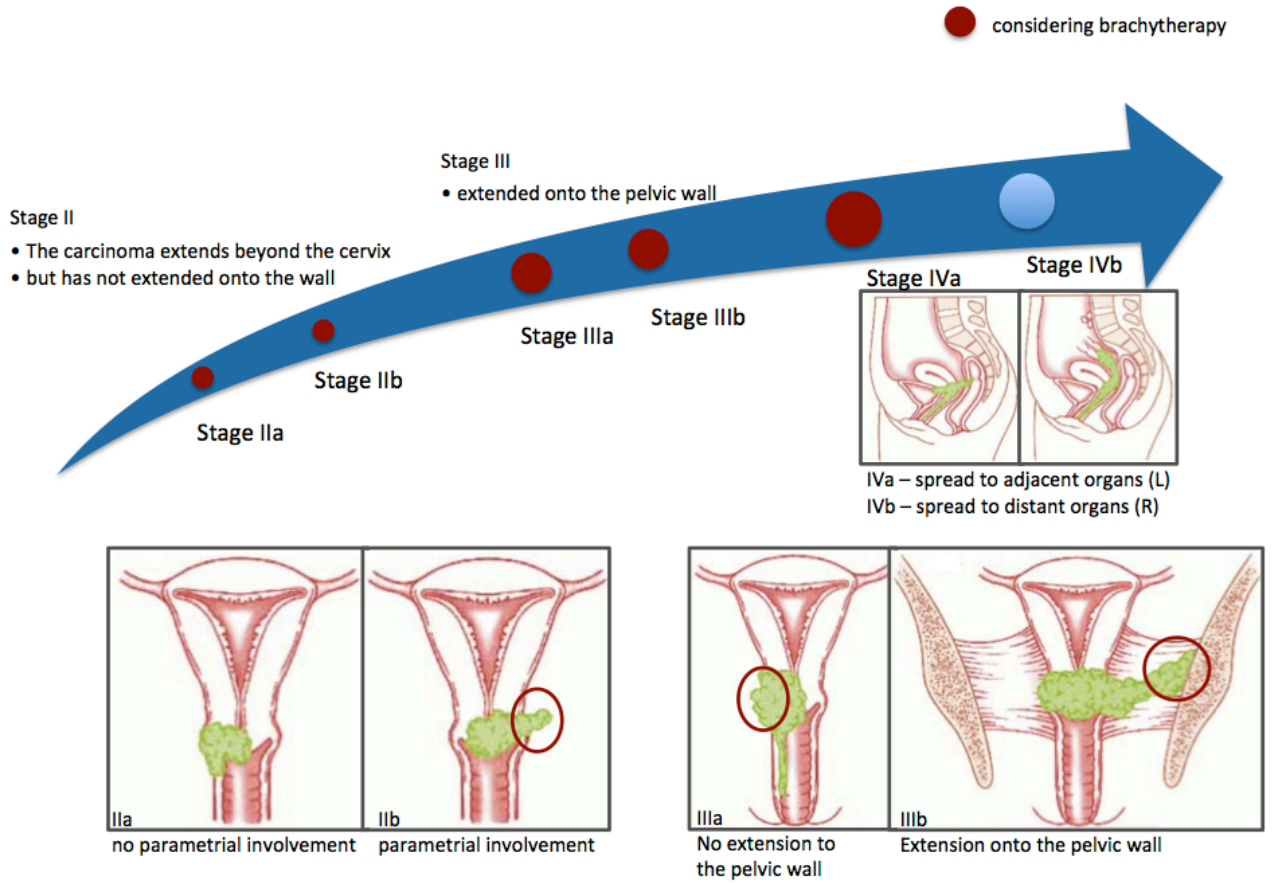

Figure 1-2. FIGO Stage II - Stage IV. [1]

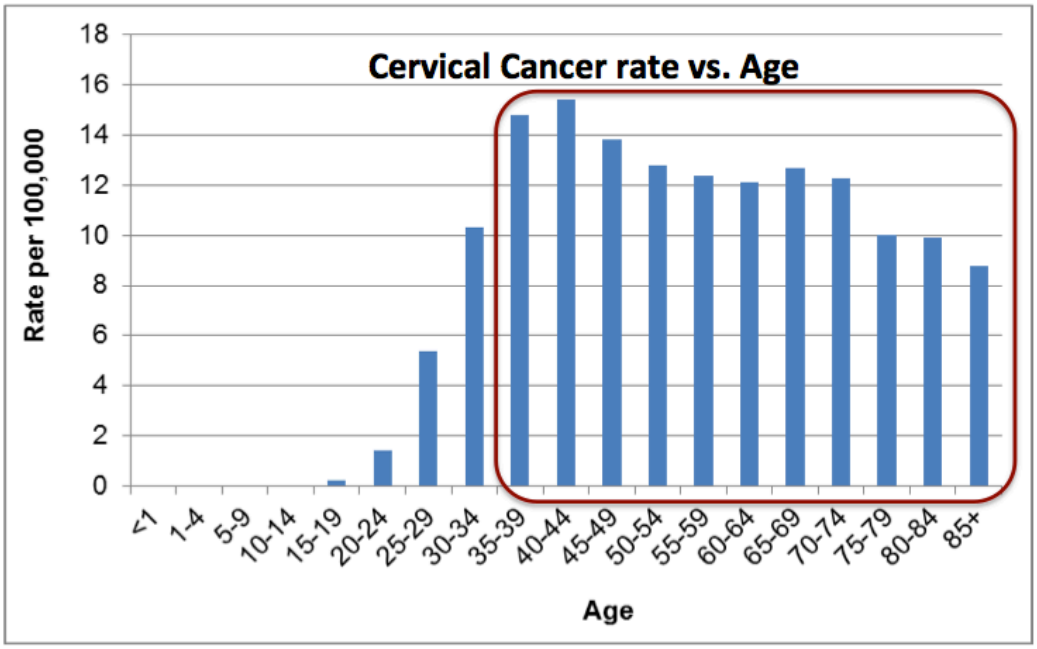

Figure 1-3. Cervical cancer rate vs. Age. [4]

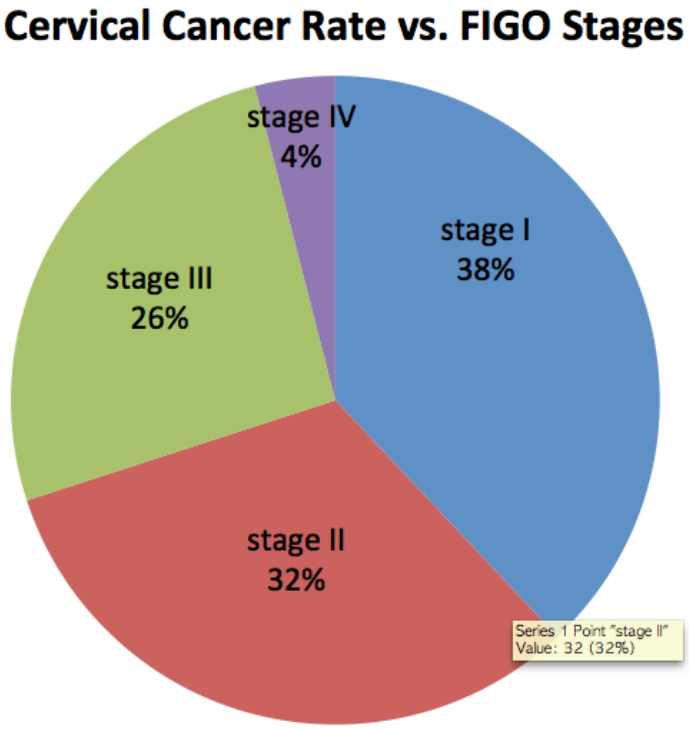

Figure 1-4. Cervical cancer rate vs. FIGO stages. [4]

Table 1-1. Distribution of the cervical cancer extension according to spread sites [2]

Site		[%]
Right lateral parametrium alone		8.47
left lateral parametrium alone		20.34
Right+left lateral parametria		18.64
	Subtotal	47.46
Vesicovervical ligament alone		11.86
Vesicovervical septum alone		6.78
Vesicocervical ligament+vesicocervical septum		3.39
Vesicocervical ligament+vesicocervical septum+uterosacral ligament+rectovaginal septum		1.69
Uterosacral ligament+rectovaginal septum		6.78
	Subtotal	30.51
Complex		22.03

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Chapter 2

Direction Modulated Brachytherapy (DMBT) for HDR Treatment of Cervical Cancer (I): Theoretical Design

2. 1. INTRODUCTION

In current state, external beam radiation therapy (EBRT) followed by brachytherapy (with/without concurrent chemotherapy) is the standard treatment for cervical cancer [1]. With EBRT alone, it has been shown to be difficult to deliver prescription dose to tumors without significant side effects such as inflammation, fibrosis, necrosis, and fistulas because of the anatomical location of the normal pelvic organs surrounding the cervix [2]. For this reason, high-dose-rate (HDR) intracavitary brachytherapy plays a major role in the therapeutic management of patients with cervical cancer [2-6]. Traditionally, many systems of applicators (e.g., Manchester, Fletcher, Stockholm, etc.) have been proposed for cervical cancer treatment, typically localized with 2D X-ray imaging [1,2,7]. 2D X-ray images, however, are not adequate in identifying anatomic organs, thus potentially increasing the risk of complications [7-9]. Furthermore, this system assumes that all tumors are the same size and shape. If the tumor happens to extend to the pelvic sidewall, for example, then this would increase the relapse rates [10,11].

Modern 3D imaging technologies, such as CT and MRI, give more valid and reliable information about individual tumor extension and organ configurations [2-6]. Compared with traditional treatment approaches utilizing 2D imaging, image guided adaptive brachytherapy (IGABT) using 3D imaging leads to better tumor coverage and organ-at-risk (OAR) sparing, thus providing superior outcomes [7,12-15]. To help ease the 2D-to-3D transition to clinic, the Groupe Européen de Curiethérapie (GEC) and European Society for Radiotherapy and Oncology (ESTRO) formed a GYN working group to publish a series of guidelines for acceptable treatment practices [2-5]. According to the guidelines, the high risk clinical target volume (HRCTV) for brachytherapy is at least the entire cervix for any stage and treatment protocol plus the palpable disease. In addition, depending on the residual tumor extent, some parts of the corpus uteri, vagina, or parametrium should be included [1,2]. Due to the frequent abutment of the OARs to the HRCTV, such as bladder, rectum, and sigmoid, however, making adherence to the desired dose volume objectives challenging. Ideally, due to the geometric positioning of the HRCTV and the surrounding OARs, the dose distribution should generally be compressed in the anterior-posterior (AP) direction for maximal OAR sparing. With the conventional intracavitary applicators, such as tandem, ovoids, and rings, this is very challenging to achieve (i.e., AP-compressed isodose lines). Such is why the combined intracavitary-interstitial applicators are finding more frequent utilization in IGABT [15]. Although the interstitial needles are useful, the adequate training of physicians and the dependence of the treatment plan quality on skill and experience of the physician inserting the needles into the

appropriate positions are some of the challenges. Obviously, the intracavitary-alone applicators are less prone to these issues.

There are broadly two types of growth patterns for cervical cancer: 1) exophytic and 2) endophytic growth patterns [1]. For the exophytic growth pattern, the cervical cancer tends to grow outwards (favorable for Pap tests), whereas for the endophytic growth pattern, the cervical cancer tends to grow inward towards the uterus along the cervical canal. The length of the canal is typically 2-5 cm. For intracavitary applicators, if the gross disease did not regress by the time brachytherapy is administered (e.g., extended disease), the cancer can be too far in the superior direction to be reached by the dose from the ovoids (or rings). Therefore, virtually, the entire dose must come from the tandem, which has an extremely limiting fluence modulation capability as the 192-Ir source is isotropic and that the tandem is single-channeled. Therefore, limiting dose to OARs, especially the bladder and sigmoid, becomes quite challenging in these cases. Innovations such as the Fletcher-Williamson applicator, (balloon-) spacers, and rectal retractors [16] can help reduce the dose to OARs, but these technologies typically assist in dose limitations from the vagina, thus, mostly benefiting the rectal dose at and below the cervix only. Thus, to date, the best treatment option for extended diseases remains with using the combined intracavitary-interstitial applicators [15].

To address the seemingly apparent lag in the intracavitary applicator technology development, and to complement the recent trend of 3D-imaging-based IGABT, we propose a novel intrauterine tandem design that is capable of creating *anisotropic* 192-Ir radiation profile that can generate highly conformal dose

distributions to non-symmetrical target volumes. The design allows modulation of directional radiation profiles (process called *anisotropic modulation*), in combination with inverse planning and algorithmic optimizations, to achieve superior levels of dose conformality. The concept is called Direction Modulated Brachytherapy (DMBT), and recently has been applied successfully for rectal and breast cancer applications [17-19]. This paper will discuss the concept, design, and performance analysis with 15 patient cases (total 75 plans) clinically treated with a conventional tandem & ovoids (Conv. T&O) applicators. The study aims to demonstrate that utilization of the DMBT concept can significantly improve treatment plan quality in the setting of cervical cancer HDR brachytherapy.

2. 2. METHODS AND MATERIALS

A. Applicators and Designs

The titanium Fletcher-Suit-Delclos-style T&O applicator set (Varian Medical Systems, Palo Alto, CA) was used for all HDR treatments. The tandem is hollow and is composed of titanium (ρ=4.5 g/cc) [20] with a 3-mm diameter, and each ovoid is wrapped by Delrin™ (polyoxymethylene, ρ=1.41 g/cc) around the titanium channel.

In this study, the intrauterine tandem was re-designed to conform to the DMBT concept [17-19]. The ovoids were left unchanged and are compatible with the new tandem design. Figure 2-1 illustrates our proposed design. As can be seen, the DMBT tandem design has six peripheral holes of 1.3-mm diameter, grooved along a non-magnetic tungsten-alloy rod (ρ=18.0 g/cc), enclosed in Delrin™ tubing, with the tungsten rod and total thickness of 5.4 and 6.4 mm, respectively. Materials were

chosen carefully to be MRI compatible with the tungsten-alloy rod composition of 95%-tungsten, 3.5%-nickel, and 1.5%-copper. Due to the gun-revolver-type design with 60° angular channel spacing (Figure 2-1d), it allows for *anisotropic modulation* of radiation profiles as opposed to the conventional *isotropic* radiation profile of the 192-Ir source (Figure 2-1f).

B. Patient Data

The patient planning dataset was comprised of 75 individual plans (15 patients with 5 fractions/patient), non-surgical and non-interstitial candidates, treated with the Varian's T&O applicator (described above). The clinical cases were wide ranging with age = 49.1±11.3 [24-62] years, HRCTV volume = 24.3±10.4 [5.0-55.0] cc, and FIGO stage IB1-IIIB. The prescription dose was 6 Gy. All patients received EBRT of 1.8 Gy × 25 fractions to the whole pelvis prior to brachytherapy, which were initiated near the end of the EBRT. Total course of treatment was completed within 56 days. All plans were CT based, with at least one MRI taken during/prior to the brachytherapy course, and planned on BrachyVision™ (Varian Medical Systems, Palo Alto, CA). Every plan had at least the HRCTV, bladder, rectum, and sigmoid contoured.

C. Monte Carlo Simulations

The Monte Carlo N-Particle (MCNP) version 2.6.0 simulations package was used to calculate the dose distributions resulting from the VariSource iX 192-Ir source (Varian Medical Systems, Palo Alto, CA). It has two identical adjoining iridium cores 0.34 mm in diameter and 2.5 mm in length each, and is encapsulated by a 0.59 mm

diameter nitinol wire of density 6.45 g/cc. For each decay event simulated, an average of 2.363 gamma emissions were generated [21]. In order to achieve better simulation efficiency, a lower energy cutoff of 10 keV for electron transport simulations was enforced [17]. All space outside of the applicator was treated as water. All simulations were run through the San Diego Supercomputer Center, using 512 CPU cores, each simulating 100,000 particles with the total of 51 million decay events. A uniform cubic voxel size of 2.5 mm^3 was used and subsequently interpolated (using exponential-interpolation) down to a 1.0 mm^3 dose grid. Due to the rotational symmetry of the applicator, it was only necessary to simulate dwell positions along a single channel.

D. DMBT Plan Optimization

D. 1. Plan Optimization

Both the T&O and DMBT plans were re-optimized to receive the exact same V100 coverage as achieved in the clinically-treated T&O plans, using the in-house-coded gradient projection convex optimization algorithm [17-19]. A quadratic objective function, with variable weights that are kept constant between the two applicator plans, was used to minimize the dose to the OARs while matching the V100 coverage. Except for a non-negativity condition on the dwell times, no additional dose constraints were enforced. Weights and optimization conditions were kept constant during the generation of the T&O and DMBT plans. A rigorous explanation of the optimization process used is presented in the first DMBT work [17]. No manual adjustments by an expert physician followed after the optimization. This was done to

maintain the integrity of comparing the capability to generate conformal, asymmetric plans by the T&O and DMBT applicators, without introducing external bias. Thus, the plans can deviate from the classical "pear-shape" (and are not of clinically-treatable quality). This was acceptable because the main objective of this planning exercise was to demonstrate the flexibility in the DMBT applicator to achieve conformal dose distributions to non-symmetric target volumes, driven by the *anisotropic modulation*. The clinically relevant parameters [22] such as D0.1cc and D2cc for OARs, and V100, V150, V200, and D90 for HRCTV were calculated thereafter.

2. 3. RESULTS

A. MCNP Dose Calculations

The variance of energy deposition calculations was <1% for most regions of clinical interest. Typically, the variance within 20 mm from the source was <0.5%. The open source simulation was compared with TG-43 standards [23,24], and the agreement was within 2%.

Figures 1e and 1f show the resulting dose distributions corresponding to the open source, from the Monte Carlo simulations, in the conventional tandem and DMBT tandem, respectively. Compared with the isotropic dose distribution typical of an open source for the conventional tandem (Figure 2-1e), the DMBT tandem is characterized by a marked directionality (Figure 2-1f), due to the tungsten shield design with 14.7% backside leakage, measured at 10 mm from the center. Due to the off-center position of the 192-Ir source (i.e., 2.05 mm from the center), doses are

generally hotter on the open-side of the DMBT applicator compared with the same corresponding positions in the conventional tandem as well.

B. Plan Data and Design

Table 2-1 lists the HRCTV D90 values, averaged over 5 plans per patient, and the population-average of all 75 plans, for the Conv. T&O and DMBT plans. In terms of target coverage, the D90 was similar between the two plans with 6.55±0.96 Gy and 6.59±1.06 Gy, for T&O and DMBT, respectively.

Table 2-2 lists the OAR D2cc values, averaged over 5 plans per patient, and the population-average of all 75 plans, for the Conv. T&O and DMBT plans. Paired t-test showed significant differences at the p=0.05 level between the two plans for all three OARs. For D2cc of bladder, rectum, and sigmoid; on average, 0.59±0.87 Gy (8.5±28.7%), 0.48±0.55 Gy (21.1±27.2%), 0.10±0.38 Gy (40.6±214.9%) reductions were observed among 75 plans, with the best single-plan reductions of 3.20 Gy (40.8%), 2.38 Gy (40.07%), and 1.26 Gy (27.5%), respectively. The total dwell times, normalized to air kerma strength of 40.25 kU (10 Ci) source, increased on average by 27.1% (from 6.3±1.9 to 8.1±2.6 minutes), for the DMBT plans. This was expected, however, due to the increase in intensity modulation and the directionality of the radiation (i.e., *anisotropic modulation*) that accompanies the DMBT plans [17].

Figure 2-2 shows two representative clinical cases where 1) the HRCTV is sandwiched in between the bladder and rectum (Figure 2-2a), and 2) the sigmoid wraps around the HRCTV (Figure 2-2b). In both cases, it is easily seen that DMBT allows significant OAR sparing while giving comparable target coverage (e.g., same

V100), as the prescription isodose lines are significantly more conformal. In the second case (Figure 2-2b), due to the superior location of the HRCTV, the dose contributions from the ovoids were negligible, which meant the tandem dose determined the entire quality of the treatment plan, thus underscoring the need for *anisotropic modulation*.

Figure 2-3 shows a CAD drawing of the prototype DMBT tandem design and an X-ray image showing a 192-Ir source successfully traveling through the 3D-printer-printed applicator, tested with a Flexitron™ afterloader (Nucletron, The Netherlands). Bend angle and bend radius were 60° and 25 mm, respectively.

2. 4. DISCUSSION

The new DMBT tandem design should be compatible with the traditional intracavitary applicators such as the ovoids, rings, and cylinders due to the classic shape of a curved tandem with thickness no greater than a typical stainless steel LDR tandem (~6.3-6.6 mm). As well, with moderate-to-general anesthesia typically administered during HDR treatments, we do not foresee any more difficulty and/or logical issues with inserting the applicator as before. In addition, due to the high directionality of the radiation profiles, it may turn out that at least some of the advanced clinical cases where interstitial needles are necessary (e.g., parametrial or utero-sacral extensions) [15] can be replaced with the DMBT applicator. For this study, the selected patients were limited to the intracavitary applicator cases, so none of this is proven as of yet. Nonetheless, this will be a huge advantage to those select patients, if the (unforeseen) challenges associated with treating more advance-staged patients

can be worked out. Due to the importance of the implications, we are retrospectively evaluating our previous combined intracavitary-interstitial cases to determine the feasibility and its limitations.

There are intrinsic difficulties when optimizing an HDR cervix plan with the classic *isotropic* 192-Ir radiation profile (i.e., with classic "pear-shape" dose distribution). This is largely due to the non-symmetric shape of the HRCTV [25]. Figure 2-2 showed examples of challenging anatomy. Because of this, significant improvements ($p<0.05$) in the DMBT plans were observed in all three OARs examined with the best single-plan reductions of 3.20 Gy (40.8%), 2.38 Gy (40.07%), and 1.26 Gy (27.5%), for the bladder, rectum, and sigmoid, respectively. This was achieved without compromising the HRCTV coverage. Since higher brachytherapy doses and better target coverage are associated with improved local control rates, at the expense of increased rates of serious late side effects (~15%) [2], the DMBT applicator may allow safe(r) dose escalations with improved target coverage.

We do not currently have a prototype DMBT applicator built with the tungsten alloy (although the plastic version is made as shown in Figure 2-3). Therefore, we cannot perform end-to-end tests to determine complete feasibility in the clinical setting. However, we have designed the applicator with the MRI compatibility in mind as we carefully selected a non-magnetic tungsten material [26]. It may still turn out that achieving the image quality necessary for IGABT be challenging (e.g., hip implants). In such a case, it may be easier to make a flexible place-holder applicator, insert it during the MRI, and use the DMBT applicator for CT and co-register. A series of clinical validation studies would need to be followed, however. In terms of CT

compatibility, it may cause metal-induced artifacts that potentially obstruct with contouring/planning. This needs to be fully addressed also in the future as there are hardware solutions (e.g., increasing the X-ray energy [27]) and software solutions (e.g., metal artifact reduction techniques [28]) that can enhance the compatibility. Dose calculations with high-density metal presence was another potential concern to us since TG-43 formalism assumes a homogeneous water medium [23,24], thus needing a significant modification to the existing planning systems. However, with the recent introduction of model-based dose calculation algorithms (MBDCAs) [29], heterogeneity corrections that used to be ignored are now starting to be accounted for. This new trend could not have come at a better time as the DMBT concept is entirely based on the *anisotropicity* of 192-Ir radiation profile. Next generation afterloader designs, which may have a 3rd drive (or more), could also aid in the adoption of the DMBT treatment paradigm as the 3rd drive (or more) may have an intelligently-designed shielding attached that can move in combination with an 192-Ir source, for example, thus creating *anisotropic modulation* tailored for individual patient anatomy. Such a concept does not only complement the up-and-coming trend of 3D-imaging-based brachytherapy planning [2-5,13,22], and with dose-volume-driven objectives [4,22], but is an intuitively natural progression that was already observed in the EBRT world; i.e., transition from the 3DCRT to IMRT for improved dose conformality in 3D target volumes [30].

2. 5. CONCLUSIONS

Application of the DMBT concept (i.e., *anisotropic modulation*) to cervical cancer allowed for improved OAR sparing whilst achieving similar target coverage on a sizeable patient population. The technology is intuitive and designed to maximally utilize the abundant anatomical information contained in 3D imaging, in IGABT, in fittingly aligned with the latest dose-volume-driven brachytherapy planning trend. Since the technology is still a theoretical concept, though, a series of mechanical and clinical validations are to be followed.

2. 6. FIGURES AND TABLES

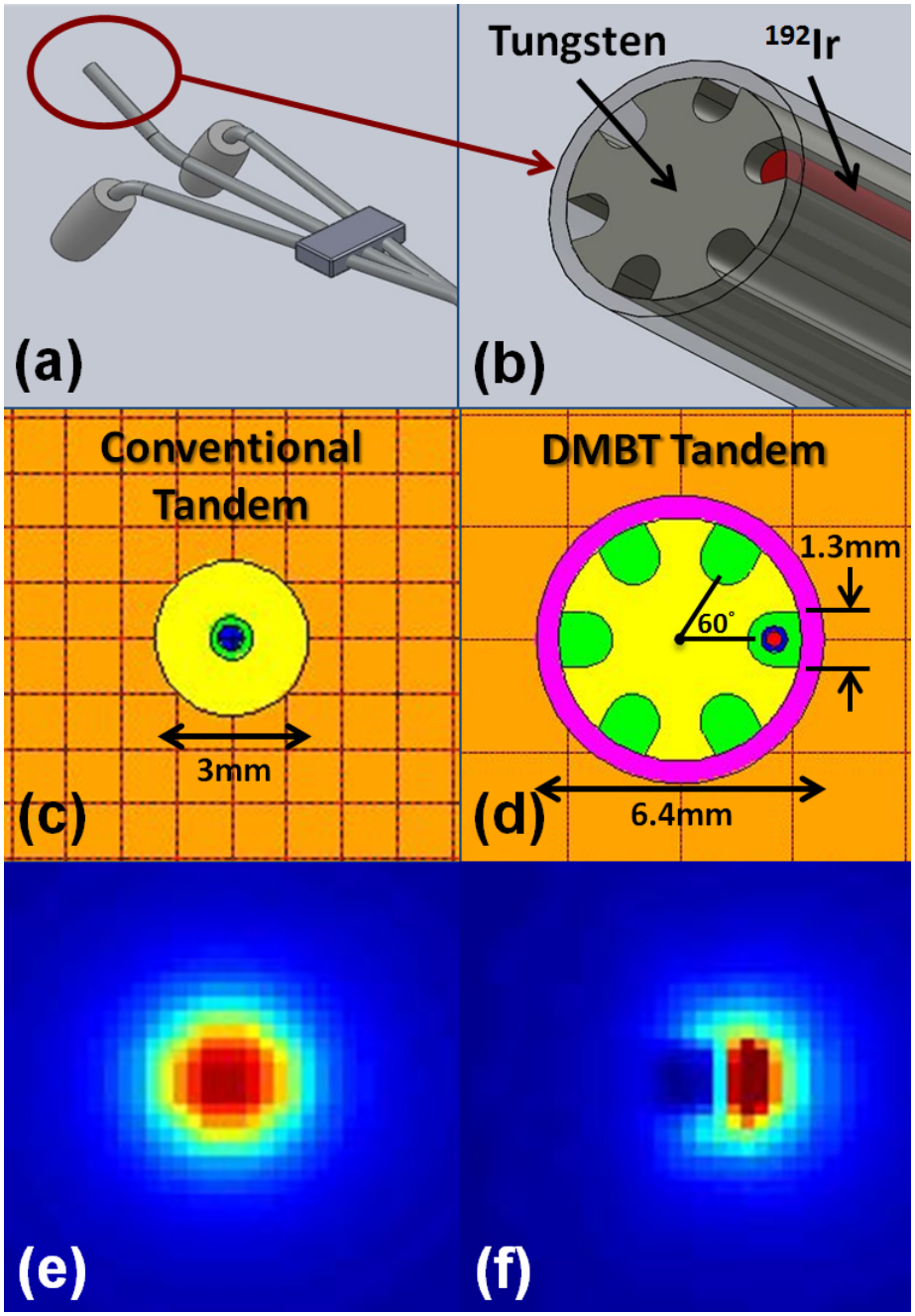

Figure 2-1. (a) A Conv. T&O. (b) The DMBT tandem design with six peripheral holes in a multi-groove design. (c) A conventional tandem cross section. (d) The DMBT tandem cross section. (e) A Monte Carlo simulated dose distribution of an *isotropic* 192-Ir source in a conventional tandem. (f) A Monte Carlo simulated dose distribution of a *directional* 192-Ir radiation profile emitted in the DMBT tandem.

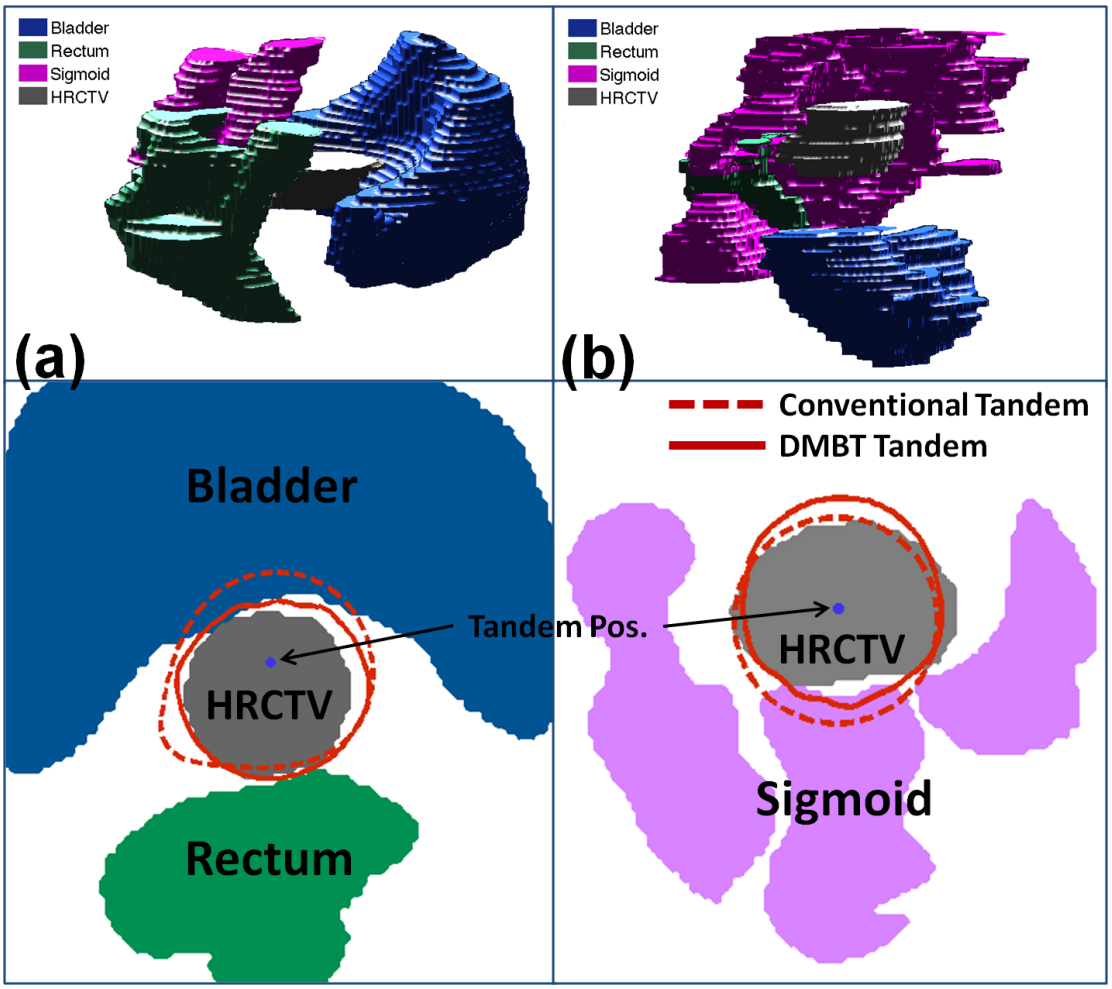

Figure 2-2. Two representative anatomies of cervix cancer: (a) a HRCTV sandwiched between a horseshoe-shaped bladder and an abutting rectum, and (b) a HRCTV wrapped around by a large sigmoid volume, representing a typical endophytic growth pattern. Dotted and solid isodose lines represent the 6 Gy prescription dose for the Conv. T&O and DMBT plans, respectively.

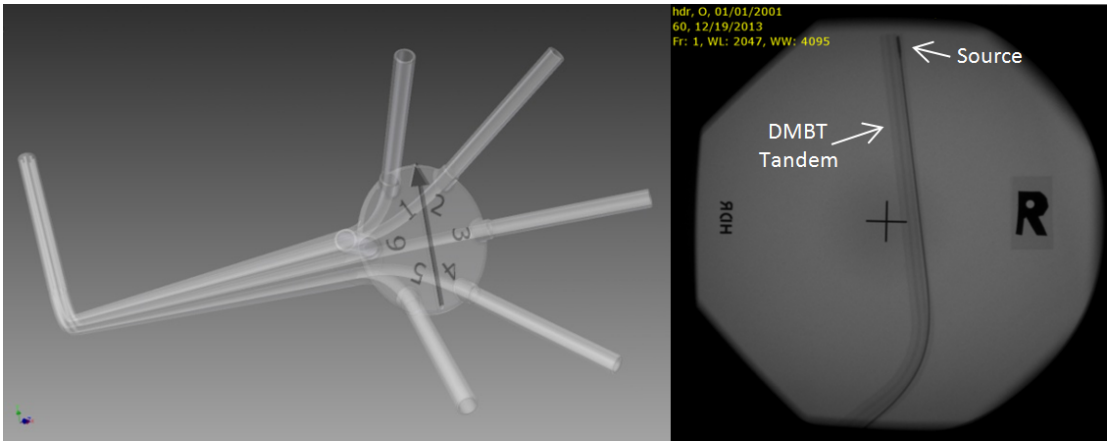

Figure 2-3. A CAD drawing of the prototype DMBT tandem design (left) with an X-ray image showing the Nucletron 192-Ir source successfully traveling through the 3D-printer-printed applicator using plastic (right). Bend angle and bend radius were 60° and 25 mm, respectively.

Table 2-1. Individual D90 values, averaged over each patient (5 plans per patient) and population (75 plans), for the Conv. T&O and DMBT plans. Diff. [Gy] = (DMBT - Conv. T&O). Diff. [%] = ((DMBT - Conv. T&O) / Conv. T&O). × 100%.

Patient #	HR CTV - D90 [Gy]			
	Conv. T&O	**DMBT**	**Diff. [Gy]**	**Diff. [%]**
1	7.2±0.4	7.3±0.8	0.1±0.4	2.0±0.2
2	6.6±0.6	6.6±0.6	0.0±0.0	0.0±0.0
3	6.9±0.5	6.9±0.5	-0.1±0.2	-0.9±0.1
4	7.9±0.5	8.6±0.8	0.7±0.6	8.4±0.9
5	6.3±0.6	6.1±0.4	-0.1±0.2	-2.2±0.2
6	4.8±1.0	4.7±0.8	0.0±0.2	-0.8±0.2
7	6.2±0.5	6.2±0.5	0.0±0.0	0.0±0.0
8	6.4±0.8	6.3±0.5	-0.2±0.4	-2.6±0.4
9	6.4±0.8	6.7±1.5	0.4±0.8	5.8±1.5
10	6.9±0.4	7.0±0.4	0.0±0.1	0.6±0.0
11	6.5±0.9	6.4±0.7	-0.1±0.2	-0.9±0.2
12	5.9±0.5	5.9±0.4	0.0±0.0	0.2±0.0
13	7.6±1.1	7.4±0.9	-0.2±0.2	-2.4±0.4
14	6.1±0.3	6.1±0.3	0.0±0.1	-0.3±0.0
15	6.7±1.2	6.7±1.2	0.0±0.0	0.1±0.0
AVG	**6.55**	**6.59**	**0.04**	**0.53**
SD	**0.96**	**1.06**	**0.37**	**4.96**

Table 2-2. Individual D2cc values, averaged over each patient (5 plans per patient) and population (75 plans), for the Conv. T&O and DMBT plans. For all three OARs, the D2cc doses were significantly different at the level of p=0.05, using paired t-test. Diff. [Gy] = (DMBT - Conv. T&O). Diff. [%] = ((DMBT - Conv. T&O) / Conv. T&O). × 100%.

Patient #	Bladder - D2cc [Gy]				Rectum - D2cc [Gy]				Sigmoid - D2cc [Gy]			
	Conv. T&O	DMBT	Diff. [Gy]	Diff. [%]	Conv. T&O	DMBT	Diff. [Gy]	Diff. [%]	Conv. T&O	DMBT	Diff. [Gy]	Diff. [%]
1	4.3±1.1	4.3±0.8	-0.0±0.4	-0.9±0.3	3.8±0.9	3.4±0.7	-0.4±0.5	-10.3±3.3	0.7±0.8	0.7±0.7	0.0±0.2	1.4±2.0
2	2.4±2.0	2.1±1.7	-0.2±0.4	-8.9±10.5	1.0±0.9	0.7±0.7	-0.3±0.4	-33.7±46.8	1.4±1.3	1.3±1.2	0.0±0.1	-1.5±2.0
3	2.4±1.2	2.2±1.4	-0.2±0.3	-8.4±6.8	2.0±0.3	1.7±0.2	-0.3±0.2	-13.3±2.8	3.5±1.2	3.2±1.1	-0.3±0.3	-7.2±3.6
4	5.2±2.7	4.1±1.7	-1.1±1.4	-20.9±14.0	2.2±1.8	1.9±1.8	-0.3±0.2	-13.8±17.1	2.5±1.5	2.7±1.5	0.2±0.7	8.5±7.1
5	6.4±2.0	4.8±1.4	-1.6±1.0	-25.0±10.8	3.4±1.7	2.3±1.1	-1.0±0.9	-30.8±21.4	0.9±1.2	1.0±1.6	0.2±0.5	18.6±38.9
6	3.2±1.2	3.3±1.2	0.0±0.5	1.5±0.8	4.3±1.3	3.9±1.4	-0.4±0.3	-10.2±4.9	1.6±1.1	1.6±1.1	0.1±0.2	3.8±3.6
7	1.3±1.5	1.1±1.3	-0.2±0.3	-16.5±27.9	1.2±1.2	1.0±0.8	-0.3±0.4	-21.8±27.6	4.1±0.5	3.4±0.2	-0.6±0.6	-15.8±2.2
8	3.8±2.2	3.4±1.9	-0.4±0.4	-10.8±8.7	1.2±1.5	0.9±1.0	-0.3±0.5	-27.1±46.3	1.5±1.6	1.3±1.3	-0.2±0.5	-16.1±23.8
9	5.0±0.3	3.9±0.8	-1.1±0.6	-22.7±4.9	1.9±0.7	0.8±0.6	-1.1±0.7	-56.6±45.7	0.1±0.1	0.1±0.1	0.1±0.1	116.7±179.3
10	2.7±2.5	2.4±2.3	-0.3±0.3	-10.6±14.2	0.8±0.4	0.7±0.2	-0.1±0.3	-13.4±6.8	1.4±2.0	1.3±1.9	-0.1±0.1	-5.0±9.7
11	6.8±0.7	4.3±0.4	-2.5±0.4	-36.2±5.2	2.0±0.9	0.6±0.5	-1.4±0.6	-70.7±73.9	0.0±0.0	0.0±0.0	0.0±0.0	0.0±0.0
12	3.7±0.9	3.6±1.1	-0.1±0.2	-2.4±0.9	2.0±0.9	1.7±0.8	-0.3±0.1	-12.7±8.2	3.4±1.4	3.0±1.3	-0.4±0.4	-11.0±6.6
13	4.8±1.3	4.5±1.1	-0.3±0.5	-5.7±2.1	2.0±1.1	1.9±1.0	-0.1±0.2	-4.0±3.1	1.0±1.8	1.0±1.4	-0.1±0.4	-8.7±19.8
14	4.9±0.5	4.3±1.0	-0.6±0.8	-11.7±3.0	3.7±2.0	3.0±2.0	-0.6±0.5	-16.9±14.4	0.5±0.9	0.3±0.6	-0.2±0.3	-38.9±95.1
15	2.6±0.6	2.3±0.7	-0.3±0.3	-12.1±4.9	3.2±1.0	2.8±1.1	-0.4±0.2	-12.0±6.0	1.3±1.1	1.2±1.0	-0.1±0.2	-6.2±7.3
AVG	**3.95**	**3.37**	**-0.59***	**-8.47**	**2.30**	**1.82**	**-0.48***	**-21.13**	**1.58**	**1.48**	**-0.10***	**40.63**
SD	**2.08**	**1.62**	**0.87**	**28.69**	**1.52**	**1.42**	**0.55**	**27.24**	**1.62**	**1.48**	**0.38**	**214.93**

* Statistically significantly different (paired t-test)

2. 7. ACKNOWLEDGEMENTS

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Chapter 3

The Use Of DMBT-Concept T&O Applicator In Cervical Cancer: A Case Study

3. 1. INTRODUCTION

The radiation therapy is the standard treatment for cervical cancer [1]. Because of an anatomic position of cervix, surrounded by pelvic organs, EBRT alone is hard to deliver a prescription dose to a HR-CTV without side effects, such as fibrosis, fistulas, and necrosis [1,2]. However, EBRT followed by brachytherapy is easily achievable the prescription dose to the HR-CTV avoiding dose to the organs through an intra-cavity [1-6]. For this reason the HDR brachytherapy plays major role in the cervical cancer therapy.

Since introducing new 3D image technologies, such as CT and MRI, traditional point 'A' based cervical cancer treatment planning systems, such as Fletcher, Manchester, and Stockholm, were re-evaluated [1,2,7] because the conventional applicators were developed and used on the 2D X-ray image diagnosis. The X-ray image is not adequate to identify projected soft tissue organs, such as bladder, rectum, and sigmoid, thus considered all tumors and organs are same shape, size, and position [10,11]. As improving image quality, soft tissue could be delineated and an anatomic variations were ascertained, thus an unconsidered potential of the risk

of complication or relapse rates related to over dose to the organs was issued [7-9,12-14].

For adopting 3D IGRT, recent brachytherapy research groups, such as GEC-ESTRO, are trying to re-evaluate conventional brachytherapy treatment protocols [2-6]. GEC-ESTRO working group was suggested new clinical concepts, such as D100, D90, V100 for a HR-CTV and D2cc, D0.1cc for OARs to evaluate clinical treatment plans. Depends on a patient anatomy, some cases were hard to cover HR-CTV since a growth pattern [26] and location of the HR-CTV and relative distance from OARs. To sole the problem, new applicator design concepts, such as a conventional applicator attached to a retractor or a balloon [18], were introduced for increasing a distance from an ovoid/ring to a rectum/bladder.

Some intra-cavitary cervical cancers (squamous cell carcinomas) tend to thicker and less getting affected by ovoids/ring ($1/R \cong 0$). Furthermore, an erratic growth pattern of the cervical cancer and a geometric complexity make harder to cover the tumor volume with keeping low dose to OARs. In these cases, additional free needles are required for covering extra tumor volume of outside of the prescription iso-dose line [15]. The main limitation of the conventional treatment applicator was using a non-dose-intensity-modulate-able applicator (i.e, non-shielded applicator). For doing intensity modulation, directional dose are essential and some researchers, recently, were trying to build intensity modulate-able applicators, such as DMBT [16] and RSBT [17], for the cervical cancer. In this paper, we evaluate the DMBT tandem for cervical cancer to find a possibility of reducing a number of additional free needles

of the conventional tandem and ovoid applicators using for optimal covering a HR-CTV of a specific clinical patient case.

3. 2. MATERIALS AND METHODS

A. PATIENT DATA

A patient who was treated with radiation therapy was chosen for evaluating DMBT tandem. The patient was IIIB FIGO stage [1]. A volume of the HR-CTV was 48.3cc at the first fraction. At the second fraction the volume was increased (73.1cc) and than the volume was decreased to 46.1cc with following fractions. The patient was treated with 6Gy/fraction using titanium Fletcher-Suit-Delclos Tandem and ovoids (T&O) applicator set (Varian Medical Systems, Palo Alto, CA) with the VariSource iX 192-Ir source (Varian Medical Systems, Palo Alto, CA) following EBRT of total dose of 45Gy in 25 fractions to the whole pelvis. An erratic growth pattern of the tumor, a ration of minimum-maximum distance from cervical os, which is the tandem place in, was about 1.5, minimum was 1.83cm and maximum was 2.85cm. For covering laterally invaded cancer site with sparing adjacent OARs, extra needles were used. The first two fractions were using only the T&O applicator and rest fractions were added free needles: 5 needles for fx3, 6 needles for fx4, 7 needles for fx5.

The patient underwent a T2 MRI before starting of EBRT courses. For each brachytherapy fraction, the patient underwent a CT prior to brachytherapy planning. The HR-CTV and OARs were delineated following GEC-ESTRO guideline [3,4] on BrachyVision™ (Varian Medical Systems, Palo Alto, CA). The plans had constrains

to achieve 85Gy EQD_2 uniform dose to HR-CTV with limitation OARs dose to 2cc of bladder (< 90Gy), rectum (< 70-75Gy), sigmoid (< 70Gy) [19].

B. APPLICAOTR DESIGNS AND DOSE CALCULATION

The conventional tandem, Fletcher-Suit-Delclos T&O applicator set, has 3 mm in diameter and hollow inside for delivering Ir-192 HDR source. The T&O applicator is made of titanium (ρ=4.5 g/cm^3) [22] and the ovoids are rapped by Delrin™ (ρ=1.41 g/cm^3).

The DMBT intrauterine tandem was designed for replacing the conventional tandem. The DMBT tandem has 5.4 mm in diameter non-magnetic tungsten alloy (ρ=18.0 g/cm^3) rod [22,28], enclosed in 6mm in diameter Delrin™ (ρ=1.41 g/cm^3) tubing. 6 peripheral channels are 1.3mm in diameter, which are evenly distributed (60°) on a surface of the tungsten alloy rod. The ovoids are kept in same position and size as the conventional tandem. Specific design details described our previous work [16].

The VariSource iX 192-Ir HDR source (Varian Medical Systems, Palo Alto, CA) energy and geometry was calculated on the Monte Carlo N-Particle (MCNP), version 2.6.0 simulation package [16,20,21]. The after loader has two identical iridium cores which are longitudinal aligned a center of the 0.95 mm diameter nitinol wire (ρ=6.45g/cm^3). Each core has 0.34 mm diameter and 2.5 mm length. Out side of the applicator was considered as water (ρ=1.00g/cm^3) and filled with 1×1×1 mm^3 mesh grid. For each decay event simulated, an average of 2.363 gamma emission were generated [23]. To achieve better simulation efficiency, a lower energy cutoff of 10keV for electron transport simulation was enforced [16,20,21]. All the Monte Carlo

calculations were run through a supercomputer, using 512 CPU cores. Each CPU calculates 100,000 particles, for a total of 51 million decay events.

C. PLAN OPTIMIZATION

For evaluating a performance of the DMBT tandem, two additional DMBT tandem plans were re-optimized by in-house-coded gradient projection convex optimization algorithm [16,20,21]; one is only replace the conventional tandem with the DMBT tandem (i.e. kept needles in the same position) and the other is replacing the tandem and remove needles. Both plans kept same ovoids positions as the clinical plan. The plans were re-optimized to deliver the same 90% of HR-CTV dose (D90) as clinically treated T&O plans using Eclips™ (Varian Medical Systems, Palo Alto, CA). For better optimization performance, a surface of the HR-CTV was chosen, in contrast whole HR-CTV was chosen for DVH evaluation. A quadratic objective function was used to minimize the dose to the OARs and not to violate the plan constrains (In fraction 2, a sigmoid was not considered since it was not delineated). The organ weights were set differently reflect a difference of a radiation tolerance of the each OARs and gap distance between OAR and HR-CTV. Except for a nonnegative condition on the dwell times, no additional dose constrains were enforced. An intimate explanation of the optimization process used is presented in the first DMBT cervical cancer applicator work [16,20,21].

The clinical parameters [3,4,24], such as D0.1cc and D2cc for OARs and D90, V100, V200 for HR-CTV, were calculated using DVH evaluation.

3. 3. RESULTS

The variance of MCNP dose calculation was less than 1% for most regions of clinical interest. Within 20mm from the Ir-192 source, the variance was less than 0.5%. The open source simulation was compared with TG-43 standard, and the agreement was within 2% [25,26]. Figure 1 shows MCNP dose calculations of conventional T&O (left) and DMBT tandem (right).

Table 1 lists clinical treated dose to the OARs, bladder, rectum, and sigmoid, using conventional T&O (some were used additional needles, fx 3-5) and simulated dose to OARs only using the DMBT tandem and ovoids (i.e. remove all needles). The prescription of 45Gy to HR-CTV using EBRT was accumulated to the total EQD2 dose. All total doses to OARs are reduced, 2.46% to the bladder, 1.05% to the rectum, and 9.66% to the sigmoid. The average of each fraction EQD2 dose were reduced 0.44±1.53Gy to the bladder, 0.16±0.98 to the rectum, and 1.43±1.18 to the sigmoid.

Table 2 lists doses to the OARs using DMBT tandem and ovoid with needles as clinical treatment. All individual fraction dose were reduced and total EQD2 dose are reduced 5.35%, 4.48%, and 11.91%, bladder, rectum, and sigmoid respectively. The average dose reductions were 0.96±1.13, 0.67±0.59, and 1.76±0.79, bladder, rectum, and sigmoid respectively.

Figure 2-6 show iso-dose line of clinical treated (pink), DMBT tandem & ovoids (solid red), and DMBT tandem & ovoids with needles (dashed red line). In fraction 1 and 2, DMBT tandem & ovoids and DMBT tandem & ovoids with needles are identical since no any needles are involved. In fraction 3-4, DMBT tandem &

ovoid performed as the clinically treated coverage. The DMBT tandem & ovoid with needles shows better conformal coverage to the HR-CTV than the clinical treatment.

3. 4. DISCUSSION

The mechanical design of DMBT tandem is compatible with current cervical cancer treatment systems [19]. To find a compatibility of DMBT tandem in current treatment system, we choose a patient who was treated with conventional T&O and T&O with free needles. This study is limited to a specific patient case, but well shown that the patient anatomy is varying [27] through clinical treatment courses and not easy to predict a number of required needles. The first 2 fractions of the 5 fraction courses are treated with T&O only and the last 3 fractions are treated using T&O with free needles. Deciding a number of needles insertion and implementing quality are highly physician depend [1,2]. In this case, even the conventional T&O applicator with free needles had a good HR-CTV coverage, DMBT tandem can be a good option for reducing efforts with reducing number of needles insertions.

In the first 2 fractions, DMBT tandem gave batter OARs sparing than conventional tandem with the same HR-CTV coverage, D90. The most difference was sigmoid at the first fraction (-0.84Gy) and bladder at the second fraction (-0.99Gy). All of contoured organs were better spared using DMBT tandem. As the HR-CTV is more involved to entophytic region (squamous cell carcinoma), the iso-dose line will less controllable since a distance from ovoids. Only replacing to the DMBT tandem, it could give flexibility for sparing organs.

Last 3 fractions are treated with conventional T&O with extra needles. Among the last 3 fractions, sigmoid had the most differences, -1.21 Gy (Fx3), -3.00 Gy (Fx4), and -0.16Gy (Fx5). Most of all organs had better dose spared even without free needles insertion. In case of fraction 4, which had a gap in between HR-CTV and bladder/rectum, DMBT tandem and ovoids (without free needles) could make better plan than conventional T&O with 5 free needles. Since iso-dose line of DMBT tandem can be shifted to any direction along the cervical os, which is DMBT tandem/conventional tandem was inserted, DMBT tandem can effectively cover the HR-CTV without any additional needle insertion. Even all plans using DMBT tandem and ovoid with free needles could spare OARs better than treatment plans in fraction 3 and 5 (Table 2), the bladder and rectum in fraction 3 (+0.38 Gy at bladder and +0.19 Gy at rectum) and fraction 5 (+1.13 Gy at bladder and +1.04 Gy at rectum) could not meet the same as treatment plans. These cases shown that well positioned free needles were most effective/optimal approaching to cover HR-CTV and to spare OARs (not only for the cervical cancer but also any other cancers). However DMBT tandem could reduce the effort with approaching intra cavity without any pain, bleeding, and traumas.

Of course, DMBT tandem and ovoids with free needles showed best OARs sparing results. As increasing distance from DMBT tandem to peripherals of erratic growth pattern of HR-CTV, the dose wedge covering area (arc) are increased ($\pi r^2 \times 60°/360°$) and less easier to spare OARs than isolated iso-dose line, which was created spots by inserted free needles if the OARs are closed (surround) to the HR-CTV. Most of the cases, inserted needles are used for covering peripherals (cold spot)

of lateral HR-CTV, however, anterior-posterior directional shift was mainly controlled by DMBT tandem when the HR-CTV was closed to the bladder.

3. 5. CONCLUSIONS

Though the re-optimized data using DMBT tandem instead of conventional tandem, DMBT tandem has a potential of an improvement of a treatment plan treated using conventional T&O applicator with additional needles for covering an erratic growth patterned cervical cancer. Some cases were even can cover the HR-CTV with out using any additional needles. For adopting IGBT, DMBT tandem help reducing burden of implementing needles with directional intensity modulation.

3. 6. FIGURES AND TABLES

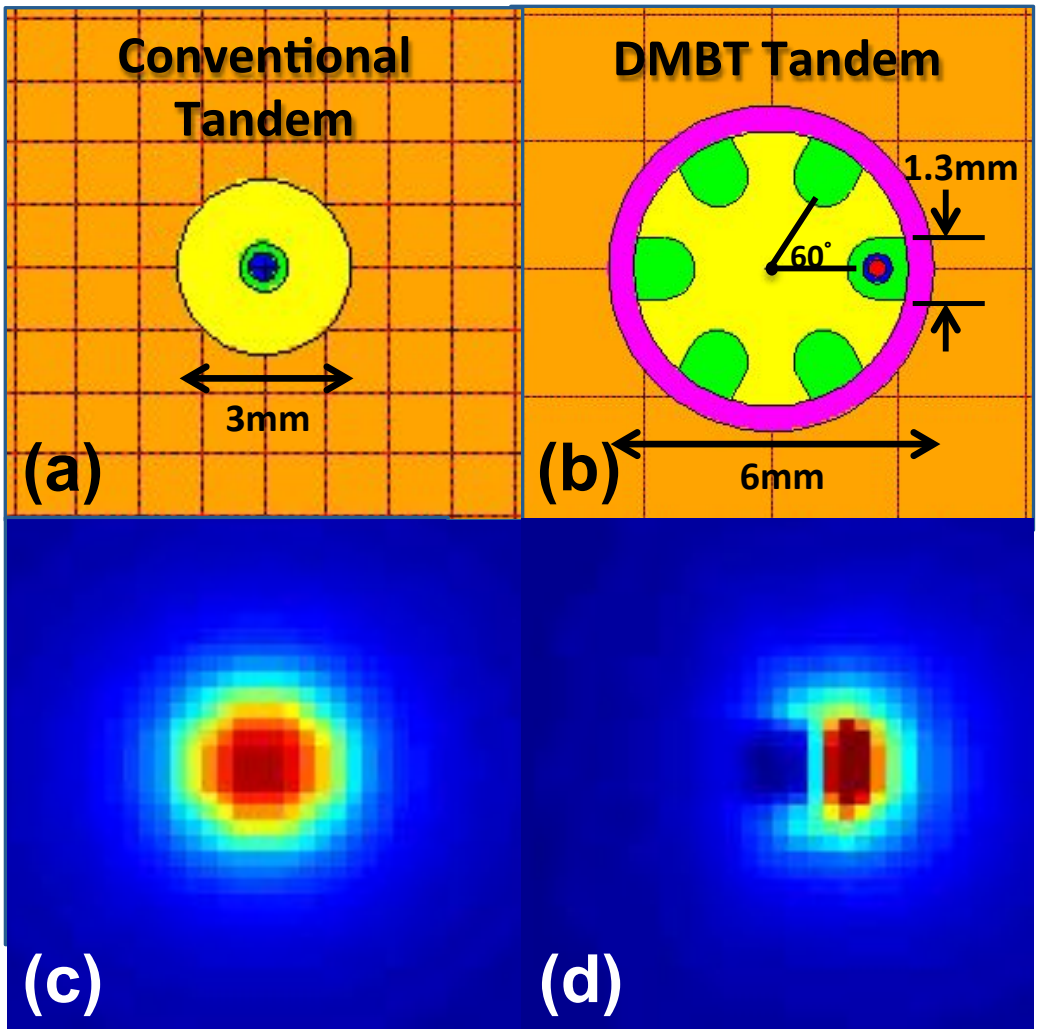

Figure 3-1. Monte Carlo N-Particle (MCNP) simulation of conventional tandem (left) and DMBT tandem (right)

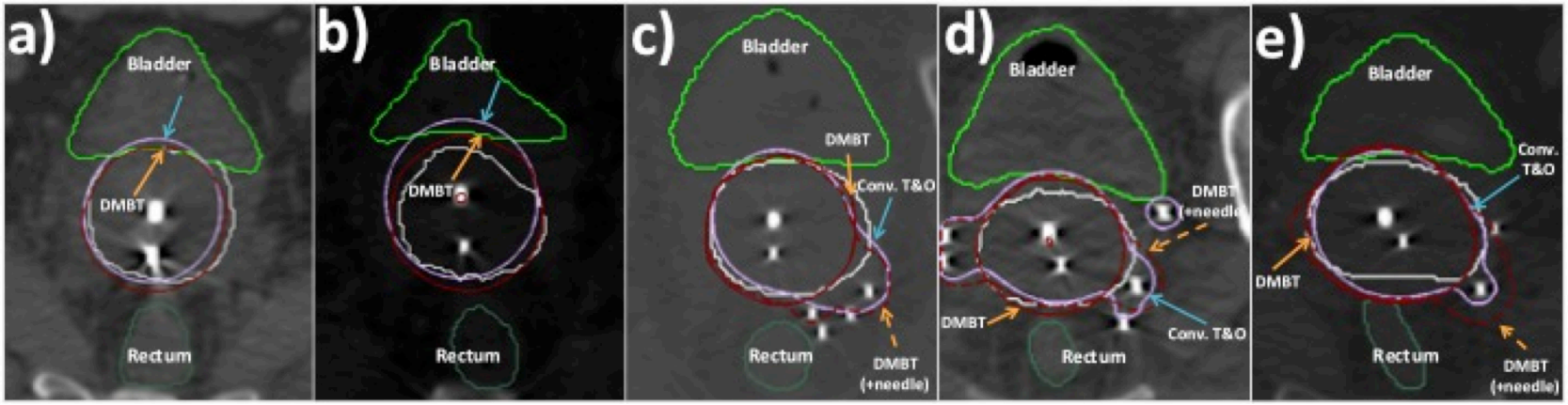

Figure 3-2. Plan compare among the conventional tandem (pink, solid), DMBT tandem (red, solid) , and DMBT tandem with free-handed needles (red, dashed) in fraction 3-5.

Table 3-1. Dose compare between conventional tandem and ovoids (with free-handed needles, fx3-5) and DMBT and ovoids.

	Bladder				Rectum				Sigmoid			
fx no.	T&O (+NDL)	DMBT (- NDL)	Diff. (Gy)	Diff (%)	T&O (+NDL)	DMBT (- NDL)	Diff. (Gy)	Diff (%)	T&O (+NDL)	DMBT (- NDL)	Diff. (Gy)	Diff (%)
fx1	5.80	5.53	-0.27	-4.66	4.30	3.54	-0.76	-17.67	2.90	2.06	-0.84	-28.97
fx2	6.30	5.31	-0.99	-15.71	4.70	4.55	-0.15	-3.19				
fx3	5.70	5.83	0.13	2.28	4.50	4.58	0.08	1.78	2.20	1.26	-0.94	-42.73
fx4	4.80	4.78	-0.02	-0.42	4.10	4.10	0.00	0.00	3.40	1.50	-1.90	-55.88
fx5	4.70	5.14	0.44	9.36	3.70	4.18	0.48	12.97	4.10	4.03	-0.07	-1.71
Average	5.46	5.32	-0.14	-1.83	4.26	4.19	-0.07	-1.22	3.15	2.21	-0.94	-32.32
SD	0.69	0.40	0.54	9.29	0.38	0.42	0.45	11.03	0.80	1.26	0.75	23.18
EQD2	Bladder				Rectum				Sigmoid			
fx no.	T&O (+NDL)	DMBT (- NDL)	Diff. (Gy)	Diff (%)	T&O (+NDL)	DMBT (- NDL)	Diff. (Gy)	Diff (%)	T&O (+NDL)	DMBT (- NDL)	Diff. (Gy)	Diff (%)
fx1	10.21	9.43	-0.77	-7.58	6.28	4.63	-1.65	-26.25	3.42	2.08	-1.34	-39.08
fx2	11.72	8.83	-2.89	-24.69	7.24	6.87	-0.37	-5.08				
fx3	9.92	10.30	0.38	3.81	6.75	6.94	0.19	2.86	2.29	1.07	-1.21	-53.08
fx4	7.49	7.44	-0.05	-0.67	5.82	5.82	0.00	0.00	4.35	1.35	-3.00	-68.98
fx5	7.24	8.37	1.13	15.61	4.96	6.00	1.04	21.07	5.82	5.67	-0.16	-2.68
Total	89.77	87.56	-2.21	-2.46	74.25	73.47	-0.78	-1.05	59.08	53.37	-5.71	-9.66
Average	9.31	8.87	-0.44	-2.70	6.21	6.05	-0.16	-1.48	3.97	2.54	-1.43	-40.95
SD	1.91	1.08	1.53	14.91	0.88	0.94	0.98	17.00	1.50	2.13	1.18	28.29

Table 3-2. Dose compare between conventional tandem and ovoids (with free-handed needles, fx3-5) and DMBT and ovoids (with free-handed needles, fx3-5).

	Bladder				Rectum				Sigmoid			
fx no.	T&O (+NDL)	DMBT (+ NDL)	Diff. (Gy)	Diff (%)	T&O (+NDL)	DMBT (+ NDL)	Diff. (Gy)	Diff (%)	T&O (+NDL)	DMBT (+ NDL)	Diff. (Gy)	Diff (%)
fx1	5.80	5.53	-0.27	-4.66	4.30	3.55	-0.75	-17.44	2.90	2.06	-0.84	-28.97
fx2	6.30	5.31	-0.99	-15.71	4.70	4.55	-0.15	-3.19				
fx3	5.70	5.62	-0.08	-1.40	4.50	4.47	-0.03	-0.67	2.20	1.26	-0.94	-42.73
fx4	4.80	4.46	-0.34	-7.08	4.10	3.81	-0.29	-7.07	3.40	1.50	-1.90	-55.88
fx5	4.70	4.67	-0.03	-0.64	3.70	3.39	-0.31	-8.38	4.10	4.03	-0.07	-1.71
Average	5.46	5.12	-0.34	-5.90	4.26	3.95	-0.31	-7.35	3.15	2.21	-0.94	-32.32
SD	0.69	0.52	0.38	6.07	0.38	0.53	0.27	6.42	0.80	1.26	0.75	23.18
EQD2	Bladder				Rectum				Sigmoid			
fx no.	T&O (+NDL)	DMBT (+ NDL)	Diff. (Gy)	Diff (%)	T&O (+NDL)	DMBT (+ NDL)	Diff. (Gy)	Diff (%)	T&O (+NDL)	DMBT (+ NDL)	Diff. (Gy)	Diff (%)
fx1	10.21	9.43	-0.77	-7.58	6.28	4.65	-1.63	-25.92	3.42	2.06	-1.36	-39.80
fx2	11.72	8.83	-2.89	-24.69	7.24	6.87	-0.37	-5.08				
fx3	9.92	9.69	-0.23	-2.31	6.75	6.68	-0.07	-1.06	2.29	1.26	-1.03	-44.93
fx4	7.49	6.65	-0.83	-11.13	5.82	5.19	-0.63	-10.87	4.35	1.5	-2.85	-65.53
fx5	7.24	7.16	-0.07	-1.03	4.96	4.33	-0.63	-12.62	5.82	4.03	-1.79	-30.78
Total	89.77	84.97	-4.80	-5.35	74.25	70.92	-3.33	-4.48	59.08	52.05	-7.03	-11.91
Average	9.31	8.35	-0.96	-9.35	6.21	5.54	-0.67	-11.11	3.97	2.21	-1.76	-45.26
SD	1.91	1.37	1.13	9.49	0.88	1.17	0.59	9.47	1.50	1.26	0.79	14.73

3. 7. ACKNOWLEDGEMENTS

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Chapter 4

Direction Modulated Brachytherapy (DMBT) for HDR Treatment of Cervical Cancer (II): Clinical Potential Assessment

4. 1. INTRODUCTION

Brachytherapy followed by EBRT plays a major role in the therapeutic management of cervical cancer patients [1-6]. Recent Surverillance, Epidemiology, and End Results (SEER) reported utilizing brachytherapy to the International Federation of Gynecology and Obstetrics (FIGO) stage [1] IB2-IVa cervical cancer was independently associated with a significantly higher cause specific survival (CSS) rate and an overall survival (OS) rate [7]. In a same context, a cervical cancer intrauterine tandem applicator system (e.g., Manchester, Fletcher, Stockholm, etc.) with afterloader have been selectively used for delivering dose to the patients using empirical isodose shape, 'point A' system [2].

Modern 3D image technology, especially MRI, gives reliable an organ and a cancer configuration and leads to IGBT [4-6,11]. Based on 3D image volumetric dose assessment of point A system verified impact of IGBT [8,9]. Evaluating dose-volume-histogram (DVH), D90 to the HRCTV is closely connected with a recurrence [10]. Recent the Groupe Européen de Curiethérapie (GEC) and European Society for

Radiotherapy and Oncology (ESTRO) formed a GYN working group published a guideline for MRI guided cervical cancer radiation treatment [2-6].

Computer-based treatment planning system using an optimization algorithm (e.g., inverse-planning-stimulated-annealing) [32] can produce a successful plan from modulating a dose intensity of the traditional plan, point A, considering a factor of HRCTV and organs in a clinically applicable time, and the modified plan can reduce of a relapse rate [11-16]. Since an intricate anatomical location of cervix [1] and a diversity of tumor site [1,17], retaining HRCTV coverage using a conventional cervical cancer brachytherapy applicator involves inevitable organ risks such as necrosis, fibrosis, and fistulas [2].

For adapting IGBT, the conventional brachytherapy applicators and radioactive sources (HDR and PDR) has limitation for an intensity modulation [18,20]. Usually, upper HRCTV is encircled by bladder and rectum is closely located beneath HRCTV [1]. The intrauterine tandem based a conventional cervical cancer applicators were designed for a historical pear shape isodose distribution and the pear shape isodose distribution is bisymmetry and ovoid (ring) makes thicker portion of the isodose shape for covering exophytic part of the cervical cancer volume [1]. Only less than 3 bisymmetry channels of T&O applicator (2 channels for T&R) also not enough for an intensity modulation for covering irregular growth pattern with sparing tangled OARs [20]. Thus, lots of innovations, such as rectal retractors and balloon spacers, were designed for reducing a rectal dose with increasing a distance from rectum to HRCTV [21], but these technologies are benefiting the rectal or bladder dose below the cervix only. For a resolution of the geometrical complication and effectively covering

irregular growth pattern of a cancer, combined intracavitary-interstitial applicator was suggested and has been utilized in clinics [20].

Recently proposed the DMBT cervical cancer intrauterine tandem applicator had better approaching to resolve the conflictions [22]. The DMBT tandem has 6 channels for directional dose deliberation to effectively covering irregular HRCTV shape as a facility of combined intracavitary-interstitial applicator. Furthermore, the DMBT tandem is compatible with current cervical cancer treatment system, such as tandem and ovoids (or ring) with appendages (e.g., supplementary needles, rectal retractors). The DMBT tandem has same physical dimensions as conventional cervical cancer intrauterine tandem for easier intra-cavity implantation to a patient.

To utilize the DMBT tandem, which is a novel directional intensity modulate available intrauterine tungsten alloy shielded tandem applicator, for 3D image based IGABT, we need to compare DMBT and combined intracavitary-interstitial applicator, which is current the best treatment option for the extended cervical cancer disease. This paper will discuss a performance analysis with consecutive 45 patients clinically treated with a T&R applicator with (or without) combined intracavitary-interstitial applicator. The study aims to demonstrate that utilization of the DMBT concept can significantly improve treatment plan quality and can simplify applicator implementation setting of a cervical cancer HDR brachytherapy.

4. 2. MATERIALS AND METHODS

A. PATIENT DATA

The first fraction of consecutive 45 PDR cervical cancer brachytherapy patient plans treated in Aarhus University were re-evaluated. All organs and HRCTV were delineated on MR image and planned on the BrachyVision (Varian Medical Systems, Palo Alto, CA) treatment planning system. The FIGO stage was Ib-IVb and at least one of the HRCTV, bladder, rectum, and sigmoid were contoured. All patients received one of EBRT courses of 1.67 Gy × 30 fractions, 2.0 Gy × 25 fractions, and 1.80 Gy × 25 fractions, to the whole pelvis prior to a brachytherapy. HRCTV prescription dose was boosted to 15 Gy or 17.5 Gy with GammaMedphus iX 192-Ir PDR source (Verian Medical Systems, Palo Alto, CA) and Ring & Tandem Combination Set (Verian Medical System, Palo Alto, CA) with (or without) attached needles to the ring (AN) and free-loaded needles (FN). Among 45 patients plans, 27 patients plans used only T&R applicator without using any needles and the others 18 patients plans utilized needles (AN only or AN + FN) with T&R applicator. Implemented needles number variation of FN, and AN was 2-4, and 1-8, respectively.

B. DMBT MONTE CARLO SIMULATION

DMBT tandem has been re-designed from previous work [22]. Total Diameter of DMBT tandem was 6.0 mm, and 6 channels, which is 1.3mm in diameter, are evenly distributed (60°) on a surface of 5.4 mm diameter MRI compatible tungsten alloy road (ρ=18.00g/cc, 95%-tungsten, 3.5%-nickel, and 1.5%-copper) [26]. Biocompatible and dry-heat sterilize-able FEP tubing (ZEUS, Orangeburg, SC), 0.3 mm in thickness, used for packing tungsten shield.

CT-MR compatible Ring & Tandem Combination Set (Verian Medical System, Palo Alto, CA) was used for PDR treatment plans. The tandem Smit Cervical Sleeves (Verian Medical System, Palo Alto, CA) and the ring are hollow and is composed of Delrin™ (polyoxymethylene, ρ=1.41 g/cc) [26]. The tandem is hollow and total diameter is 6 mm in diameter. Interstitial Plastic Needles (Verian Medical System, Palo Alto, CA) was used for AN and FN and was 2.0 mm in diameter.

GammaMedphus iX 192-Ir PDR source (Verian Medical Systems, Palo Alto, CA) was simulated on Monte Carlo N-Particle X (version 2.6.0) with conv. tandem and DMBT tandem. For better simulation efficiency, a lower energy cutoff of 10 keV for electron transport simulations was enforced [23-25]. For each decay event simulation, an average of 2.363γ emission s were generated [22,27]. All outside of applicator, 20.0 cm from a center of the applicator, was consider as water. Central area, 5.0 cm from the center of the applicators, used 1.0 mm3 cubic mesh-grid and peripheral area, and rest of area, 5.0 – 10.0 cm from the center of the applicators, used 1.5 mm3 cubic mesh-grid and exponential interpolated down to a 1.0 mm3 mesh-grid. AN, FN, and ring were also simulated as the conventional tandem.

C. DMBT PLAN OPTIMIZATION

All the 45 clinical treated patients data were individually re-optimized to receive the same D90 to HRCTV, using the in-house-coded gradient projection convex optimization algorithm [22]. Simulated annealing was used to find optimal variable weights on T&R with (or without) needles plans and kept constant between two applicator plans. A quadratic objective function was used to minimize the dose to

the OARs while matching the D90 dose to HRCTV. To meet a clinical dose constrain, individual tandem and needles (AF, FN) dwell time and accumulated ring dwell time was constrained. The tandem and the needles individual dwell time were constrained not to exceed 800 sec and 100 sec, respectively. The accumulated ring dwell time was constrained not to exceed 3000 sec and in between 50-100% of accumulated tandem well time.

All the 45 patients plans were re-optimized with the DMBT tandem instead of the conventional tandem. The ring kept in the same position. For the 27 patients plans of 45 patients plans were treated with conventional T&R applicator only, no needles (AN, FN) utilized. However, the others 18 patients plans utilized the supplementary needles and the supplementary needles were controlled by the optimization; included or excluded the needles to the D&R or T&R applicator set. The 18 cases, which used supplemented needles (AN and FN) with conventional T&R applicator, were modified to 3 groups by different needles setting. The first group included all possible needles (T&R+AN+FN), the second group includes all possible needles but AN (T&R-AN+FN), and the last group did not use any supplement needles (T&R-AN-FN). The needles variation was also applied to DMBT and ring applicator and the diagram in Figure 4-3 shows the possible needles combinations to the T&R applicator and the D&R applicator.

For evaluating a potential of a directional intensity modulation ability of the DMBT tandem comparing with combined intracavitary-interstitial applicator, manual adjustments by an expert followed after the optimization were not accepted and all the plans were normalized to D90 of clinical treated plans.

The clinically relevant parameters [28] such as D90, D98, V100, V200 for HRCTV and D2cc, D0.1cc for OARs were calculated.

4. 3. RESULTS

A. DMBT DESIGN AND MCNP DOSE CALCULATION

Figure 4-1a and 1d show computer aided design (CAD) drawings for the DMBT tandem design and Figure 4-1b shows a prototype of the DMBT tandem. The total diameter of prototype DMBT tandem was 6.0 ± 0.05 mm, and bending angle and radius were 60 ± 0.5° and 25.0 ± 0.05 mm, respectively. Figure 4-1c shows a 1.5T MR image T2-weighted turbo-spin-echo with 8 channels body coil and the TR/TE parameter was 7000/109.2 ms. Diameters of the MR image of the DMBT tandem were measured at 5 different angles and average of the 5 measurements was 5.72 ± 0.39 mm in diameter.

Figure 4-1e-h show cross sections of MCNP drawing and Figure 4-1f-g show the MCNP dose calculation of the DMBT and the conventional tandem, respectively. For most of clinical interested regions, the variance of MCNP energy deposition calculation was less than 1% and the variance within 20mm from the source was less than 0.5%. The MCNP calculation was compared with TG-43 standard [29,30] and the agreement was within 2%. Due to the DMBT tandem has a tungsten alloy shielding material, Figure 4-1f of the DMBT tandem has a directional dose distribution.

B. PLAN DATA

Table 1 shows an average D2cc to OARs difference of DMBT tandem and conventional tandem. For T&R only plans, Both AN and FN were not used in clinic. For the re-optimization, the conventional tandem was replaced to the DMBT tandem while the same ring applicator kept in same position. The average D2cc difference was -0.20 ± 0.64 Gy, -0.34 ± 0.43 Gy, and -0.23 ± 0.44 Gy to bladder, rectum, and sigmoid, respectively. Figure 4-2 shows D2cc difference to OARs of individual plans of T&R only clinical cases. In overall the T&R only clinical cases, 74.1% of D2cc to OARs using the D&R applicator were better than the plans using the conventional T&R applicator. Comparing with conventional T&R plans, 66.7%, 81.5%, and 74.1% plans of the D&R were reduced D2cc to bladder, rectum, and sigmoid, respectively.

The D&R applicator supplemented by AN and FN plans showed superiority average plan quality in D2cc to OARs, except 3 cases, D&R(-AN)(-FN) - T&R(+AN)(+FN), D&R(-AN)(+FN) - T&R(+AN)(+FN), and D&R(-AN)(-FN) - T&R(-AN)(+FN). Among the 3 cases, average D2cc difference of bladder of D&R(-AN)(-FN) - T&R(+AN)(+FN) shown the most different with 1.27 ± 0.64 Gy. Overall, the most D2cc average difference was -4.38 ± 2.76 Gy to bladder of D&R(-AN)(-FN) - T&R(+AN)(+FN). Figure 4-3 shows an individual to D2cc OARs difference of all cases corresponding all combinations of AN and FN.

Figure 4-3 shows an individual D2cc to OARs difference between the conventional T&R and the D&R with different combination of supplemented needles (AN, FN). As more the needles are involved, from left to right column of Figure 4-3, the D&R can spare OARs better than the conventional T&R with utilized needles.

With keeping the same needles combination to the D&R, the T&R plans were getting same or worse as decreasing utilized needles combination to the T&R.

Figure 4-4 shows 3 transverse plane of representative clinical cases treated with conventional T&R applicator with AN and FN. The first case used 6 AN and 2 FN with conventional T&R applicator for delivering 15 Gy prescription dose to HRCTV, and another case used 3 AN and 2 FN with conventional T&R applicator for delivering 17.5 Gy prescription dose to HRCTV, Figure 4-1-a, b respectively. The last case, Figure 4-4-c, used 3 AN with conventional T&R applicator and the prescription dose was 15 Gy to HRCTV. The first two cases, Figure 4-4a-b, contoured T&R(+AN)(+FN), T&R(+AN)(-FN), D&R(-AN)(-FN), D&R(-AN)(+FN), and D&R(+AN)(+FN) isodose line. The last case contoured T&R with AN, T&R(+AN)(+FN), and D&R without AN, D&R(-AN)(-FN), isodose line. Both the cases were normalized to D90 of clinical treated plans. The T&R(+AN)(+FN) shows the best coverage with sparing OARs. D&R(+AN)(+FN) shows almost same plan trend as T&R(+AN)(+FN). For the last case, Figure 4-4c, the isodose line of D&R without AN matched to the isodose line of the T&R with AN for covering dorsal HRCTV without increasing dose to bladder. Furthermore, DMBT tandem can increase lateral HRCTV coverage with anisotropic directional dose modulation.

4. 4. DISSCUSSION

The DMBT tandem applicator was designed and assessed as a directional intensity modulate-available applicator for IGBT. The new DMBT tandem design is compatible with any current intrauterine tandem based applicator systems. Especially,

T&R combined intracavitary-interstitial applicator. The total outer diameter was 6.0 ± 0.05 mm in diameter to match the outer diameter of a tandem in the CT-MR compatible Ring & Tandem Combination Set (Verian Medical System, Palo Alto, CA). Since overall dimensions of the DMBT tandem agree to the conventional tandem, any extra difficulties or logical issues during implementing the DMBT tandem applicator to a patient were expected. Since a nonmagnetic tungsten alloy [31] was selected as a shielding material for the DMBT tandem, MR image does not contain an artifact. Measured on the MR image average diameter of the DMBT tandem was 5.72 ± 0.39 mm and 5.92 % difference compare with physical dimension of DMBT tandem diameter, 6.00 ± 0.005 mm. For defining channels, we did not test MR contrast, yet.

For covering an irregular growth pattern of HRCTV, more AN can guarantee dose conformity to HRCTV (Figure 4-4a-b). In the same reason, the DMBT tandem has better dose conformity to HRCTV than the conventional tandem. Achieving the same HRCTV coverage, the DMBT tandem has a potential to reduce a number of AN or FN in the T&R combined intracavitary-interstitial applicator with the same effort for implementing the DMBT tandem to a patient as the conventional tandem (Figure 4-4c). Furthermore, the DMBT tandem, which has built-in 6 channels shielding, does not require a pre-decision of number and position of AN for covering irregular HRCTV and can reduce an operation time. Even the D&R applicator are available a directional dose modulation as the T&R combined intracavitary-interstitial applicator, an extreme irregular pattern or larger diameter of HRCTV makes hard to cover HRCTV and require extra FN. Since the DMBT tandem is an intrauterine applicator (not an interstitial applicator) and place in a cervix os, an arc of an wedged shape of

the DMBT isodose line is increased as increasing a distance from the cervix os. The enlarged arc is causing less dose localization comparing with the localized isodose line from the combined intracavitary-interstitial applicator of the T&R applicator (Figure 4-4a-b).

In general, a planning quality is affected by intensity modulation availability. Both conventional T&R and D&R applicators plans were improved as increased involving needle type. In Figure 4-3, a top of the same column, the same needle setup on the D&R applicator, showed better planning quality among the same column of the T&R plans, and a right of the same row plans were better than the others DMBT plans in the same row.

For D2cc difference verses number of needles, the same needle combination setup, (+AN)(+FN), (-AN)(+FN), and (-AN)(-FN), showed less a number of needles dependency. Average slope (ΔD2cc/number of needles) of OARs were 0.1 ± 0.1, 0.0 ± 0.2, and -0.1 ± 0.1, D&R(+AN)(+FN)-T&R(+AN)(+FN), D&R(-AN)(+FN)-T&R(-AN)(+FN), and D&R(-AN)(-FN)-T&R(-AN)(-FN), respectively. Even the D&R and the T&R has small number of needles dependency with the same needle combinations, average of y-axis cross was -0.8 ± 0.6, -0.7 ± 1.2, and -0.8 ± 0.6, T&R(+AN)(+FN), D&R(-AN)(+FN)-T&R(-AN)(+FN), and D&R(-AN)(-FN)-T&R(-AN)(-FN), respectively. The y-axis cross shows directional modulate-ability helps an OARs sparing. Table 1 shows averages of all planes of each OARs D2cc differences. Most of the D&R averages of D2cc to OARs were better than the T&R averages of D2cc to OARs, but D&R(-AN)(-FN)-T&R(+AN)(+FN), D&R(-AN)(+FN)-T&R(+AN)(+FN), and D&R(-AN)(-FN)-T&R(-AN)(+FN). For the D&R(-AN)(-FN)-T&R(+AN)(+FN), it is

obvious that the T&R plans with large number of needles can make better plan than the D&R plans, but D&R has competitiveness in a case of involving a small number of needles. Average trend line equation was y=0.4x-0.9 and 2.5 needles were expected to compete. For the D&R(-AN)(+FN)-T&R(+AN)(+FN), the average trend line equation was y=0.2x-1.3 and 5.4 needles were expected to compete. For the D&R(-AN)(-FN)-T&R(-AN)(+FN) was almost same, the trend line equation of y=0.1x-0.1. Even the DMBT get less supported by needles, the DMBT tandem can effectively cover HRCTV with a directional modulation availability. Obviously, the D&R with more supplement needles than T&R showed better OARs sparing with the same D90 coverage.

4. 5. CONCLUSIONS

The current cervical cancer treatment system, such as the T&R with combined intracavitary-interstitial applicator, can get more flexibility on an intensity modulating for IGBT with a directional modulation availability, a structural compatibility with conventional cervical cancer treatment applicators, and MRI compatibility if the DMBT tandem. Furthermore, using DMBT tandem is expected to reduce efforts and time on implementing an applicator and planning for a cervical cancer.

4. 6. FIGURES AND TABLES

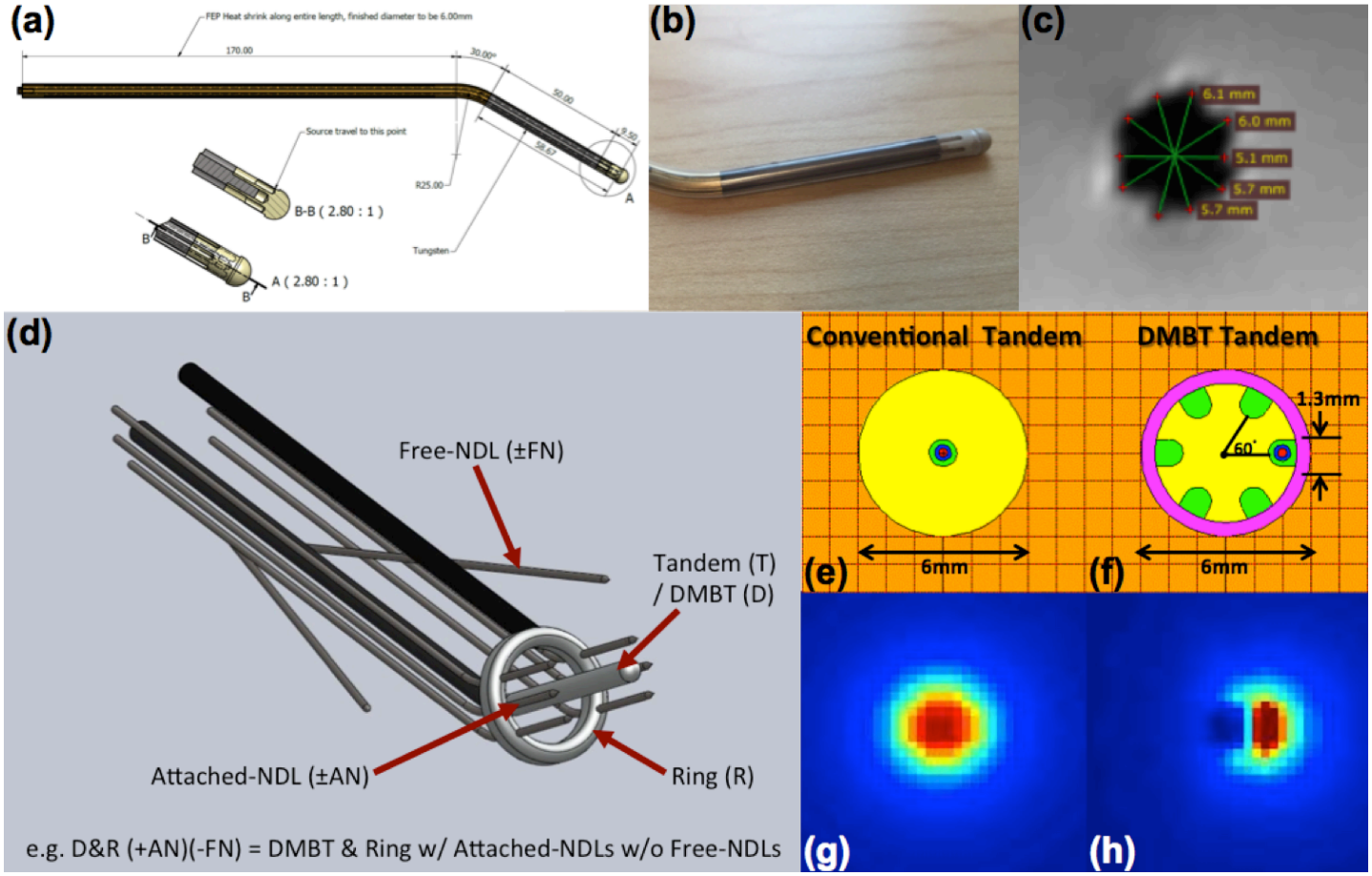

Figure 4-1. DMBT tandem design and prototype. MCNP dose calculation of DMBT tandem

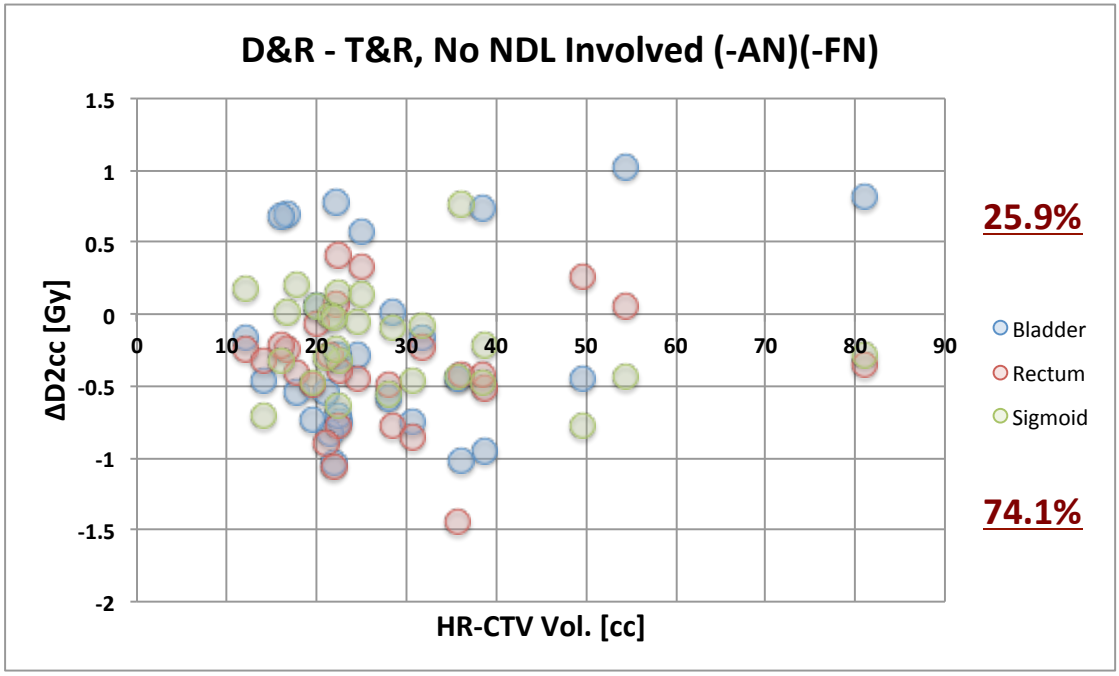

Figure 4-2. D2cc difference of DMBT and conv. T&R applicator (not a supplement needles were involved)

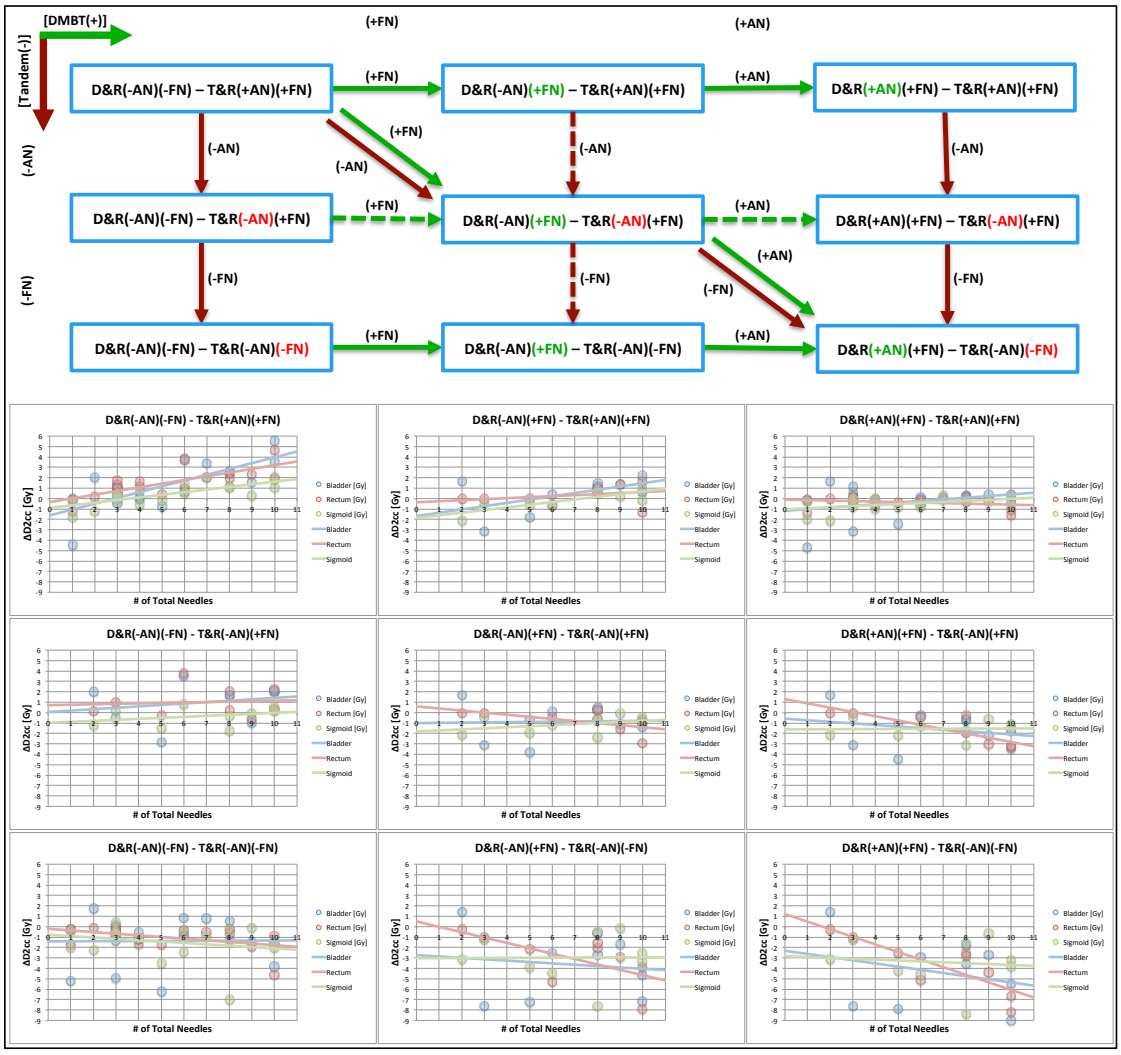

Figure 4-3. D2cc difference of DMBT and conv. T&R applicator (supplement needles were involved)

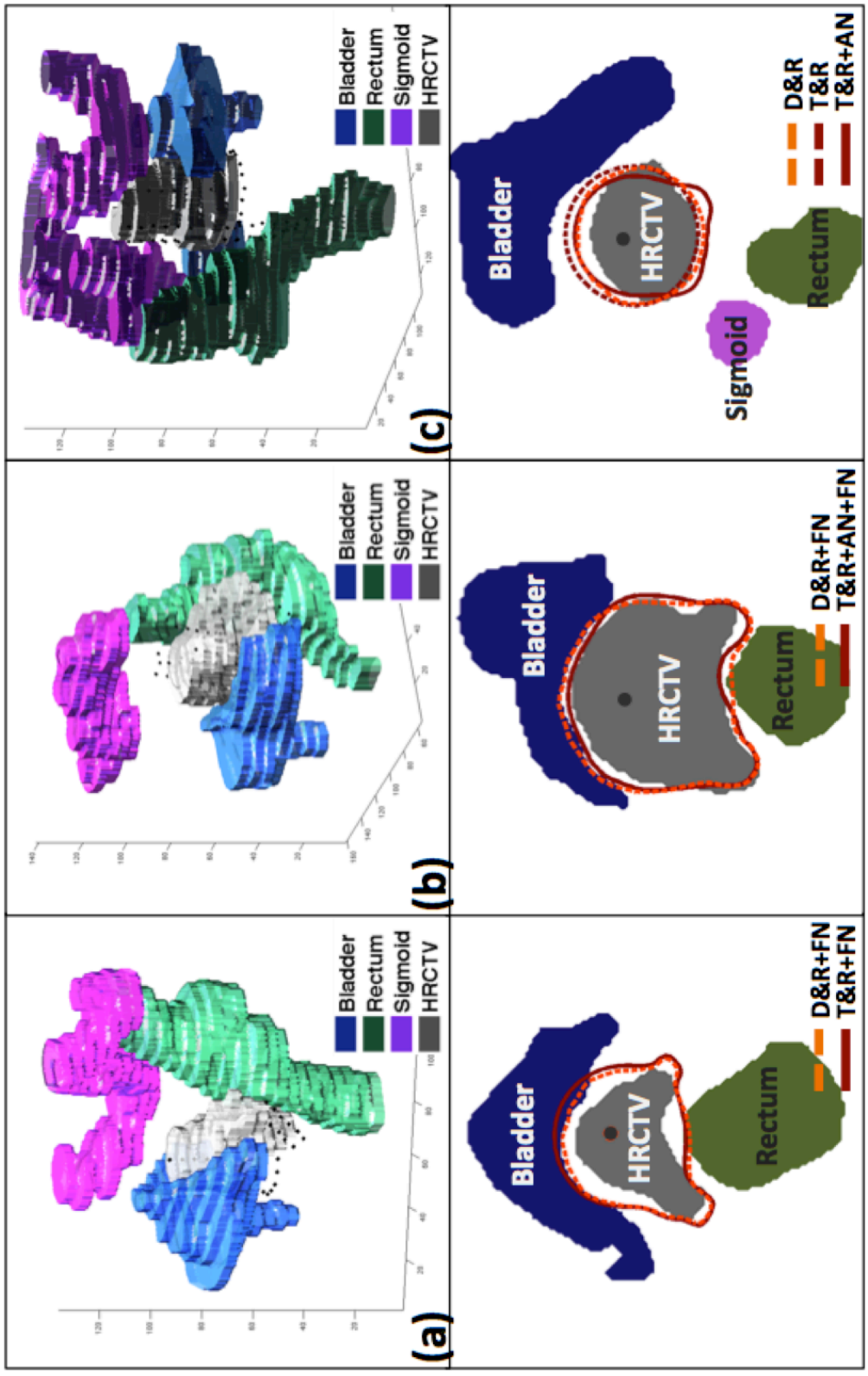

Figure 4-4. DMBT tandem and ring with supplement needles example cases.

Table 4-1. DMBT tandem and ring with supplement needles average differences

OARs D2cc Diff. [Gy]		T&R only	T&R(±AN)(±FN)								
			Group 1 T&R(+AN)(+FN)			Group 2 T&R(-AN)(+FN)			Group 3 T&R(-AN)(-FN)		
		D&R(-AN)(-FN)-T&R(+AN)(+FN)	D&R(-AN)(-FN)-T&R(+AN)(+FN)	D&R(-AN)(+FN)-T&R(+AN)(+FN)	D&R(+AN)(+FN)-T&R(+AN)(+FN)	D&R(-AN)(-FN)-T&R(-AN)(+FN)	D&R(-AN)(+FN)-T&R(-AN)(+FN)	D&R(+AN)(+FN)-T&R(-AN)(+FN)	D&R(-AN)(-FN)-T&R(-AN)(-FN)	D&R(-AN)(+FN)–T&R(-AN)(-FN)	D&R(+AN)(+FN)-T&R(-AN)(-FN)
Bladder	Ave±SD	-0.20±0.64	1.27±2.24	0.46±1.82	-0.36±1.55	0.98±2.06	-0.85±1.58	-1.61±1.50	-1.37±2.26	-3.62±2.78	-4.38±2.76
	T-Test	0.12	**0.02**	0.31	0.36	0.15	0.21	**0.00**	**0.02**	0.06	**0.00**
	≤ 0 (%)	66.7%	22.2%	22.2%	50.0%	33.3%	**55.6%**	88.9%	72.2%	88.9%	88.9%
Rectum	Ave±SD	-0.34±0.43	1.50±1.36	0.31±1.00	-0.42±0.57	1.01±1.49	-0.76±1.00	-1.49±1.43	-1.23±1.44	-3.00±2.29	-3.73±2.40
	T-Test	**0.00**	**0.00**	0.18	0.02	0.15	0.02	0.00	**0.00**	0.13	0.03
	≤ 0 (%)	81.5%	11.1%	55.6%	88.9%	22.2%	**88.9%**	100.0%	100.0%	100.0%	100.0%
Sigmoid	Ave±SD	-0.23±0.44	0.41±1.00	-0.14±0.62	-0.57±0.67	-0.33±0.93	-1.12±0.79	-1.55±0.89	-2.18±2.12	-2.97±2.44	-3.40±2.47
	T-Test	**0.01**	**0.03**	0.90	**0.01**	0.20	**0.00**	**0.01**	**0.00**	0.23	**0.02**
	≤ 0 (%)	74.1%	33.3%	55.6%	83.3%	55.6%	**100.0%**	100.0%	94.4%	100.0%	100.0%

4. 7. ACKNOWLEDGEMENTS

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Chapter 5

Conclusions

This dissertation presents the novel direction modulate brachytherapy (DMBT) tandem applicator for a HDR cervical cancer treatment. The DMBT tandem applicator has been shown that the compatibility with conventional treatment system, such as tandem and ovoid (T&O), tandem and ring (T&R), T&R with combined intracavitary-interstitial applicator. The external dimensions, especially total diameter of the DMBT tandem, were matched to conventional tandem, which is 6 mm in diameter. Since the DMBT tandem has 6 channels on the surface of tungsten alloy shield in the DMBT tandem, the DMBT tandem has more degree of freedom in delivering directional dose to the HRCTV than the conventional tandem.

In Chapter 2, the capabilities of DMBT tandem were investigated for possibility of improving a conventional HDR T&O cervical cancer treatment system. The conventional tandem was replaced to the DMBT tandem and 75 clinical treated plans were re-optimized with DMBT tandem. With the same HRCTV coverage, V100, dose to OARs were dramatically reduced. Mean 2cc doses to the bladder were 4.0 ± 0.2 Gy and 3.37 ± 0.19 Gy, for T&O and DMBT, respectively. For the rectum, they were 2.30 ± 0.17 Gy and 1.82 ± 0.1 Gy. For the sigmoid, they were 1.58 ± 0.19 Gy and 1.48 ± 0.17 Gy.

In Chapter 3, an ability of the DMBT tandem for covering an irregular HRCTV growth pattern was evaluated. All of 5 fractions in a brachytherapy course of a patient treated with HDR T&O with a free loaded needles (fraction 3-5) were re-

optimized only with DMBT tandem and ovoids. Without free loaded neeldes the most dose difference was sigmoid (40.8% (0.84Gy)) in fraction 1, and bladder (15.7% (0.99Gy)) in fraction 2. For fractions 3-5, where free-hand needles were supplemented to the T&O applicator, mostly improvements were seen in OARs but some did get worse. However, in terms of total EQD2 doses accumulated over the treatment course, for all OARs, the DMBT plans improved over the clinical plans. That is, 89.77 Gy reduced to 87.27 Gy, 74.25 Gy reduced to 73.47 Gy, and 62.51 Gy reduced to 53.53 Gy, for the bladder, rectum, and sigmoid, respectively. For the DMBT+needles plans, as expected, improvements were even greater compared with the clinical plans with 89.77 Gy reduced to 84.99 Gy, 74.25 Gy reduced to 70.92 Gy, and 62.51 Gy to 53.38 Gy, for the bladder, rectum, and sigmoid, respectively.

In Chapter 4, the DMBT tandem was evaluated a compatibility of T&R with combined intracavitary-interstitial applicator for PDR brachytherapy. The clinical treated individual 45 patients cases were re-optimized with the DMBT tandem. The free loaded needles and the attached to ring applicator needles were modified to investigate the DMBT tandem covering availability of an irregular the HRCTV and concluded 2-5 less supplemented needles were required, depends on patients, when the DMBT tandem was utilized.

The DMBT tandem prototypes were also manufactured and tested under MR. The DMBT tandem did not have an unexpected artifact on the 1.5T MR image. Furthermore, the Ir-192 HDR radiation source was tested to investigate possibility of traveling a radiation source through 1.3 mm in diameter channels. The current Ir-192

radiation sources were compatible with the 1.3 mm in diameter channels in the DMBT tandem.