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Dose Summation Strategies for External Beam Radiation Therapy and Brachytherapy in Gynecologic Malignancy: A Review from the NRG Oncology and NCTN Medical Physics Subcommittees

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Abstract

Definitive, nonsurgical management of gynecologic malignancies involves external beam radiation therapy (EBRT) and/or brachytherapy (BT). Summation of the cumulative dose is critical to assess the total biologic effective dose to targets and organs at risk. Cumulative dose calculation from EBRT and BT can be performed with or without image registration (IR) and biologic dose summation. Among these dose summation strategies, linear addition of dose-volume histogram (DVH) parameters without IR is the global standard for composite dose reporting. This approach stems from an era without image guidance and simple external beam and brachytherapy treatment approaches. With technological advances, EBRT and high-dose-rate BT have evolved to allow for volume-based treatment planning and delivery. Modern conformal therapeutic radiation involves volumetric or intensity modulated EBRT, capable of simultaneously treating multiple targets at different specified dose levels. Therefore, given the complexity of modern radiation treatment, the linear addition of DVH parameters from EBRT and high-dose-rate BT is challenging to represent the combined dose distribution. Deformable image registration (DIR) between EBRT and image guided brachytherapy (IGBT) data sets may provide a more nuanced calculation of multimodal dose accumulation. However, DIR is still nascent in this regard, and needs further development for accuracy and efficiency for clinical use. Biologic dose summation can combine physical dose maps from EBRT and each IGBT fraction, thereby generating a composite DVH from the biologic effective dose. However, accurate radiobiologic parameters are tissue-dependent and not well characterized. A combination of voxel-based DIR and biologic weighted dose maps may be the best approximation of dose accumulation but remains invalidated. The purpose of this report is to review dose summation strategies for EBRT and BT, including conventional equivalent dose in 2-Gy fractions dose summation without image registration, physical dose summation using 3-dimensional rigid IR and DIR, and biologic dose summation. We also provide general clinical workflows for IGBT with a focus on cervical cancer.

Introduction

Definitive, nonsurgical standard-of-care therapy for patients with gynecologic malignancies involves external beam radiation therapy (EBRT) and/or brachytherapy (BT).[1–3] For more than a century, BT was delivered via 2-dimensional low-dose rate (LDR) approaches with doses specified to an anatomic surrogate reference point (point A).[2] The composite total dose was calculated via summation of the physical dose from the EBRT and BT components when EBRT and LDR BT were delivered. Modern gynecologic BT practice embraces high-dose-rate (HDR) BT over LDR BT owing to improved dosimetric flexibility and delivery speed among others. Initial gynecologic HDR BT approaches simulated the historic 2-dimensional LDR BT treatments using orthogonal film-based point dosimetry.[1,4] However, in accordance with advances in delivery technologies, EBRT approaches shifted to volumetric modulated arc therapy (VMAT) and intensity modulated radiation therapy (IMRT) and 3-dimensional HDR image guided brachytherapy (IGBT) for cervical malignancies. The paradigm shift from point-to volume-based optimization is a landmark advancement in BT, and has greatly influenced clinical practice for the last decade.[5,6]

Composite dose summation strategies for VMAT/IMRT and IGBT plans are challenging because there is considerably more geometric, spatial, and dose heterogeneity than with point-based planning. Based on the linear-quadratic (LQ) model, biologic effective dose (BED) has long been used to report composite doses from multimodal treatments.[7–9] The radiobiologic effect of treatment depends on the radiation dose rate, fraction size, absorbed dose distribution, and treatment time (both overall treatment time [OTT] and interfraction time). BED derives a biologic weighted dose in a 2 Gy per fraction dose equivalent to either tumor or normal tissues (α/β = 10 for tumor, α/β = 3 for normal tissue, and T 1/2 = 1.5 hour for repair half time). Conversion from BED to the equivalent dose in 2 Gy per fraction (EQD2) is common. This quantity may be used to generate a crude composite dose inclusive of dose contributions from both EBRT and BT into a single metric.[10,11] The Groupe Européen de Curiethérapie-European Society for Radiotherapy and Oncology (GEC-ESTRO) and American Brachytherapy Society (ABS) have recommended that BED be used to generate composite dose for EBRT and each HDR BT fraction, and assume that EBRT dose distributions are homogenous.[10,12–16] This relatively simple approach is widely accepted for clinical use and frequently adopted for use in gynecologic clinical trials. However, the calculation of BED EQD2 does not account for OTT nor interfraction treatment time, and both have shown to negatively affect oncologic outcomes for cervical and uterine malignancies.[11] Additionally, the BED EQD2 calculation does not account for spatial and geometric variations in target and organ-at-risk (OAR) positioning during EBRT and BT delivery, interapplication variation, applicator displacement, and dose heterogeneity.[11,17–19] Notably, spatial and geometric dose-volume histogram (DVH) assessment of composite DVH using BED EQD2 via commercial treatment planning systems are of limited clinical utility.[20,21]

Herein, we summarize modern IGBT approaches with a focus on cervical cancer, and provide examples of various IGBT clinical workflows. We review the literature and strategies to calculate cumulative radiation doses from EBRT and BT in gynecologic cancers, including conventional BED EQD2 dose summation without image registration, physical dose summation using 3-dimensional rigid and deformable image registrations (DIR), and biologic dose summation. Based on these strategies, treatment recommendations are provided for both broad clinical practice and standardized use in clinical trials using multimodal radiation therapy treatment for accurate cumulative dose reporting in the treatment of gynecologic malignancies.

IGBT in Cervical Cancer

Shift from point-based dosimetry to volume-based prescription and optimization

With improved imaging technology, the utilization of IGBT has evolved in recent decades.[21,22] Volumetric imaging data (computed tomography [CT] or magnetic resonance imaging [MRI]) improved both radiation target and OAR delineation and facilitated volume-based planning and dose tracking.[23] As a result, clinical outcomes using IGBT have improved compared with therapy that relied on treatment plans using point-based dosimetry and 2-dimensional orthogonal films.[24] Pulsed dose rate (PDR) BT allows for combined benefits of the radiobiologic advantage of LDR and 3-dimensional volume-based dose

optimization in HDR. However, PDR BT use has been adopted on a limited basis in the United States and is decreasing worldwide.[25] Thus, in the present review, IGBT refers to 3-dimensional image-based HDR BT.

CT image−based brachytherapy

Three-dimensional CT imaging is widely used for BT and enhances the visualization of both the tumor and OARs. Multiple studies report uncorrelated HDR BT dosimetry at the conventional point A and International Commission on Radiation Unit (ICRU) points when treatments are delivered based on plans considering 2-dimensional planar film images versus 3-dimensional CT image−based volumetric studies.[24,26–28] Additionally, the use of 3-dimensional CT image−based HDR BT has demonstrated a significant reduction in gastrointestinal and genitourinary toxicities compared with 2-dimensional film-based HDR BT.[24,29,30]

MRI-based brachytherapy

MRI is considered the gold-standard imaging modality for gynecologic malignancies, and provides superior soft-tissue resolution compared with CT. This enhanced visualization improves target and OAR delineation and facilitates simultaneous tumor dose escalation and OAR avoidance with HDR BT treatments.[5,6,23] MRI use for every HDR BT fraction has been considered an ideal approach for cervical cancer.[10,14,23,31–33]

CT-based HDR BT is widely used in the United States, but MRI-based HDR BT is used less frequently.[5,34,35] Repetitive MRI scans during the course of BT is commonly performed in Europe.[35] MRI utilization for HDR BT is increasing in North America and in other countries over time, but widespread implementation has been hindered by challenges in workflow logistics (eg, MRI access, shared imaging resource), coordinating multidisciplinary efforts (scheduling), cost, increased labor demand, and longer procedure times (inefficiency).[5,34–39] To minimize the operational burden of MRI-based HDR BT, the efficacy of combined MRI and CT imaging (eg, MRI at first fraction and CT imaging for subsequent fractions) has been shown to be effective for relatively simple applications and small tumor volumes.[34]

IGBT clinical workflow

Various clinical approaches in IGBT have been used based on the unique availability of resources and clinical workflow for any given center (Table 1). Clinical IGBT scenarios are described below.

CT-based IGBT imaging approach

CT images are used for the delineation of targets and OAR structures and treatment planning. The NRG Oncology group has published CT-based contouring guidelines along with an online CT and MRI contouring training atlas.[40] This is the most common approach for IGBT in current clinical practice in North America.[36,37]

CT-based IGBT with MRI-informed imaging approach

CT images are used as the primary image data set for BT planning and target/OAR delineation. Preimplantation or diagnostic MRI scans can be used to assess target contours on BT planning CT image sets. If the preimplant MRI scans are registered to the CT images with the applicator in situ acquired during the course of treatment, caution should be taken due to potential deformations and anatomic variations with and without the presence of the BT applicator. DIR can be applied in this scenario; however, DIR is not yet robust enough for routine registration performance between image sets with and without the presence of the BT applicator.[11]

MRI/CI combined IGBT imaging approach

CT images are used as the primary image set for treatment planning. For each BT fraction (BT1, BT2...BTx), CT and MRI scans are acquired after implantation with the applicator in situ. Rigid, gray-level registration is performed between CT and MRI data sets using the BT applicator to drive the registration. MRI is used as the secondary data set for delineation of target, and CT images are used for applicator reconstruction and OAR contouring. If obtaining an MRI scan for each BT fraction is not feasible, then obtaining a postimplantation MRI for (at least) BT1 is recommended. For the remaining BT fractions, CT images can be used for planning with target contours transferred (or adapted) from the BT1.

MR guided IGBT imaging approach

MRI with the applicator in situ is used as the primary image set for planning and target/OAR delineation for each BT fraction. This approach represents the optimal, recommended clinical practice for gynecologic BT when feasible. Postimplantation CT images may be obtained as a secondary image data set for improved applicator reconstruction accuracy and definition of the most distal dwell position.

Dose Summation Approaches

Conventional dose summation approach

Dose reporting with reference points: Classic 2-dimensional image-based plan—Calculation of the absorbed dose at point A has been used to reproduce dose prescribing and reporting based on orthogonal x-ray radiographs for cervical cancer brachytherapy since 1938. Originally, BT was planned based on 2-dimensional radiographs using LDR sources. Point A is defined relative to the geometry of a cervical applicator (eg, tandem and ovoids or tandem and ring), and serves as a surrogate of the tumor and paracervical triangle, where the ureter crosses posterior to the uterine artery.[41] Although merely a tumor-adjacent anatomic surrogate, point A has been widely used in global clinical practice due to decades worth of data using point A as an effective point of calculation and dose-reporting metric.[4,41] The ICRU 38 report recommended tracking and reporting dose to the bladder (ICRU bladder point) and rectum (ICRU rectal point) using 2-dimensional orthogonal radiographs. The ICRU bladder and rectal points are still part of routine clinically reported values. The composite dose was reported for reference points

(Point A, ICRU rectum, ICRU bladder) and calculated via physical dose summation from the EBRT and LDR BT. After shifting to HDR BT from LDR BT, 2-dimensional x-ray film-based plans still have been widely used, and the standard total dose reporting remained based on reference points (eg, point A, ICRU points).

Dose reporting with reference volume: Isodose surface volume—The ICRU 38 report also introduced a 60-Gy reference volume concept (60 Gy isodose encompassing the volume) to report the total absorbed dose with BT or a combination of EBRT and BT based on the classic LDR intracavitary brachytherapy dose prescriptions for cervical cancer.[41] ICRU 38 described the pear-shaped 60 Gy isodose surface as a reference volume to be reported based on the dimensions of the width, thickness, and height of the volume. When EBRT and LDR BT dose were combined, the 60-Gy composite dose volume was recommended. The 60-Gy reference volume is now used in the intermediate-risk clinical target volume structure in HDR brachytherapy.[11,14]

DVH parameter addition: Current 3-dimensional IGBT consensus—Reporting of composite DVH parameters for 3-dimensional IGBT were initially established and recommended by the GEC-ESTRO gynecology working group and ABS.[10–12] The suggested parameters include $D2cm^3$ and $D0.1cm^3$ (maximum to most exposed 2 cm^3 and 0.1 cm^3 volume of normal tissue) for OARs (eg, bladder, rectum, sigmoid, and small bowel), and D90% and D98% (dose received by at least 90% and 98% of the volume) for target volumes (eg, high- and intermediate-risk clinical target volumes [CTVs]). Point A and ICRU normal tissue structure point doses remain part of the suggested reporting metrics.[11]

To calculate the composite BED and EQD2 from EBRT combined with HDR BT using the LQ model, the ABS and GEC-ESTRO currently recommend using the worksheets located at http://www.americanbrachytherapy.org/resources/for-professionals/physics-corner.[12] In the worksheet, the total dose is calculated via linear EQD2 summation from EBRT and from each HDR BT fraction. Current expert consensus for EBRT and HDR BT dose summation strategies is linear DVH parameter addition without image registration. In current practice and consensus for reporting, the total absorbed dose of 45 Gy EBRT delivered using 1.8 Gy fractions corresponds to a homogeneous EQD2 of 43.2 Gy for OARs ($\alpha/\beta = 3$ Gy) and 44.3 Gy for the tumor ($\alpha/\beta = 10$ Gy). Each fraction physical dose of HDR BT is converted to EQD2 using the same LQ formula for tumors and OARs and summated with the uniform EBRT EQD2 dose. Linear parameter addition can be a good approximation of D2cc for OARs without EBRT boost dose to the region where BT is delivered. The linear summation of doses relies on 2 assumptions: Pelvic EBRT dose distributions are uniform and delivered at a single dose level, and each BT implantation yields reproducible spatial, geometric, and dosimetric hotspots for OARs.[10,11] These assumptions may not be valid based on the following.

Challenges with static spatial dose summation of EBRT and BT: When the EBRT plan does not include a boost (eg, pelvic lymph nodal boost, parametrial boost, para-aortic boost), DVH parameter addition can be a good approximation for the total dose reporting of EBRT and BT.[42,43] When EBRT is delivered using highly modulated VMAT/IMRT to multiple targets (simultaneous integrated boost [SIB]) and/or includes boosts, pelvis dose

distributions from these plans are highly conformal to multiple targets and often result in nonuniform (heterogeneous) dose. As such, linear dose summation assuming uniformity may not be valid. This is especially true when regions containing high dose gradients from EBRT intersect with a high-dose HDR BT region or when the dose contributed by a sequential EBRT boost must be considered.[42,44,45]

Interapplication variation and applicator displacements in BT—In clinical situations in which multiple BT insertions are performed, variations in organ deformation and displacement may exist. OAR volume and dose, as well as spatial distribution of the high dose volume (ie, 0.1cc and 2 cc) may vary widely interfractionally depending on relative bladder filling, bowel gas, applicator position, uterine wall thickness, and vaginal packing. Thus, performing DVH parameter addition of EBRT and BT is challenging.[42,46] Intrafraction variations during EBRT and BT treatments may also exist, but these variations have not been fully investigated.[21,22] Also, applicator displacements may occur within the window of clinical application of 1 HDR BT fraction due to patient transfers and patient motion after applicator implantation, imaging, and treatment delivery. Multiple studies have demonstrated that intrafraction, interfraction, and interapplication variations can affect the delivered absorbed dose on the order of 10% for targets and 20% for OARs, respectively.[43,46,47–51]

Current treatment planning systems have limitations in calculating cumulative dose distributions and deriving a composite DVH from EBRT and BT plans in EQD2.[44] To estimate the total EQD2 dose for treated volumes via voxel-by-voxel contributions from EBRT and each fraction of BT, accurate image and dose registrations are required. These calculations may be performed using commercially available software, such as VelocityAI (Varian Medical Systems, Palo Alto, CA), MIM Maestro (MIM Software Inc, Cleveland, OH), RTx (Mirada Medical Ltd, Oxford, UK), and RayStation (RaySearch Laboratories, Stockholm, Sweden), although the utility of image registration for multimodality image DIR or EBRT + BT hybrid treatment is still in the research phase.[11]

Image registration−based dose summation approaches

Three-dimensional rigid image registration—Image registration (IR) is an important step in calculating cumulative doses from different plans created based on multiple image data sets. Rigid image registration (RIR) is a simple approach based on anatomic correspondence (typically gray-level) that allows for relatively precise positioning of ≥2 different image sets by 3-dimensionally shifting and/or rotating images relative to a reference image.[46,52,53] However, RIR between the EBRT plan and fractional BT plans is not accurate due to soft-tissue deformation in BT images caused by applicator implantation that is not recapitulated in EBRT image data sets.[54,55] Therefore, RIR using the bony anatomy as the reference may not be optimal due to organ positional changes, organ volume change, and complex organ deformation. The impact of registration errors on DVH parameters of the target volume and OARs can be significant and lead to inaccurate cumulative dose calculations for EBRT and BT.

For IR between sequential BT fractions, RIR can be applied using the BT applicator as the reference because tumor and OARs are located with respect to the applicator.[11,53] The first BT fraction is set as the primary image, and the subsequent fractions are registered as secondary image sets via RIR using the applicator-to-applicator alignment for the BT dose accumulation. However, several studies have reported that RIR was limited given the inaccuracies of the BT dose summation due to changes in OARs between BT fractions.[56,57] In this regard, DIR is more suitable for dose summation than RIR use. When the total dose to pathologic pelvic lymph nodes needs to be assessed, BT dose contribution to the lymph nodes can be estimated using RIR on bony anatomy between EBRT and BT images.[58–60]

Three-dimensional DIR

The use of DIR is to establish spatial correspondence between different image sets and account for anatomic variations between EBRT and BT and/or between BT fractions[61] so that the dose in each tissue voxel from each fraction can be tracked. DIR tools and commercial software have become widely available, and several studies have compared dose accumulation of EBRT and BT to OARs between DIR and DVH parameter addition.[44,62–64]

Hayashi et al. performed dose accumulation of EBRT and BT to the rectum using the Velocity AI software.[62] DVH parameter addition was found to overestimate D_{2cc}, D_{1cc}, and $D_{0.1cc}$ to the rectum compared with DIR addition. Differences between the 2 methods tended to be larger for smaller DVH volume parameters, indicating that D_{2cc} is more reliable when DVH parameter addition is used. Kim et al. reported that dose summation of EBRT and BT using DIR via Velocity AI was consistently higher than the DVH parameter adding, particularly when SIBs were given during the EBRT course.[63] Teo et al. evaluated accumulated D_{2cc} of EBRT and BT to both the bladder and the rectum using MIM Maestro software, and no significant difference between DIR and parameter addition was found.[44] Abe et al. demonstrated that the cumulative D_{2cc} doses of the bladder, rectum, and high-risk CTV D90 were not significantly different between DIR and DVH parameter addition using MIM Maestro, noting that the results from DIR use were smaller than those for DVH parameter addition.[64] Also, larger differences would be expected if midline blocks (an EBRT boost) or intensity modulation techniques were used.[44,63,64]

In addition to dose accumulation of EBRT and BT, a few studies reported BT dose summation from all BT fractions using DIR compared with DVH parameter addition for OARs.[46,65–67] RIR using the applicator-to-applicator alignment between BT fractions (first fraction BT as the reference/primary image set) was performed and visually assessed. After RIR, DIR was applied for subsequent BT fractions for contour matching and dose mapping to the first BT fraction (reference image set). In these studies, changes in bladder filling and gas in the rectum between BT fractions affected D0.1cc, D2cc, and D5cc for OARs. Andersen et al.[46] and Flower et al.[65] reported that D2cc for the bladder and rectum was a stable parameter to estimate the accumulated dose and comparable with the DVH parameter addition, but others reported the statistical difference in doses for OARs between DIR and DVH parameter addition because different DIR algorithms vary in performance.[68] When intensity-based DIR algorithms are used, the results may vary depending on the anatomic site due to the change in image intensity distribution. Artificially

bias registrations may occur in regions that contain high local image intensity dissimilarity owing to differences in bladder and rectum fillings or the position of critical organs by the applicator displacement, leading to inaccuracies. This effect is observed with DIR when objects of starkly dissimilar image intensity reside in close anatomic proximity (eg, bladder Foley balloon, radiographic contrast, air pockets). Generally, DIR algorithms balance metrics that describe image similarity and regularization to drive the registration process. The presence of these objects is of no clinical consequence with respect to clinical dose analysis and to mitigate their effect of DIR, voxels within the structures they reside should be overridden to a high-intensity value. Doing so eliminates the differences and increases the contrast between OARs and surrounding tissues, resulting in an increase in the overall accuracy of DIR in these areas.[45,62] Intensity-based DIR algorithms have also been shown to be inaccurate when the margin of segmentation is not well defined or when the dissimilarity of images is so great that registration is implausible (eg, tissue erosion, wildly varying applicator geometry or type, significant differences in organ filling or position).[69] To improve DIR performance accuracy, structure-based DIR algorithms have been suggested. Multiple studies have demonstrated that structure-based DIR performs better than intensity-based DIR for hollow organs, such as the bladder and rectum.[70–72] Further evaluation of deformation errors for tumor and nonhollow organs remains to be explored.

DIR using a hybrid algorithm combining organ contour, intensity, and biomechanical models may outperform intensity or point-based deformations for the accumulation of BT dose in the pelvis where highly deformable organs are present in high-dose gradients.[46,61,73] For example, Dyer et al.[74] used commercially available DIR algorithms ANACONDA and MORFEUS (RayStation Treatment Planning System; RaySearch Laboratories, Stockholm, Sweden) with a hybrid approach to evaluate MRI-to-CT image deformation accuracy. Preimplantation MRI-defined gross tumor volume and targets (CTVs) can be propagated to the postimplantation CT image set and cervix structure used to control the region of interest for deformation. The anatomically constrained deformation algorithm (ANACONDA) provides a hybrid approach for image registration considering both image intensity and anatomic information. The bio-mechanical, model-based, finite-element, deformation algorithm (MORFEUS) drives image deformation based on interface conditions of the defined controlling region(s) of interest. The authors also explored the clinical utility of deformation for locally advanced cervical BT and modes of deformation failure.[74] To do so, the pre-BT MRI (without applicator[s]) was registered to the postimplantation CT images for BT planning (applicator in situ) using a cervix-controlling region of interest. Quantitative evaluation of deformation performance was conducted using the Dice index, distance to agreement, center-of-mass differences, cervical/uterus volume, and geometric change in organ position for MRI-projected structures. The authors demonstrated the association with clinical utility scores using image data sets to quantify a metric to predict the clinical benefit of MRI-to-CT deformation.

Of note, the degree of DIR accuracy for deformed contours is not necessarily correlated to dose warping/deformation accuracy. Therefore, multiple validation methods for different algorithms or different software packages are required.[68] An automated tool, such as AUTODIRECT, has shown utility in testing the performance of DIR software by estimating the uncertainty of deformed dose distributions.[75]

Currently, clinical use of DIR is limited, and there is no standard recommendation for DIR use in BT. Although the dice similarity coefficient and surface distance error are commonly used metrics to quantify DIR performance accuracy, relatively high variations of dice similarity coefficient or surface distance error have been reported depending on the algorithms investigated.[68–70] Further validations are needed to apply DIR for clinical use in dose accumulation of EBRT and BT.[73,76,77]

Biologic dose summation

BED is commonly used for iso-effective dose calculations and is a measure of the true biologic dose delivered by a combination of dose per fraction and total dose to a tissue characterized by a specific α/β ratio and the treatment modality.[9–11,78] The calculation of biologic tissue effects depend on chosen tissue parameters for irradiated targets, surrounding normal tissues, irradiation volume, dose delivered, dose distribution, dose rate, fractionation, OTT, and interfraction treatment time.[7–9] The concepts of equivalent uniform dose (EUD) can be used to include the biologic effects of fractionation when DVH is assessed. EUD is expressed as a single metric, assuming any nonuniform dose distributions are equivalent if they result in the same radiobiologic effect.[79] A generalized EUD can be applied using a tissue-specific value input parameter for each tissue in the irradiated field. Another concept, equivalent uniform biologic effective dose, is a combination of EUD and BED, providing a step that reduces dose distributions to an equivalent uniform dose in a particular fraction size, allowing for plan comparison using different fraction sizes.[79,80]

Equivalent uniform biologic effective dose and generalized EUD can quantify voxel-level BED, considering dose heterogeneity from EBRT and each HDR BT fraction. When EBRT and BT dose distributions are combined, both must be represented by the biologic dose, and each tissue-volume element from EBRT should match the same tissue-volume element in BT, requiring complex image registrations and validated calculation software that is currently limited in scope for clinical use.[81,82] Van de Kamer et al.[81] computed 3-dimensional biologic dose summation (BED and EQD2) voxel by voxel for EBRT and BT dose distributions, and compared the results to DVH parameter addition. Without an EBRT boost, 3-dimensional biologic dose summation was not significantly different from the results based on DVH parameter addition. However, other studies demonstrated that 3-dimensional radiobiologic dose summation was noticeably different from the DVH parameter addition.[82,83]

There are some limitations in using BED for dose summation. First, an accurate α/β ratio for each type of tissue is not yet known. The extraction of clinically relevant α/β ratio data for either tumor or normal tissue requires comparison of various fraction sizes for each target tissue, which are difficult to obtain in clinical practice. Moreover, different α/β values result in relatively large differences in EQD2. In practice, the α/β and $T_{1/2}$ values that are most often used in LQ models are 10 Gy and 1 hour for early effects (tumor) and 3 Gy and 1.5 hour for late effects (normal tissue), respectively.[10,11] Even though these values represent the best estimate and expert consensus, tumor and normal tissue repair and dose rate effect have not been fully explored, and the derived values are debated.[11] Second, the linear quadratic model is inaccurate when fractional doses are >6 Gy. When HDR BT doses

>6 Gy per fraction are applied, EQD2 calculations based on the current LQ model can cause large uncertainties.[84] Third, the current EQD2 model might be too simplistic using a mono-exponential recovery model and not account for tumor cell repopulation.[85] For that reason, ICRU 89 recommends that the total absorbed dose, dose distribution, dose rate, time between fractions, and fraction sizes be reported in Gy without biologic correction, allowing for the recalculation of EQD2 when new radiobiologic data become available.[11] Biologic dose summation approaches remain in the research phase and are currently limited in scope for clinical use.

Discussion and Conclusions

We reviewed dose summation strategies for EBRT and BT, mainly focusing on cervical cancer treatment because clinical outcome data, guidelines, and clinical acceptance of IGBT for cervical cancer have been relatively higher than those of other gynecologic cancers.[21–23,30–33,36] Repetitive imaging is important to monitor tumor response during the course of BT and account for changes in the position of OARs and tumor volume reduction. MRI use for planning is considered the most accurate tool for tumor and OAR assessment during the BT treatment course. Obtaining an MRI with applicator in situ, at least for the first fraction, is recommended to improve subsequent CT-MRI image registrations and overcome soft tissue deformations caused by applicator implantation. Table 1 summarizes clinical scenarios for BT use.

Table 2 describes dose summation strategies. Each approach has distinct advantages and disadvantages. Linear DVH parameter addition without image registration strategy has been clinically validated, with accumulated dosimetric parameters correlated to clinical outcomes. However, due to highly conformal EBRT plans with interfractional BT changes, linear EQD2 summation may be challenging to assess accurate composite dose using any EBRT sequential boost or pelvic lymph node boost or SIB. Of note, the dose summation uncertainties are relatively larger for intermediate total dose levels of V50 Gy and V30 Gy (representing the gradient of both modalities, EBRT and HDR BT) than the high-dose area, D2cc, for OARs.

Using the image registration for dose summation, RIR using the bony anatomy between an EBRT plan and BT fractions is strongly discouraged due to soft tissue deformation in BT images caused by the applicator that is not recapitulated in EBRT image data sets. The impact of registration errors on DVH parameters of the target volume and OARs can be significant, resulting in inaccurate cumulative dose calculations for EBRT and BT. However, when HDR BT doses delivered to the pelvic lymph nodes are assessed, bony anatomy-based image fusion can be reasonable between EBRT plan and BT fractions.

DIR is considered potentially more accurate than RIR when modulated EBRT is delivered, multiple dose levels are used (eg, SIB), or a sequential boost or midline block are used.[44,63,64] However, the choice of DIR algorithm may affect dose summation results, possibly adding large uncertainties from relatively large pelvic organ deformation for complex dose warping with multiple image registrations.[68] ICRU-89 states that “adding EBRT and BT without deformation is a good approximation, as DIR algorithms may

cause additional uncertainties."[11] As such, the use of DIR must be undertaken as part of a clinical trial to better understand the benefits and pitfalls of its use for dose accumulation. Visual inspection is often used to assess deformation performance in contour or dose warping.[86,87] However, this approach is infrequently reproducible, has high interobserver variation, and greatly depends on the ability to predict organ and dose deformation/misalignment due to variation in spatial and geometric positioning. Also, there is a lack of efficient evaluation tools or consensus to quantify DIR accuracy.[68,86,87] Due to this complexity, DIR requires validation and comprehensive quality assurances before clinical use, as recommended in American Association of Physicists in Medicine Task Group 132.[54] Clinical trials for gynecologic cancers that adopt DIR should involve a credentialing process and provide explicit procedures for cumulative dose reporting for point- and volume-directed approaches.[88] Current dose-volume constraints in IGBT have been established on conventional linear dose summations that are derived from prospective clinical data. Thus, DIR is promising and likely to be the future of adaptive radiation therapy, but cannot be applied in conjunction with current IGBT dose planning protocols. Therefore, a priority of this research is to advance dose summation in IGBT with modern DIR techniques by establishing standardized protocols that can be implemented in clinical trials to collect prospective clinical data.[88]

Biologic parameters, such as α, β, α/β, and m, are not well known, and biologic dose summation has limitations.[11] The use of lookup tables containing clinical ranges of biologic parameters and dose delivery parameters will help address parameter variability.[89]

Correction factors, such as biologic effects due to dose rate and time interval between EBRT and BT, should be included in BED calculations. Biologic dose summation from EBRT and BT needs complex image registrations and validated calculation software and compounds the uncertainties introduced by DIR that are currently limited in scope for clinical use. This is an active area of research and thus should only be explored on trial. Future clinical practice and trials are expected to move forward using a combination of voxel-based DIR and biologic weighted dose maps to accurately calculate and report comprehensive, composite, volumetric, biologic dose.

A summary of the recommendations for future clinical practice and trials is shown in Table 2. Understand the limitations of each dose summation approach is imperative, as are the recommendations in this article, before employing a given approach in clinical practice and trials.

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Table 1

Clinical imaging and planning scenarios for cervical cancer high-dose-rate BT

Designation	Primary planning image data set	Secondary imaging	Frequency of secondary imaging	Timing of secondary imaging	Primary method of prescribing dose	Secondary method of prescribing (tracking) dose
2-dimensional	Orthogonal pair of 2-dimensional planar images	None	N/A	N/A	ICRU-defined point A	TRAK
CT-based	3-dimensional CT	None	N/A	N/A	CT-defined HR-CTV	ABS-defined point A or TRAK
CT-based, MRI-informed	3-dimensional CT	MRI, applicator not present	Once	<1–2 weeks before first BT procedure	MRI-informed CT-defined HR-CTV	ABS-defined point A or TRAK
MRI-CT hybrid	3-dimensional CT	MRI, applicator *in situ*	Each fraction or at least for first fraction	First fraction, postinsertion	MRI-defined HR-CTV	ABS-defined point A
MRI-guided	3-dimensional MRI	None, or CT may be acquired for better applicator reconstruction and/or applicator position verification purpose	N/A (or each fraction)	N/A	MRI-defined HR-CTV	ABS-defined point A

Abbreviations: ABS = American Brachytherapy Society; BT = brachytherapy; CT = computed tomography; CTV = clinical target volume; HR = high risk; ICRU = International Commission on Radiation Unit; MRI = magnetic resonance imaging; N/A = not applicable; TRAK = total reference air kerma.

Table 2

Advantages, disadvantages, and recommendations for each dose summation approach

Dose summation approach		Advantages	Disadvantages	Recommendations
Linear DVH addition		• Simple to apply; DVH parameter addition not generating full 3-dimensional DVH	Not accurate under certain conditions, such as 1) inhomogeneous EBRT dose in BT treatment region, or 2) substantial organ motion, such as bowel motion. Inter/intrafractional organ motion and changes in EBRT and BT, interapplicator variations or applicator displacements in BT not considered	D_{2cc} for bladder-, rectum-, sigmoid-, and bowel-based on GEC-ESTRO gynecology/ABS guidelines; point A, ICRU bladder point, ICRU recto-vaginal point, posteriorinferior border of the pubic symphysis doses based on GEC-ESTRO gynecology guideline
Image registration–based	RIR	• Simple to apply; – relatively time-honored; – automatic or manual method available	Image fusion required; significant limitations for EBRT images fused to BT images due to soft tissue deformation with BT applicators in place	IR in reference to the applicator, not to bone for intracavitary BT; calculation of lymph node doses and estimation of doses from lymph node boosts in BT region; EQD2 conversion required
	DIR	• Accurately account for complex organ deformation and variations of applicator geometry when appropriately validated; – automatic or semiautomatic methods available; – interfraction BT organ and tissue deformation considered if CT images available	• Image fusion required; – EQD2 conversion required; – limitations for OARs; choice of DIR algorithm may impact results; intrafraction motion not considered; – implausible dose/contour warping may happen	• Image preprocessing (overriding CT number within OAR contours) before applying DIR; – verification of DIR results via both qualitative and quantitative review; – when EBRT used midline blocks, boost, or intensity modulation techniques and register with BT; – EQD2 conversion required; validation/quality assurances before clinical use
Biologic dose mapping for voxel-to-voxel matching		• Some biologic parameters considered; – plan comparison among different fractionation schemes possible	• Voxel-wise EQD2 conversion required using a DICOM transfer and software; – matching each voxel between EBRT and BT or between BT fractions requires DIR and complex calculations; – inaccuracies exist in calculations due to multitude of variables; – biologic information (eg, α/β ratio required in treatment planning system, but α/β for tumor), and QARs not well known;	Generation of comprehensive lookup tables that contain clinically supported ranges for biologic parameters (eg, α, α/β and μ); inclusion of correction factors (eg, proliferation and interval between EBRT and BT in BED calculation); performing DIR before biologic dose summation for voxel-to-voxel matching calculations

Dose summation approach	Advantages	Disadvantages		Recommendations
		–	LQ model fails at extremely large fraction sizes and LDR and does not account for hot spots in dosimetry, breaks in treatments, vascular pathology, previous surgery or chemotherapy;	
		–	BT biologic parameters (eg, repair time and exposure duration not factored in BED calculation of HDR);	
		–	difference in relative biologic effectiveness for photon energy between external beam and BT sources not considered	
Future clinical practice and trials				Volume-based dose prescription, optimization, and dose reporting for BT planning are preferred in clinical trials. Pilot studies using DIR-based dose accumulation should be established to assess voxel-based dose accumulation and compare to conventional dose summation method; recognize limitations of current knowledge, models, and parameters; continue to advance knowledge through research and refine radiobiologic models/parameters; periodically update models/parameters and explore on clinical trials

Abbreviations: ABS = American Brachytherapy Society; BED = biologic effective dose; BT = brachytherapy; CT = computed tomography; DICOM = Digital Imaging and Communications in Medicine; DIR = deformable image registration; DVH = dose-volume histogram; EBRT = external beam radiation therapy; EQD2 = equivalent dose in 2 Gy per fraction; GEC-ESTRO = Groupe Européen de Curiethérapie - European Society for Radiotherapy and Oncology; HDR = high-dose-rate; ICRU = International Commission on Radiation Unit; IR = image registration; LDR = low-dose rate; LQ = linear quadratic; OAR = organ at risk; RIR = rigid image registration.