BETTER IDENTIFICATION OF NORMAL TISSUE DOSE CONSTRAINTS FOR USE IN HIGH DOSE RATE BRACHYTHERAPY IN THE TREATMENT OF LOCALLY ADVANCED CERVICAL CANCER

By

Sonam K. Choudrie

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Abbreviations

EBRT: External beam radiation therapy

BT: Brachytherapy

BED: Biologically effective dose

CTV: Clinical treatment volume

$D_{2cc}/D_{2\ cm^3}$: Minimum dose to the most exposed 2 cm^3 of tissue

DVH: Dose volume histogram

DSB: Double stand break

EMBRACE: Image-Guided Intensity Modulated External Beam Radiochemotherapy and MRI-Based Adaptive Brachytherapy in Locally Advanced Cervical Cancer

EQD2: Equivalent dose in 2 Gy fractions

EQDX: Equieffective dose

GTV: Gross tumor volume

Gy: Gray

GYN GEC-ESTRO WG: Gynecological Groupe Européen de Curiethérapie and the European Society for Radiotherapy & Oncology Working Group

HDR: High dose rate

HR: High risk

IC: Intracavity

IGABT: Image-guided adaptive brachytherapy

IR: Intermediate risk

IS: Interstitial

ITV: Internal treatment volume

LQ: Linear quadratic

LR: Low risk

OAR: Organs at risk

OTT: Overall treatment time

PLD: Potentially lethal damage

PTV: Planning treatment volume

QoL: Quality of life

SIB: Simultaneous integrated boost

SLD: Sublethal damage

SSB: Single stand break

T&O: Tandem and ovoids

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Abstract

Purpose: The potential limitations of the use of D_{2cc} as implemented in the EMBRACE protocol are recognized and evaluated against a localized method for determining dose constraints in brachytherapy (BT) treatment planning. This study seeks to better understand the normal tissue dose constraints for HDR BT in the treatment of locally advanced cervix cancer.

Methods: A retrospective analysis was performed for 10 patients that received EBRT via IMRT or VMAT in accordance with the EMBRACE protocol (45 Gy in 25 fractions with concomitant chemotherapy). All patients received a concurrent or sequential EBRT nodal boost according to potential risk of spread. D_{2cc} to the bladder, rectum, sigmoid and small bowel as defined in EMBRACE and measured within localized volume expansions around the HR-CTV (1 cm, 2 cm, and 3 cm). D_{2cc} values were converted into EQD2 using a LQ model ($\alpha/\beta = 3$ Gy). Data were statistically analyzed using a single-tail paired t-test (H_0: $\mu = 0$) for the two different DVH parameters. An additional analysis is performed to determine the BT influence on OAR within these localized regions.

Results: Statistically significant differences ($p < 0.05$) are found for the bladder, sigmoid and small bowel. Additionally, the small bowel is found in most cases to be well out of reach of the BT dose. The BT dose-rate observed to drop to 50% at 1 cm outside the HR-CTV, 30% at 2 cm and 20% at 1 cm.

Conclusion: The standard of treatment of locally advanced cancer is a brachytherapy (BT) boost following EBRT and concomitant chemotherapy, with the following hard constraints for the prescribed dose: Bladder, $D_{2cc} < 80$ Gy $_{\alpha/\beta=3}$; Rectum, $D_{2cc} < 65$ Gy $_{\alpha/\beta=3}$, Sigmoid $D_{2cc} < 70$ Gy $_{\alpha/\beta=3}$, Bowel, $D_{2cc} < 70$ Gy $_{\alpha/\beta=3}$. The objective of this study

was to assess the EMBRACE-recommended DVH parameter against localized method for determining D_{2cc} within BT influence. Our findings suggest that this revised DVH parameter may improve treatment outcome through better understanding of the actual normal tissue dose limits.

1 Introduction

The current standard for treatment of locally advanced cervical cancer is external beam radiation therapy (EBRT) with concurrent chemotherapy followed by a brachytherapy (BT) boost. This standard was established by the Gynecological Groupe Européen de Curiethérapie and the European Society for Radiotherapy & Oncology Working Group (GYN GEC-ESTRO WG), which formed in 2000 with the purpose of establishing international recommendations on adaptive target definition and dose reporting in 3D image-guided adaptive brachytherapy (IGABT) for locally advanced gynecological cancer.[1,2] This group initiated a series of studies, Image-Guided Intensity Modulated External Beam Radiochemotherapy and MRI-Based Adaptive Brachytherapy in Locally Advanced Cervical Cancer (EMBRACE), with a focus on improving clinical outcome of image-guided radiotherapy in cervix cancer. Recommendations I-IV published by the GYN GEC-ESTRO WG provided the conceptual framework for the standardization and implementation of IGABT and for the development of ICRU Report 89: Prescribing, Recording, and Reporting Brachytherapy for Cancer of the Cervix.[3–7]

The EMBRACE protocol prescribes EBRT to the pelvis (45 Gy in 25 fractions delivered via IMRT or VMAT) and concomitant chemotherapy (weekly Cisplatin). An additional (concurrent or sequential) EBRT boost is given to nodes with or at risk of disease. Nodal clinical target volumes are determined by nodal pathology at the time of diagnosis and the potential risk of nodal spread, and are classified into low- (LR LN), intermediate- (IR LN) and high-risk (HR LN) groups. These volumes, shown below in **Figure 1**, may also be referred to as “small pelvis”, “large pelvis”, and “large pelvis + para-aortic”, respectively. The LR LN group contains the internal iliac, external iliac,

obturator and presacral lymph node regions. The IR LN expands on the "small pelvis" target volume to include the common iliac region, mesorectal fascia and, in some cases, the inguinal lymph nodes. The "large pelvis + para-aortic" target volume extends to at least 3 cm cranial of the highest pathological para-aortic node in addition to the LR LN and IR LN risk groups.[8]

While EBRT may be applied with BT in various combinations, the pelvis typically receives a daily EBRT dose of 1.8–2.0 gray (Gy) to the planning treatment volume (PTV), while the nodes are boosted via EBRT, also referred to as the simultaneous integrated boost (SIB), until the nodal dose (EBRT plus BT) equals 60 Gy EQD2, or equivalent dose in 2 Gy fractions (see section 3).[1,3]

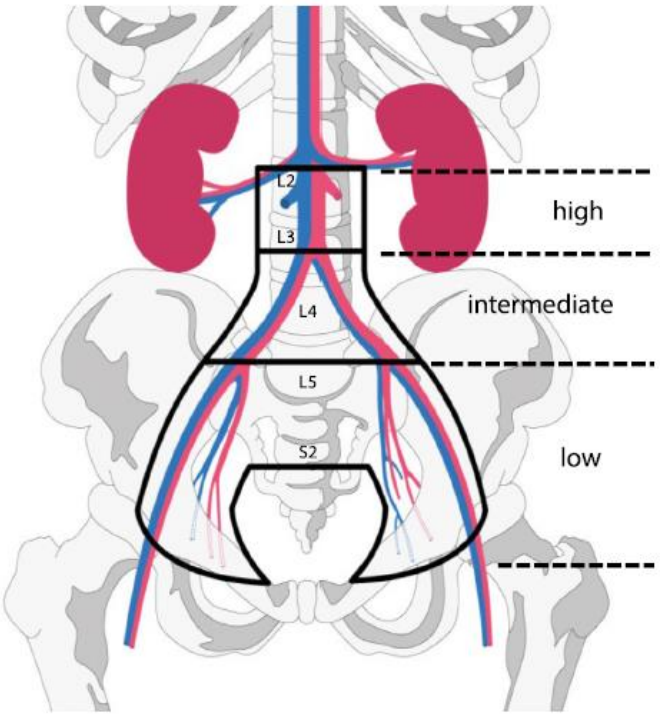

Figure 1 A concurrent or sequential EBRT nodal boost is delivered prior to BT boost, with the nodal target volumes varying with risk of lymphatic spread. Reprinted with permission from Clinical and Translational Radiation Oncology.[1]

While radiotherapy has a higher curative potential than that of alternative treatment methods, e.g., surgery, any radiation oncology treatment regimen will have impact on surrounding healthy tissue. Normal tissue within the vicinity of the tumor may have treatment-related morbidities associated with overdosage and therefore must be considered carefully during the treatment planning process[3].

Critical structures of concern in GYN radiotherapy that are directly adjacent to target volumes include the bladder, rectum, sigmoid and small bowel.[1] Significant dose relationships for these organs at risk (OAR) have been established through the EMBRACE trials, as well as the thresholds at which morbidities significantly increase, which may adversely affect patient quality of life (QoL).[1,3,8–10] EMBRACE II specifies dose volume constraints for adaptive targets and OAR to be implemented in treatment planning, provided in **Table 1**. D_{2cc}, or the minimum dose to the most exposed 2 cm^3 volume of tissue, is used as a limiting factor in planning the BT boost to avoid overdosage to OAR in GYN radiotherapy.

Table 1: Planning aims and normal tissue dose constraints (EQD2) for use BT boost planning in the EMBRACE protocol.[a,b]

Target	D90 CTV_{HR} $EQD2_{10}$	D98 CTV_{HR} $EQD2_{10}$	D98 GTV_{RES} $EQD2_{10}$	D98 CTV_{IR} $EQD2_{10}$	Point A $EQD2_{10}$
Planning Aims	>90 Gy <95 Gy	>75 Gy	>95 Gy	>60 Gy	>65 Gy
Limits for Prescribed Dose	>85 Gy	-	>90 Gy	-	-
OAR	Bladder D_{2cc} $EQD2_3$	Rectum D_{2cc} $EQD2_3$	Recto-vaginal point $EQD2_3$	Sigmoid D_{2cc} $EQD2_3$	Bowel D_{2cc} $EQD2_3$
Planning Aims	<80 Gy	<65 Gy	<65 Gy	<70 Gy	<70 Gy
Limits for Prescribed Dose	<90 Gy	<75 Gy	<75 Gy	<75 Gy	<75 Gy

[a]Adapted from Clinical and Translational Radiation Oncology[1]

[b]For targets and OAR, EQD2 is calculated using $\alpha/\beta = 10$ and $\alpha/\beta = 3$, respectively

Moderate or high doses to large volumes of the bladder or to the whole organ can increase detrusor muscle tone and volume shrinkage, causing accidental voiding, or bladder fibrosis. There are also morbidities linked with dose to sub-structures. For example, high absorbed dose to the bladder trigone and neck may lead urgency and incontinence.[3]

Furthermore, high doses to the rectum (> 70 Gy) and sigmoid have been linked to telangiectasia-induced bleeding, as well as changes in bowel habits. As with the bladder and its sub-structures, high absorbed dose to the recto-anal wall may lead to urgency and incontinence due to damage to associated muscle and nerve structures.[1,3]

Studies have shown the small bowel to be more radiosensitive than the bladder, rectum and sigmoid. Late toxicities for the small bowel have been shown for GYN BT at low dose rates.[11] However, EMBRACE I data showed no significant dose response for the small bowel, but recommends a dose planning aim of 70 Gy.[1,9,11,12] Definitions of target volumes listed in **Table 1**, as well as the concepts of D_{2cm3} and $EQD2_x$ will be discussed in the following sections.

2 Study Aims

The current standard for measuring normal tissue dose constraints is D_{2cc}, as established through the EMBRACE studies. This analysis seeks to better understand the normal tissue dose limits for use in HDR BT in the treatment of locally advanced cervical cancer, as well as quantify the BT influence on OAR dose limits for regions surrounding the HR-CTV.

Motivation for this study is based on recognition the BT planned dose may be artificially limited by high doses to OAR volumes near the IR LN and HR LN lymph node regions. As dose to normal tissue within the immediate vicinity of BT influence may be independent of EBRT boost delivered to these regions, a localized method is proposed for identification of normal tissue dose constraints in HDR treatment planning as an alternative to the current standard set forth by the GYN GEC-ESTRO WG and ICRU Report 89.

3 Background

3.1 Radiation biology

The objective of radiotherapy is to deliver a high radiation dose to the target (tumor) volume while minimizing dose to surrounding normal tissue. Biological effects of radiation depend on various factors such as dose, dose rate, dose distribution, irradiated volume, fractionation, and overall treatment time (OTT). Understanding the mechanisms by which tumor and normal tissue respond to damage caused by irradiation is key to ensuring a successful clinical outcome.

The mechanisms by which radiation interacts with tissue can be summarized in the following steps[12,13]:

1. Photons emitted via EBRT or BT interact with orbital electrons within the target material. Because the deposition of energy occurs through excitation and/or ejection (ionization) of these orbital electrons, photons are classified as indirectly ionization radiation.

2. Ejected electrons interact with their environment, resulting in the (direct or indirect) formation of free radicals.

3. Free radicals are highly reactive molecules that cause further damage to molecules such as DNA via single- (SSBs) or double-strand breaks (DSBs) in the DNA chain.

The degree to which damage to DNA is repaired depends on the type of break and may lead to cell death. Radiation damage to mammalian cells is classified as lethal damage, potentially lethal damage (PLD), and sublethal damage (SLD). The former leads

to cell death, as this type of damage is irreversible and irreparable. PLD refers to the ability of cells to recover from radiation damage depending on their post-irradiation environmental conditions, i.e., if left under normal conditions, this type of damage leads to cell death.[14] Finally, SLD describes the repair of DNA damage under normal conditions and may be completed in as short as a few hours. However, if more SLD occurs during the time at which this repair occurs, the added number of SLD can result in lethal damage, leading to cell death during the next cell cycle or after several mitotic divisions.[12]

The effects of fractionated schemes, such as the ones shown in **Figure 2** below, can be described by the "four Rs" of radiobiology: repair, repopulation, reoxygenation, and redistribution. These refer to, respectively, the repair of SLD to DNA, the proliferation of normal tissue, oxygen as a catalyst in the process of tumor cell kill, and higher cell kill during the more radiosensitive stages of the cell cycle.[12]

While all four processes influence survival rate, the repair of SLD and proliferation of normal tissue are the most relevant in clinical radiobiology. **Figure 2** shows the cell survival curves for a course of treatment delivered in various fractionation schemes compared to a single fraction of a large dose.

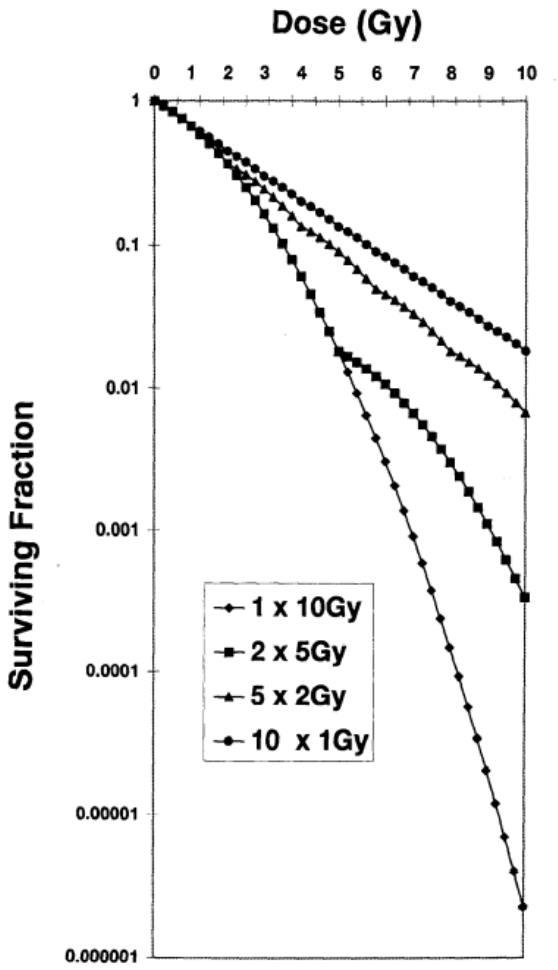

Figure 2 The effects of fractionation on cell survival. The curves describe the cell response to 10 Gy delivered in 1, 2, 5 and 10 fractions. Reprinted with permission from the British Journal of Radiology.[15]

Furthermore, the dose rate is one of the principal factors that govern the biologic response to irradiation, as this greatly affect the ability of normal tissue cells to repair SLD and proliferate. For a lower dose rate at a longer exposure time, the biologic effects are reduced as enough time is provided for significant SLD repair and normal tissue cell proliferation to occur. As the dose rate continues to decrease, the slope of the cell survival curve reduces, with the shoulder eventually disappearing. These effects are summarized in **Figure 3**.

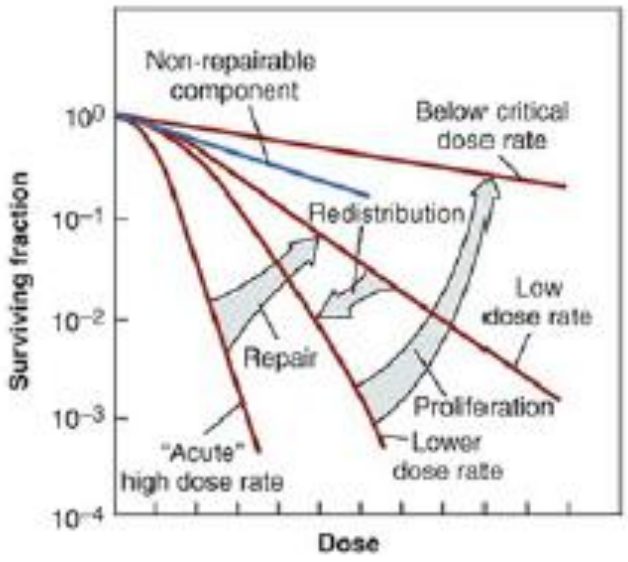

Figure 3 The four R's of radiobiology and their effect on cell survival. Reprinted with permission from Lippincott Williams & Wilkins.[12]

3.1.1 The Linear-Quadratic Model

The linear-quadratic (LQ) model arose from the need to distinguish between fractionation and dose rate sensitivities between tissue types, as significant changes in the biological outcome result from minor adjustments to total dose, dose rate and geometry.[15] The LQ model is given by

$$S = e^{-\alpha D - \beta D^2}$$

where S represents cell response to irradiation for a given cell survival curve. The LQ model is used to predict normal tissue complications and equate radiotherapy regimens via selection of the LQ parameters α and β, which represent the intrinsic radiosensitivity of the irradiated cells.[15,16]

The first term in the LQ model ($e^{-\alpha D}$) represents lethal lesions caused by single particle interactions and is tangent to the cell survival curve at the origin. The second

term ($e^{-\beta D^2}$) describes SLD caused by multiple particle interactions and dictates the downward curvature of the cell survival curve (see **Figure 4**). This quadratic component, governed by β, causes the curve to bend and results in tissue sparing in fractionated schemes, such as in **Figure 1**.[12,15]

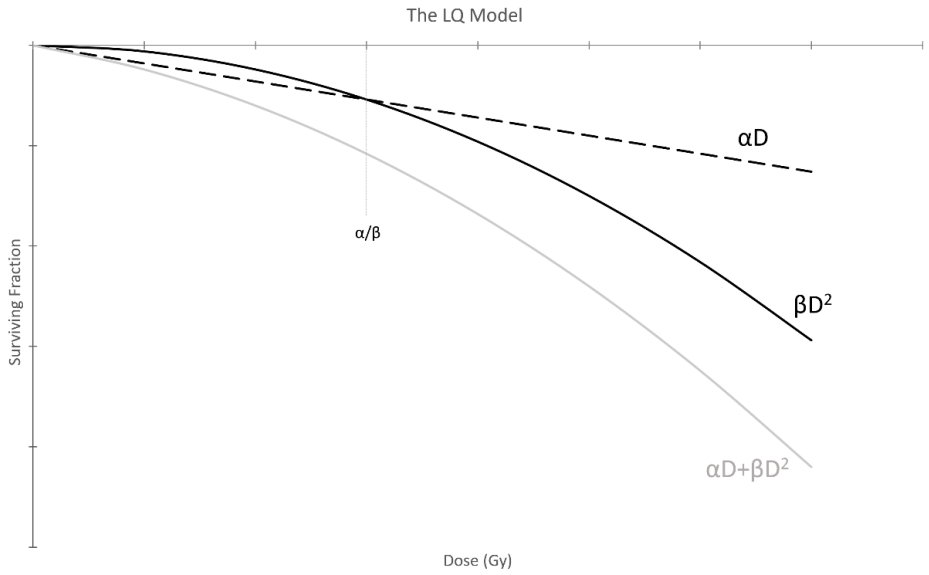

Figure 4 The linear-quadratic model of cell response to radiation describes the effect of single- and multi-track events.

The ratio α/β is of particular importance and corresponds to the dose at which the linear and quadratic killing components are equal.[12] Cells with a higher α/β ratio are more radiosensitive and, therefore, a large shoulder on the survival curve corresponds to a small α/β ratio, i.e., one that has a large repair capacity.[13] For normal tissues and tumor cells, α/β = 3 and α/β = 10, respectively.[3] Tumor cells have often been shown to be less effective at repair compared to normal tissue, with the exception of epithelial cells that are highly radiosensitive due to their limited proliferation in response to radiation.[12]

Models for the biologic effects of various radiotherapy techniques allow for the optimization of dwell times in modern BT, and hence a reduction in overdosage to

critical structures. As discussed, the biologic outcome of such schemes is highly dependent on dose, dose rate, dose distribution, irradiated volume, fractionation, and overall treatment time (OTT), calling for a method by which to translate between absorbed dose delivered via EBRT and BT in the EMRBACE protocol.

3.1.2 Equieffective Dose

Biologically effective dose (BED) allows for the comparison of various types of radiation-induced organ injuries.[12] BED accounts for the various factors that influence clinical outcome and serves as a method by which to compare different treatment types and fractionation schemes. The derivation, based on recognition that each successive fraction is equally effective for a given treatment regimen, can be found in Appendix A.[3,12,13,17] BED is defined as

$$\mathrm{BED} = \mathrm{nd}\left(1 + \frac{\mathrm{d}}{\alpha/\beta}\right)$$

Equieffective absorbed dose (EQDX), on the other hand, is used specifically to compare absorbed dose to target volumes and OAR using different fractionation regimens. EQDX is defined as the absorbed dose that produces the same probability of a given biologic effect when delivered under different conditions.[3] Most clinical data available has been obtained using a fractionation scheme of 2 Gy per fraction. The clinical outcomes using a 2-Gy fractionation scheme are well understood and is therefore recommended for the majority of EBRT patients.[3] Equieffective dose in at 2 Gy per fraction (EQD2) serves as a union between EBRT and BT in the EMBRACE protocol. EQD2 is given by

$$EQD2 = \frac{BED}{1 + \frac{2}{\alpha/\beta}} = D\frac{\alpha/\beta + d}{\alpha/\beta + 2}$$

Dose limits used in the EMBRACE protocol are evaluated against the summation of EBRT and BT contributions to absorbed dose in EQD2.

3.2 The Implementation of Modern GYN BT in the EMBRACE Protocol

Applicators are a device used in BT to hold the radioactive sources in a particular arrangement. They enhance the degree of conformity and allow for accurate source placement and dwell times.[15] In GYN BT, the standard intracavity applicators include cylinders and tandem and ovoids (T&O). A diagram of the T&O applicator following insertion is shown in **Figure 5**. The ovoids are positioned at the vaginal fornix while the tandem extends up into the uterus.[18]

Early treatment plans were based on two orthogonal radiographs (AP & lateral). However, this allowed only for a marginal personalization of the dose distribution.[18–20] Over the years, several systems of implant dosimetry have been introduced to accomplish the clinical goals of BT treatment. These systems define a set of rules that were developed from the geometric arrangement of the radioactive sources, strength, distance, and treatment time. Of these systems, the most recognized in the field of GYN BT is the Manchester system. In this method the dose is prescribed to "Point A" (**Figure 5)**.[18,19] While the definition of point A has evolved since the system was established, it was most recently defined as the point 2 cm superior from the superior edge of the ovoids in the plane of the tandem and 2 cm laterally.[3,18] This point represents the crossing of the ureter and the uterine artery, and serves as a critical point for dose specification. The choice to

limiting the dose to the location of Point A was based on its close proximity to the paracervical triangle, a region at risk of radiation necrosis in GYN radiotherapy.[21]

While Point A has the advantage of being anatomically comparable between patients, ICRU Report 38 recommended against its use due to its occurrence near high dose gradients and the limited accuracy 2D imaging provided in locating the ovoid surface, preferring a point defined relative to an anatomical structure instead of an applicator.[22]

Historically, the absorbed dose to OAR are delineated from standardized dose points to identify correlations with eventual morbidities. While point doses have the benefit of being associated with dose to specific sub-structure, as is the case with the ICRU bladder and rectal points, point doses do not represent the dose to volumes of OAR, often underestimating dose to critical structures and failing to predict late toxicities.[3,23,24]

IGABT, dubbed "the new gold standard", is an increasingly used technique, replacing 2D brachytherapy throughout the world.[1,2] The use of CT or MRI in modern brachytherapy treatment planning allows one to tailor treatments to individuals and their specific tumors with great accuracy.[20] In contrast to the use of reference point doses, modern BT uses a reference-volume approach for dose limits, typically the dose to 2 cm^3 volumes. D_{2cc}, a significant parameter in modern BT, represents the minimum dose to the most exposed 2 cm^3 volume of tissue. While not defined at an exact location within a structure, they do have the benefit of being associated with specific sub-structures within the OARs due to their finite size.

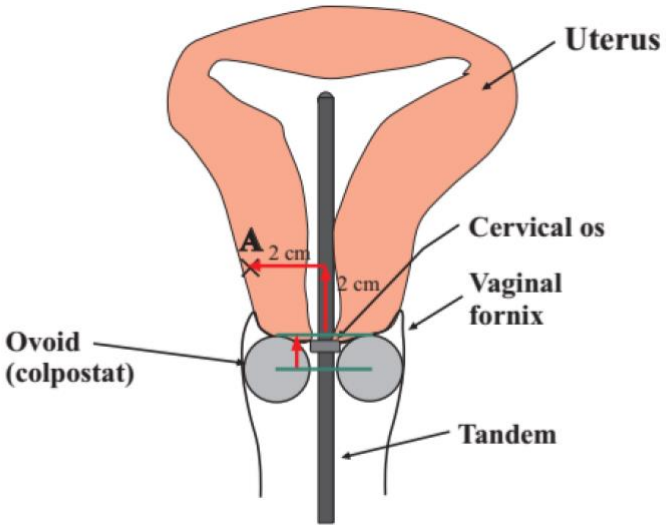

Figure 5 Definition of Point A, used as a prescription point for BT tandem and ovoid (T&O) treatments. Reprinted with permission from Medical Physics Publishing.[18]

In recent years, applicators have been developed for the combined use of intracavity radiotherapy and MRI-compatible interstitial needles, allowing for an expansion of the Manchester system via the optimization of dwell positions and dwell times.[3,25] Unlike traditional dosimetry systems, hybrid applicators allow for more patient-centered treatment planning to conform the dose distribution to tumor volumes according to the extent of disease.

The BT target volumes are defined by the GYN GEC-ESTRO WG as thus[4]:

1. The high-risk CTV (HR CTV): defines a volume with a major risk of recurrence due to residual *macroscopic* disease. Dose delivered to this volume should be maximized in order eradicate all residual macroscopic disease.

2. The intermediate risk CTV (IR CTV): defines a volume with a major risk of recurrence due to residual *microscopic* disease at the time of BT. Dose delivered during BT to eradicate any microscopic disease is at minimum 60 Gy.[4]

3. The low-risk CTV (LR CTV): defines a volume with potential microscopic tumor spread. The LR CTV is typically treated by external beam radiotherapy.

These volumes are described and depicted in clinical practice in the figures below (**Figure 6** and **Figure 7**).

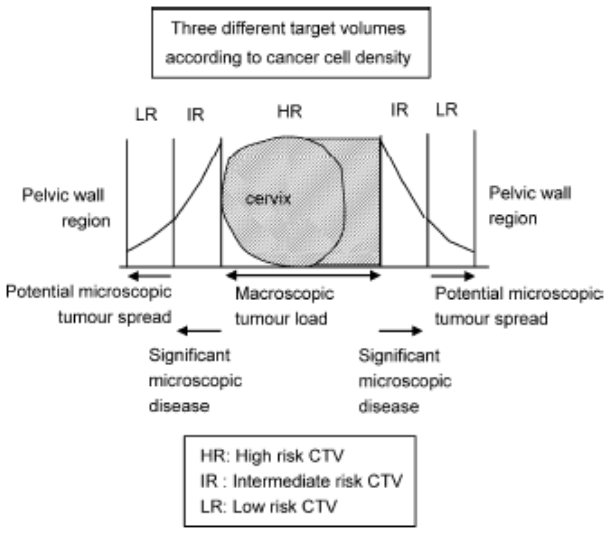

Figure 6 Target volume definition in relation to their tumor cell density. The HR- and IR-CTV contain macroscopic and microscopic disease, respectively. The LR-CTV is defined by volumes at risk of developing disease. Reprinted with permission from Clinical and Translational Radiation Oncology.[1]

EBRT target volumes, in contrast, are much larger. For EBRT, the clinical treatment volume (CTV) contains the gross tumor volume (GTV) plus suspected macroscopic disease. The internal treatment volume (ITV) encases the CTV with a margin to account for internal motion. The PTV generally includes the CTV or ITV with additional margins to account for uncertainties in the position or interfractional variations of the CTV. These uncertainties may be due to movement of internal organs or respiratory motion during treatment.[8,18,20] However, BT target volumes do not require these uncertainty margins as the interstitial (IS) or intracavity (IC) sources will move with the tissue they are embedded in. The BT prescription isodose therefore defines a

much smaller target volume compared to EBRT.[13] BT dose at a distance r from the source can be approximated as $1/r^2$ or 1/r for a point source and line source, respectively.[26]BT dose has a rapid fall-off outside the target volume, resulting in steep dose gradients and therefore a very heterogeneous dose distribution. In contrast, the planning aims for EBRT include a uniform coverage of the PTV, with the acceptable range of deviation in being 5% - 7%.

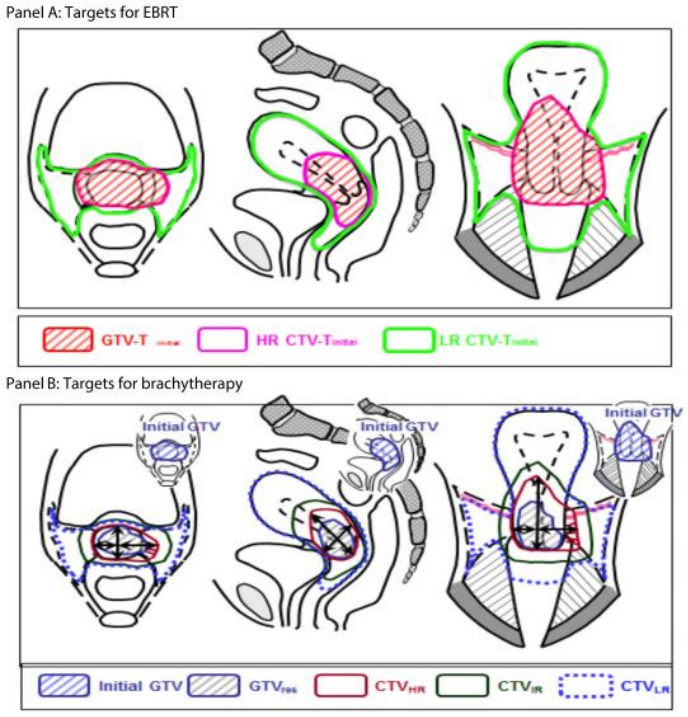

Figure 7 Target definitions as defined in the EMBRACE protocol. Reprinted with permission from Clinical and Translational Radiation Oncology.[1]

The EMBRACE protocol emphasizes a distinction on the GTV and CTV at diagnosis (GTV-T and CTV-T, respectively), recognizing that changes in these volumes frequently occur throughout treatment. GTV-T_{res} is defined as the residual macroscopic tumor at time of BT treatment. In addition, there are target volumes defined for pathologic lymph nodes defined by GTV-N and CTV-N. Delineation of these targets with accuracy is of great importance and requires 3D imaging techniques such as MRI or CT.

The EMBRACE protocol prescribes a combined EBRT + BT EQD2 dose to the HR-CTV. Planning aims for target volumes and dose limits to OARs, given in EQD2, are listed in **Table 1** in the Introduction.

4 Methods

10 patients with locally advanced cervical carcinoma received EBRT delivered as IMRT or VMAT with concomitant therapy prior to brachytherapy boost. All pelvic EBRT fields were planned using CT data to deliver 45 Gy in 25 fractions. Each patient received a concurrent or consequential nodal boost. 5 patients received EBRT treatment at outside institutions. These patients were not treated with the EMBRACE protocol and PTVs were modified to include additional EBRT boost to the nodes surrounding the GTV since, at the time, their plans were not designed to include a BT boost.

With the applicator in situ, CT-based BT fraction plans were designed using Oncentra® Brachy, along with MRI-based guidance, for hybrid T&O applicator reconstruction and optimization, with the dose prescribed to the HR-CTV. Each BT dose was tailored according to the burden of disease at the time of treatment.[3]

4.1 Identification of OAR Volumes within BT Influence

To better understand the normal tissue dose limits, the overall D_{2cc} for the bladder, rectum, sigmoid and small bowel were obtained using the Dose Statistics feature in Eclipse® Planning Station using the EBRT data for each patient. Bladder doses for patient #10 are omitted from the analysis, as the bladder is included in the CTV. The localized regions in which D_{2cc} values were to be analyzed were arbitrarily determined to be 1 cm, 2 cm, and 3 cm volume expansions around the HR-CTV.

The CT data was imported into Eclipse® Contouring (see **Figure 8**). Several features available within this software were used to create contours for a localized dose analysis. The Extract Wall tool was used to create contours expanding 1 cm, 2 cm, and 3 cm out from the HR-CTV. This tool required selection of an existing structure, in this

case the HR-CTV, and a distance (in centimeters) to which the new structure would be expanded to. Axial views of these structures are outlined in white in **Figure 8 (b-e)**, with the HR-CTV contoured in green. The sagittal and coronal views of all four volumes are shown in **Figure 8 (f-g)**.

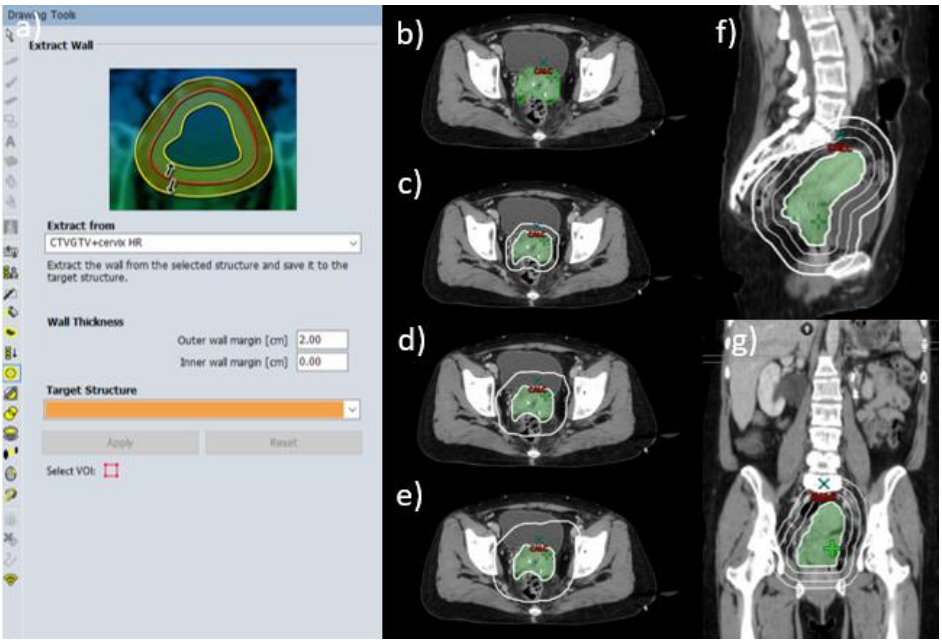

Figure 8 (c-g) Volume expansions (1 cm, 2 cm and 3 cm) around the HR-CTV (b) to which D_{2cc} would be localized. The volume expansions were created in Eclipse® Planning Station using the Extract Wall tool.

To localize D_{2cc} of OARs around the HR-CTV, the Boolean Operator tool was used to contour the intersections between the localized volume expansions (see **Figure 9**) and the bladder, rectum, sigmoid and small bowel. The Boolean Operator tool required the input of two structures for which the overlap is created and saved as a new structure. This region of overlap is shown in **Figure 9 (b)** for the bladder and 1 cm expansion around the HR-CTV. The bladder, contoured in yellow, sits anterior to the HR-CTV. A 1 cm expansion around the HR-CTV is outlined in white. In **Figure 9 (c)** the volume of the bladder within this expansion is identified by the Boolean Operator tool. The axial and

sagittal views of all 3 expansions for the bladder, i.e., volumes of the bladder within 1 cm, 2 cm, and 3 cm of the HR-CTV, are shown in **Figure 9 (d-e)**.

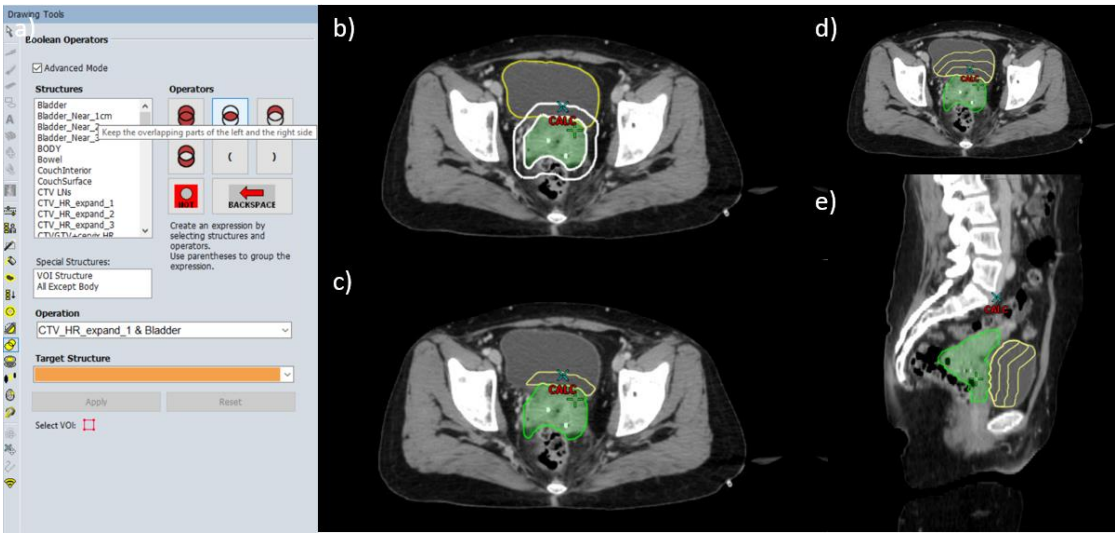

Figure 9 The Boolean Operator tool in Eclipse® TPS created contours around OAR intersecting the volume expansions.

Uncertainties in the position of the small bowel arise due to peristalsis, changes in content, patient positioning, and bladder content.[18,27] Bowel bags, containing both large and small bowel, are a structure often used in EBRT planning to account for interfractional motion. To obtain accurate dose to the small bowel, additional structures were created to separate the small bowel from the bowel bags. The small bowel was contoured using the Brush tool. These structures are shown in **Figure 10**. These contours were reviewed and approved by a certified dosimetrist. Measurements for D_{2cc} to the small bowel were obtained under the assumption that the small bowel remains static throughout the course of treatment. However, the position of the small bowel varies due to peristalsis and other sources of interfractional motion.

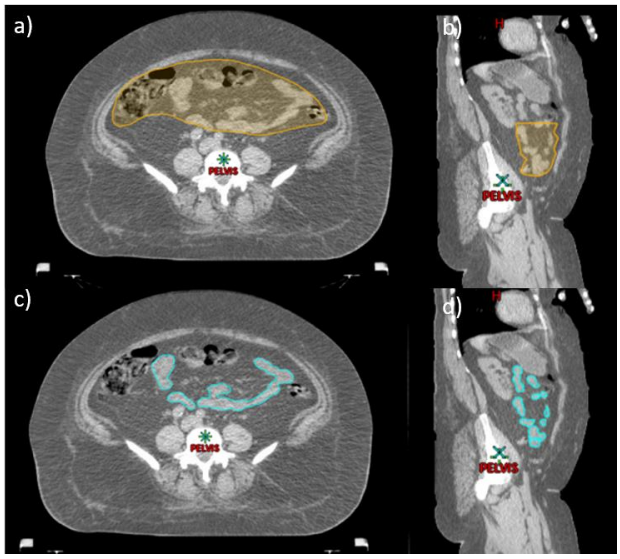

Figure 10 To obtain an accurate estimate of D_{2cc} to the small bowel, additional contours were created to separate the small bowel from the bowel bag.

4.2 DVH Analysis

Dose to OAR were calculated in Eclipse® External Beam Planning using patient CT data and treatment parameters for the delivered plan. These values were obtained via Dose Volume Histogram (DVH) Column Selection, in which D_{2cc}, in cGy, to the volume of OAR defined by the contours were generated (see **Figure 11**). D_{2cc} for the overall organ and the 1 cm, 2 cm and 3 cm volume expansions around the HR-CTV were obtained for the bladder, rectum, sigmoid and small bowel.

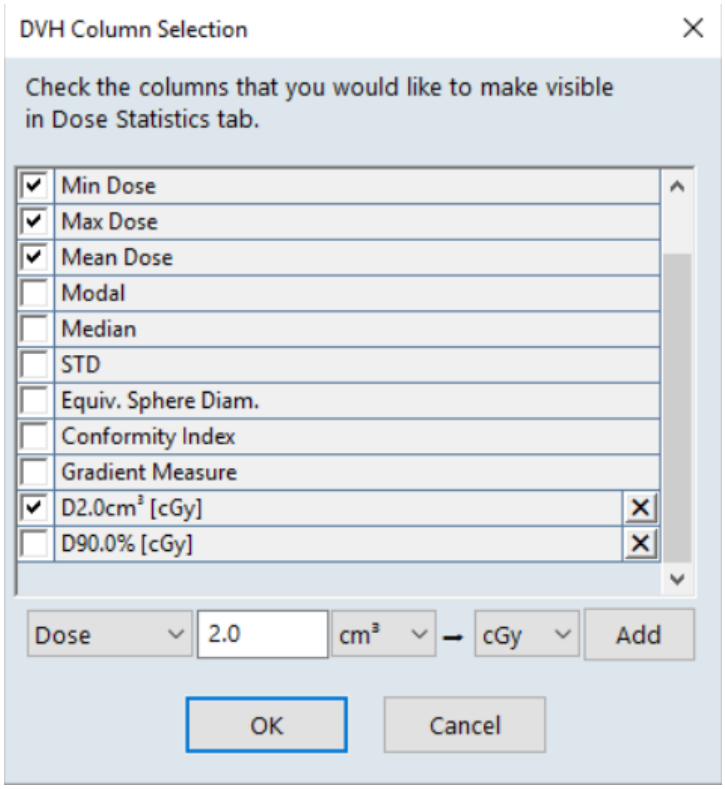

Figure 11 The DVH Column Selection tool in Eclipse® TPS allows the user to display of D_{2cc} to CT structures.

4.3 EQD2 Conversion

Absolute D_{2cc} values were converted to EQD2 using the following equation:[3]

$$EQD2 = D\frac{\alpha/\beta + d}{\alpha/\beta + 2} = dwf\frac{\alpha/\beta + d\,w}{\alpha/\beta + 2}$$

Where $\alpha/\beta = 3$ for normal tissue, d = dose per fraction in Gray, f = number of fractions and w = weighting factor. For the pelvic EBRT data, d = 1.8 Gy, and f = 25, while the weighting factor was found using the ratio of the absolute D_{2cc} dose over the prescription dose, 45 Gy.

To analyze the $D_{2cc\text{-}EQD2}$ differences between the OAR volume and each expansion, a one-tailed paired t-test was chosen based on the hypothesis that the D_{2cc} as measured at

localized volumes around the HR-CTV is less than the D_{2cc} used in the EMBRACE protocol. Data analysis was performed in Excel using a t-test (H_0: $\mu = 0$; $\alpha = 0.05$) to determine whether there is a significant mean difference for each group while keeping the data paired. The EQD2 data are shown and discussed in the following sections.

4.4 Measurement of BT Dose Influence

BT planning data for 3 patients were chosen at random to determine BT dose influence outside the HR-CTV using Oncentra® Brachy (see **Figure 12**). Each patient was prescribed a fractional dose of 7 Gy to the HR-CTV. Patient point sets were created for each distance, using the Add Points tool. Absolute dose was measured at 1 cm, 2 cm, and 3 cm out from the HR-CTV, with 10 data points collected for each distance. The percentage drop-off in dose with distance was calculated in Excel by dividing the absolute dose by the prescription dose. Our results are displayed and discussed in the following sections.

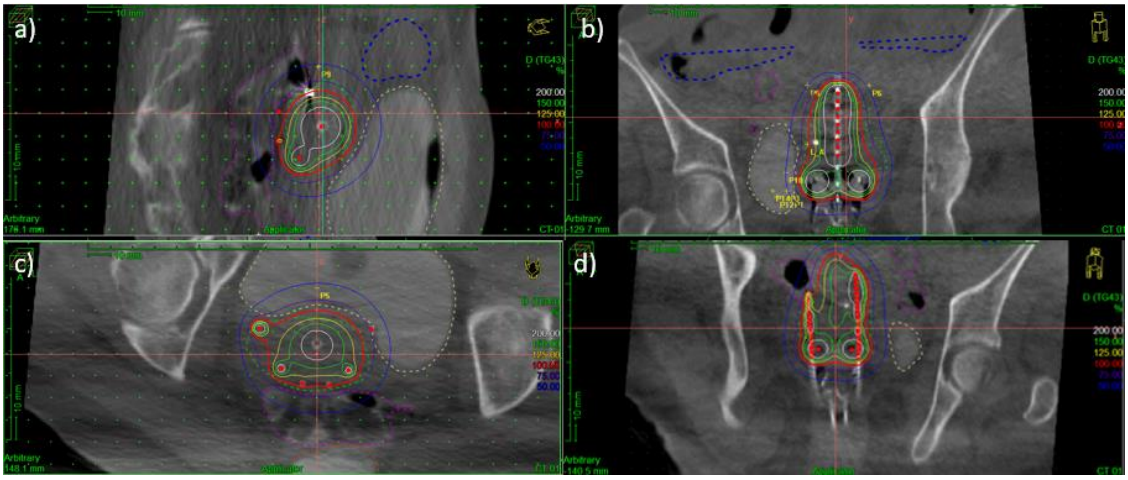

Figure 12 Absolute dose measured for patients previously treated with hybrid HDR BT using patient points in Oncentra® Brachy.

5 Results

5.1 Equieffective Dose

D_{2cc} in absolute dose for the bladder, rectum, sigmoid, small bowel, and their respective expansions are available for reference in Appendix B.

Absolute dose values were converted to EQD2 using a LQ model with $\alpha/\beta = 3$. D_{2cc} in EQD2 to whole OAR in addition to the 12 contoured intersections between the organ and the volume expansions are shown in **Table 2**. For each OAR, four EQD2 values are displayed: one for the overall organ as used in the EMBRACE protocol for BT treatment planning and three measured dose values at distances of 1 cm, 2 cm, and 3 cm from. The data is labeled as such: B = bladder; R = rectum; S = sigmoid; SB = small bowel. The numbers following each organ label represent the volume expansion around the HR-CTV, e.g., 1 = 1 cm volume around the HR-CTV.

Table 2: EQD2 D_{2cc} (Gy) for EBRT Dose Delivered Prior to BT

ID#	Bladder				Rectum				Sigmoid				Small Bowel			
	OAR	**B1**	**B2**	**B3**	OAR	**R1**	**R2**	**R3**	OAR	**S1**	**S2**	**S3**	OAR	**SB1**	**SB2**	**SB3**
1	47.02	46.95	46.95	46.95	46.68	46.53	46.54	46.55	49.61	46.86	49.09	49.57	46.40	0.00	0.00	40.87
2	48.27	48.09	48.20	48.23	47.85	47.65	47.76	47.77	47.60	46.84	47.34	47.57	55.36	0.00	51.99	52.01
3	46.10	45.75	45.87	45.87	45.86	45.72	45.81	45.83	45.40	45.00	45.14	45.24	45.84	0.00	0.00	43.72
4	52.18	51.28	51.70	51.90	48.70	47.17	47.91	48.07	50.90	0.00	48.48	50.56	49.58	0.00	0.00	20.25
5	44.87	44.58	44.71	44.78	44.55	44.43	44.50	44.52	44.84	44.56	44.70	44.81	45.39	44.95	45.05	45.15
6	48.03	46.67	46.88	46.88	57.73	54.36	54.94	54.96	50.02	49.15	49.21	49.22	49.48	44.13	48.55	48.80
7	45.24	45.20	45.22	45.22	44.58	44.45	44.52	44.56	50.31	45.12	49.94	50.20	51.71	46.76	50.93	51.12
8	46.47	46.36	46.38	46.38	45.96	45.77	45.81	45.81	45.72	0.00	45.61	45.65	46.14	0.00	0.00	0.00
9	46.24	45.61	46.07	46.13	46.53	45.90	46.38	46.51	51.22	47.96	50.72	50.89	58.48	0.00	0.00	45.64
10					44.97	44.52	44.86	44.96	45.00	44.53	44.91	45.00	45.21	0.00	0.00	0.00

A paired t-test was used to compare the overall D_{2cc} doses with the localized doses in EQD2. The results of this analysis for the 12 groups are summarized in **Table 3**, which displays the mean, variance, and p-value for each test performed.

Table 3: Paired T-Test Results

H_0: μ = 0					α = 0.05											
	Bladder				Rectum				Sigmoid				Small Bowel			
	OAR	B1	B2	B3	OAR	R1	R2	R3	OAR	S1	S2	S3	OAR	SB1	SB2	SB3
Avg Difference		0.44	0.27	0.23		0.69	0.44	0.39		1.75	0.55	0.19		35.77	29.71	14.60
Mean	47.16	46.72	46.89	46.93	47.34	46.46	46.90	46.95	48.06	46.25	47.51	47.87	49.36	13.58	19.65	34.75
Variance	4.83	3.98	4.29	4.50	15.14	8.59	9.41	9.39	6.88	2.96	5.15	6.22	21.01	478.79	646.83	414.78
p		**0.01**	**0.03**	**0.04**		**0.03**	**0.07**	**0.09**		**0.01***	**0.02**	**0.02**		**3E-4**	**2E-3**	**0.02**

*Outliers omitted from analysis

5.2 BT Dose Influence Outside the HR-CTV

BT dose relative to the prescribed dose is shown in **Figure 13.** The data for the relative dose measured at distances of 1 cm, 2 cm, and 3 cm out from the HR-CTV is plotted in a box-and-whisker plot. Absolute dose values measure in Oncentra® Brachy can be found in Appendix B.

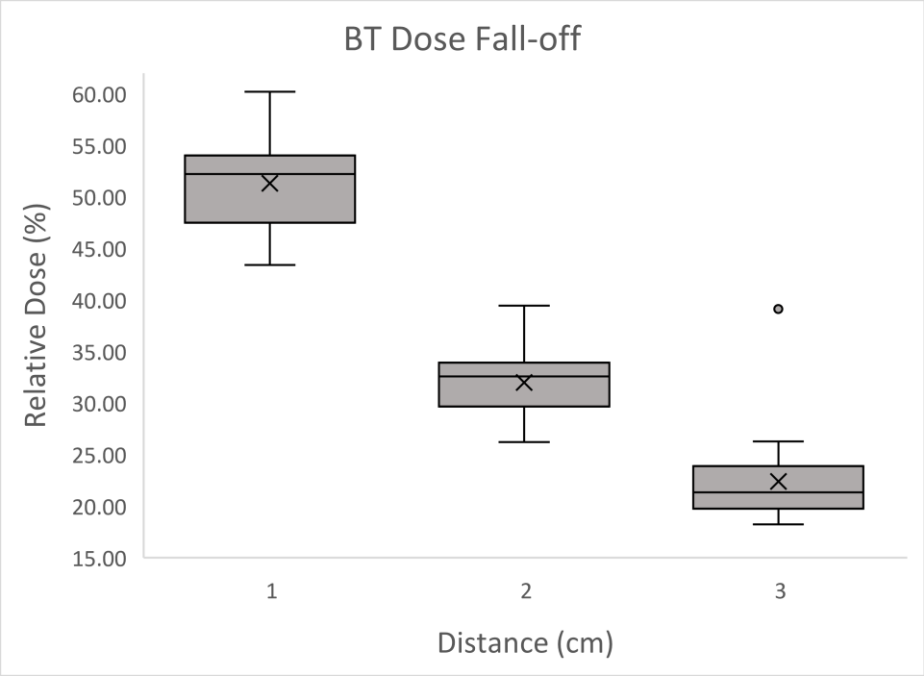

Figure 13 Dose relative to the prescribed dose (7 Gy) at distances of 1 cm, 2 cm and 3 cm from the HR-CTV.

6 Discussion

All localized EQD2 values measured for the bladder are less than the overall D_{2cc} obtained via in the EMBRACE protocol. The p-values resultant of the paired t-test (H_0: $\mu = 0$, $\alpha = 0$) are 0.01, 0.03, and 0.04 for the 1 cm, 2 cm, and 3 cm volume expansions, respectively (see **Table 3**). Statistical analysis shows that there is a significant difference between the doses as measured by the localized method compared to the D_{2cc} for the entire bladder used in the EMBRACE protocol.

For the rectum, however, statistical analysis does not yield significantly different results. A paired t-test for the overall D_{2cc} values and D_{2cc} measured in the volume of the rectum within 1 cm of the HR-CTV yields $p = 0.03$. However, dose measured to the rectum for distances greater than this, 2 cm and 3 cm, resulted in p-values of 0.07 and 0.09, respectively. This may be due the close proximity of the rectum to the mesorectal lymph node group contained in the "large pelvis" nodal CTV.[28] The rectum receives uniform dose from EBRT to this region and, therefore, statistically significant differences were not found between the two methods for measuring D_{2cc}. The bladder, on the other hand, lies anterior to the HR-CTV, with the superior portion of the bladder receiving higher dose as a result of EBRT nodal boosting compared the distal bladder.

Analysis of the variation in the absorbed dose data reveals two outliers in the dose measured within the 1 cm volume around the HR-CTV (see Appendix B). EBRT data for these patients shows the sigmoid to be absent within a 1 cm volume expansion around the HR-CTV. The figures below (**Figure 14**) show the variance in the data for the sigmoid with and without these outliers removed. As the results of the paired t-test are heavily influenced by the variance and mean of a sample, these data points were omitted in the

analysis to avoid erasure of any statistically significant difference in the data. As with the bladder, our findings show statistically different dose differences between D_{2cc} as defined by EMBRACE and D_{2cc} measured locally ($p = 0.1$, $p = 0.2$, $p = 0.2$).

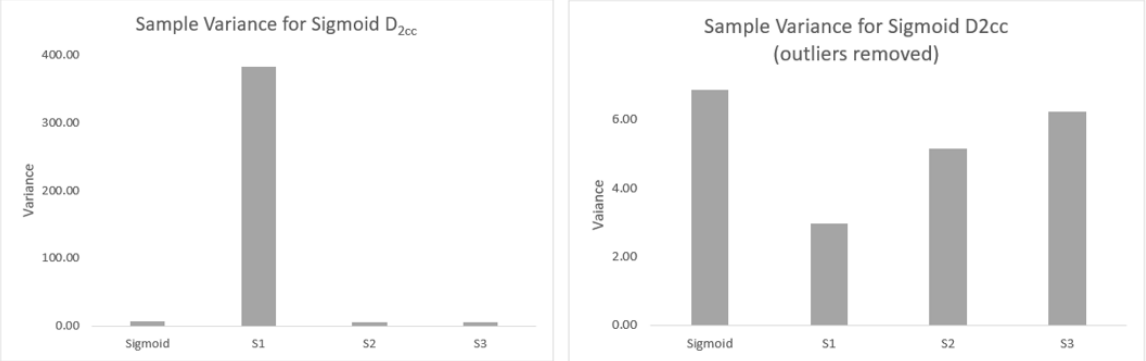

Figure 14 Sample variance of sigmoid data including the two outliers (left) and omitting the outliers (right). In these two measurements the sigmoid was not found within 1 cm of the HR-CTV.

Absorbed doses to the small bowel showed the statistically significant differences in dose measured at localized volumes around the HR-CTV compared to D_{2cc} for the small bowel ($p = 3E\text{-}4$, $p = 2E\text{-}3$, $p = 0.02$). A qualitative analysis of CT data showed that the position of the small bowel relative to the HR-CTV varies significantly among patients. As in the figure shown below, the small bowel was found to lie well outside the HR-CTV, partially included within the localized volume expansions, or have a significant portion of the small bowel situated near the HR-CTV.

This analysis is performed with the assumption that the small bowel remains static throughout the course of treatment, i.e., the same 2 cm^3 volume of tissue receives this absorbed dose. The limitations of this assumption are recognized in that the position of the small bowel actually varies due to peristalsis.

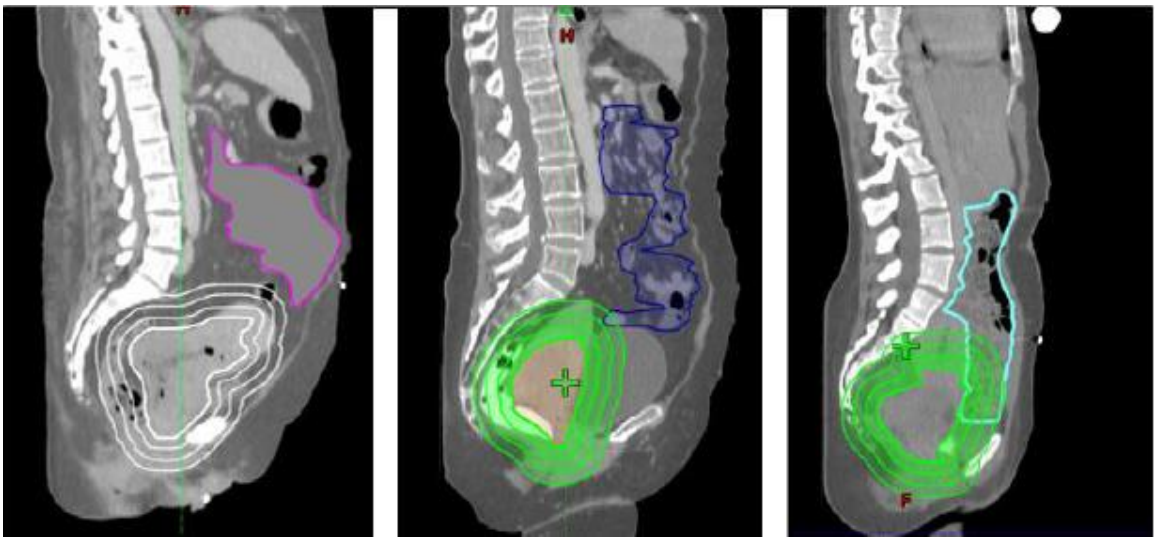

Figure 15 Position of the small bowel was found to vary between patients. In most cases, the small bowel was well outside BT influence (left) or partially within BT influence (middle). In few cases a large volume of the small bowel was found within HR-CTV (right).

Analysis of the BT dose distribution in Oncentra® using plan data reveals the dose to fall off to 51%, 32% and 22% at distances of 1 cm, 2 cm, and 3 cm, respectively. While the $1/r^2$ and $1/r$ approximations may not be appropriate estimates for the dose fall-off in hybrid BT, there is still a moderate drop-off in BT dose influence within the 1 cm, 2 cm, 3 cm volumes expansion around the HR-CTV, as seen in **Figure 13**. Normal tissue within 1 cm of the HR-CTV may receive 50% of the dose prescribed to the target volume edge, while the dose to tissue 3 cm away drops down to approximately 20% of the dose as prescribed to the boundary of the HR-CTV.

Recent studies have shown the location of D_{2cc} to OAR to vary significantly between patients treated with GYN EBRT and BT.[29] Special consideration of these hotspots during BT treatment planning may lead to the reduced development of treatment-related morbidities.

While BT treatment planning is mostly limited by dose to the bladder and rectum, this method for individualizing dose constraints may allow for more dose to be delivered

in situations where it would otherwise be limited by absorbed dose to the small bowel and sigmoid. Recognizing that D_{2cc} is higher in regions closer to the EBRT nodal CTVs and that BT influence, while limited, is present outside the HR-CTV, this study recommends dose constraints that be chosen based on the position of each OAR relative to the HR-CTV. In other words, D_{2cc} is determined by the closest intersection between the OAR and the volume expansion around the HR-CTV. These recommendations are summarized in the table below.

Table 4: Localization of D_{2cc} Based on OAR proximity to HR-CTV

Minimum distance to HR-CTV	1 cm	2 cm	3 cm
Volume expansion around HR-CTV in which to measure D_{2cc}	1 cm^3	2 cm^3	3 cm^3

6.1 Limitations

It should be noted that this study is limited by its small subject size. Data was obtained from patients that did not receive GYN BT in true accordance with the EMBRACE protocol, as BT planning was performed using CT data. Compared with MRI-based planning, CT contours may overestimate the volume of the HR-CTV by as much as 25%-30%.[30]

Absorbed doses to the small bowel were measured with the assumption that the positions of these organs do not change over the course of treatment. A true measure of D_{2cc} to the small bowel would reveal dose degradation as a result of internal motion and, therefore, this assumption does not significantly alter the results of this study.

6.2 Future Work

The field of GYN BT is continuously evolving. With the implementation of MRI-based planning, the definitions of target volumes and dose constraints in the planning aims for treatment of locally advanced cervix cancer are ever-improving. Significant results are anticipated for the expansion of this study to include a larger number of patients using MRI-based contours to localize absorbed dose constraints. In addition, it would be prudent to examine what defines a clinically significant difference in absorbed dose and whether other OAR, e.g., the large bowel, should be considered when implementing the EMBRACE protocol.

7 Summary & Conclusion

The systems by which these limits are defined has evolved over time, most recently with the implementation of 3D imaging in treatment planning and the transition from the use of point doses to D_{2cc}. This study recommends a localized method for determining the OAR dose limits as an alternative to the "worst-case scenario" method used in the EMBRACE protocol. In addition, a qualitative analysis of the OAR for each patient recommended for special cases where organs may lie outside of BT influence.

This method of identifying hotspots within localized volumes around the HR-CTV may be implemented to set patient-specific dose limits to be used in BT boost planning following pelvic and nodal EBRT. An analysis of the BT influence to each OAR within the immediate vicinity of the HR-CTV is useful in determining the dose constraints.

Understanding normal tissue dose limits is key to improving clinical outcome of the combined use of BT and EBRT in treating patients with locally advanced cervical cancer. Given that biological outcome of radiation treatment varies significantly between treatment different regimens, the introduction of dose constraints as defined in EMBRACE is of high importance maintaining patient QoL in avoiding treatment-related morbidities to the OAR in GYN EBRT and BT: bladder, rectum, sigmoid and small bowel. This analysis is step further in tailoring each BT treatment specific to the anatomy of individual patients using EBRT data.

Appendix A: Derivation of BED

The effect (E), or radiation cell kill, for a single dose D is

$E = \alpha D + \beta D^2$.

Studies have shown that each fraction delivered in a treatment series is equally effective.[13] If the total dose (D) is delivered in n fractions, the biologic effect can be rewritten as

$$E = n(\alpha d + \beta d^2)$$

where α and β are the radiosensitivity coefficients of the LQ model, d is the dose per fraction and D = nd.

Consider the case in which d approaches zero. Then $\beta d^2 << \alpha d$, since $d^2 << d$ and $\alpha/\beta > 1$. For d << 1,

$$E \approx n\alpha d = \alpha D$$

This approximation suggests that, at low dose per fraction, the dose required to obtain a specific effect E is the total dose D. Biologically effective dose (BED) is defined such that

$$BED = D = \frac{E}{\alpha}$$

$$BED = \frac{n(\alpha d + \beta d^2)}{\alpha}$$

$$BED = \frac{nd(\alpha + \beta d)}{\alpha}$$

$$\mathrm{BED} = \mathrm{nd}\left(1 + \frac{\mathrm{d}}{\alpha/\beta}\right)$$

BED is the measure of the true biological dose required to produce a given biologic effect if the total dose (D) is delivered in infinitely small doses (d) per fraction for a given α/β ratio.

For an HDR BT fractionated treatment, the BED must be corrected for tumor proliferation by the daily repopulation rate, K:

$$\mathrm{BED} = \mathrm{nd}\left(1 + \frac{\mathrm{d}}{\alpha/\beta}\right) - KT$$

where $K = \frac{0.693}{\alpha T_{pot}}$, T_{pot} is the potential doubling time and T is the overall treatment time.

Appendix B: Data

Table 5: Absolute D_{2cc} (Gy) for EBRT Dose Delivered Prior to BT																
ID	**Bladder**				**Rectum**				**Sigmoid**				**Small Bowel**			
	OAR	**B1**	**B2**	**B3**	OAR	**R1**	**R2**	**R3**	OAR	**S1**	**S2**	**S3**	OAR	**SB1**	**SB2**	**SB3**
1	47.84	47.79	47.79	47.80	47.59	47.48	47.49	47.50	49.72	47.73	49.35	49.69	47.39	0.00	0.00	43.22
2	48.76	48.62	48.70	48.73	48.45	48.31	48.39	48.39	48.27	47.71	48.08	48.25	53.75	0.00	51.41	51.43
3	47.17	46.91	47.00	47.00	46.99	46.89	46.96	46.97	46.65	46.35	46.46	46.53	46.97	0.00	0.00	45.39
4	51.55	50.91	51.20	51.35	49.07	47.96	48.50	48.61	50.64	0.00	48.91	50.40	49.70	0.00	0.00	25.25
5	46.26	46.04	46.14	46.19	46.02	45.92	45.98	45.99	46.23	46.03	46.13	46.21	46.65	46.32	46.39	46.46
6	48.58	47.59	47.74	47.75	55.36	53.06	53.46	53.47	50.02	49.39	49.44	49.44	49.63	45.70	48.96	49.14
7	46.53	46.50	46.52	46.52	46.04	45.94	46.00	46.03	50.22	46.44	49.95	50.15	51.21	47.66	50.66	50.79
8	47.44	47.36	47.38	47.38	47.07	46.92	46.95	46.95	46.89	0.00	46.81	46.83	47.20	0.00	0.00	0.00
9	47.27	46.80	47.15	47.19	47.48	47.02	47.38	47.47	50.87	48.53	50.51	50.63	55.86	0.00	0.00	46.83
10					46.33	46.00	46.25	46.33	46.35	46.00	46.29	46.35	46.51	0.00	0.00	0.00

Table 6: Absolute Dose (cGy) for BT Planned Dose Around HR-CTV			
ID	**1 cm**	**2 cm**	**3 cm**
1	368.26	229.41	147.82
	351.70	230.92	138.36
	375.42	196.66	136.13
	376.65	241.03	134.21
	332.47	262.76	132.69
	383.21	210.16	146.08
	323.85	219.74	145.77
	366.28	218.14	148.03
	421.41	203.86	138.27
	327.31	192.07	147.31
3	390.03	231.92	166.67
	397.03	237.88	161.20
	396.21	228.00	184.05
	357.71	234.23	163.90
	332.18	235.24	168.94
	380.23	236.25	146.65
	370.21	213.72	171.29
	349.86	276.21	273.75
	364.75	237.38	160.09
	377.27	220.34	169.50
7	347.80	208.86	128.27
	367.96	211.28	127.62
	325.19	183.60	165.15
	303.71	200.28	162.22
	389.37	195.31	168.42
	348.75	246.38	171.77
	367.12	250.62	164.57
	346.05	247.62	135.21
	319.10	227.93	146.56
	314.51	188.35	150.73

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