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Evidence-Based Dose Planning Aims and Dose Prescription in Image-Guided Brachytherapy Combined With Radiochemotherapy in Locally Advanced Cervical Cancer

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The last 2 decades have witnessed the development and broad adoption of image-guided adaptive brachytherapy (IGABT) combined with radiochemotherapy in patients with locally advanced cervical cancer. A variety of brachytherapy techniques and dose/fractionation schedules have been applied, and until recently, there was no strong evidence available for preferring one approach to another. However, large volumes of data have now provided high level clinical evidence for dose-effect relations for both disease and morbidity endpoints. It is therefore now possible to apply evidence based dose planning aims and dose prescription protocols in IGABT for locally advanced cervical cancer. This review gives an overview of targets/organs-at-risk and disease/morbidity endpoints which are relevant in the context of treatment planning and dose prescription in IGABT. The dosimetric and clinical evidence is summarized to support the implementation of dose prescription protocols which include hard and soft constraints for targets and organs at risk.
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Introduction

The GEC ESTRO recommendations and ICRU 89 have developed a comprehensive methodology for unified target and organ at risk (OAR) contouring in locally advanced cervical cancer (LACC).[1–3] Furthermore, a common language for dose prescription and reporting was introduced based on the equieffective dose concept, making it possible to sum-up the doses delivered by external beam radiotherapy (EBRT) and brachytherapy (BT). However, a variety of clinical approaches are currently being applied all over the world with regard to applicators, dose and fractionation. This heterogeneity is partly reflecting historical BT systems and different BT schools.[3] Until recently there was no strong evidence available for preferring one clinical approach to another. However, the rapidly spreading use of joint principles of 3D image-guided BT has now provided opportunities to compare techniques, dose volume parameters, and clinical outcome across patients, institutions, and clinical studies. Clinical evidence for correlations between dose and clinical outcome has been established for an increasing number of disease and morbidity endpoints. This evidence supports the establishment and implementation of dose planning aims and dose prescription protocols.

The overall purpose of this paper is to review and describe the current evidence for: (1) dose-effect and volume-effect relations for both disease control and morbidity and (2) relation between BT technique and dosimetric outcome. The paper gives an overview of target volumes (OARs), and reference points, which are relevant for treatment planning and dose prescription in image-guided BT in LACC. Furthermore, the methods recommended by ICRU 89 for reporting of dose and volume parameters will be summarized. Finally, it will be discussed how the clinical and physics evidence can be combined to support the use of dose planning aims and dose prescription protocols for individualized image-guided adaptive BT. The present review focuses on dose planning aims and dose prescription related to total EBRT and BT dose, while planning aims that relate solely to EBRT planning or chemotherapy are not addressed. Also, practical guidance on treatment planning is not within the scope of this paper.

Brachytherapy Target Volumes Related to the Primary Tumor

The ICRU89 report and GEC ESTRO recommendations introduced an adaptive BT target volume concept which is based on risk of recurrence and treatment response.[2,3] At time of diagnosis, the initial gross tumor volume (GTV-T_{init}) related to the primary tumor and the initial high-risk clinical target volume (initial CTV-T_{HR}) are defined. The initial CTV-T_{HR} includes the whole cervix and the GTV-T_{init}. The initial low-risk target volume (initial CTV-T_{LR}) is also defined at diagnosis and includes uterus, parametria, (upper) vagina, and the paravaginal and paracervical tissue toward bladder and rectum, which are the compartments at risk of microscopic disease. The adaptive target volumes are defined at time of BT and take into account the GTV-T_{init} as well as the response to treatment. The adaptive approach is based on the assumption that volumes containing microscopic disease at diagnosis can be controlled with external chemo-radiation of 45-50 Gy, whereas the BT boost aims to control: (1) volumes which contain residual macroscopic tumor or assumed pathologic tissue at time of BT and (2) volumes with potential residual microscopic disease in the region where GTV-T_{init} was present at diagnosis. The adaptive target volumes defined at time of BT are: (1) the residual gross tumor volume (GTV-T_{res}), (2) the adaptive high-risk clinical target volume (CTV-T_{HR}) containing GTV_{res}, the whole cervix, and adjacent residual pathologic tissue, if present, and (3) the adaptive intermediate-risk clinical target volume (CTV-T_{IR}) which represents the GTV-T_{init} as superimposed on the topography at the time of BT, together with a margin surrounding the CTV-T_{HR}.

Organs at Risk and Morbidity Relevant for Brachytherapy Dose Planning Aims

Organs, Morbidity, and Endpoints

Organ-related morbidity associated with EBRT and BT in LACC includes gastrointestinal (GI), genitourinary, and vaginal side effects. Furthermore, more general symptoms or conditions such as menopausal symptoms, fatigue, insomnia, lymph edema, pain, soft tissue fibrosis, neuropathy, and vessel injuries may also be associated with radiotherapy including BT as well as chemotherapy. The morbidity originates from a variety of processes occurring in normal tissue during and after radiotherapy such as vascular endothelium damage, parenchymal cell damage, and fibroblast damage. In the following, the most frequent OARs and morbidity endpoints related to BT are described. Grades of morbidity refer to the Common Terminology Criteria for Adverse Events with scoring from grade (G) 1-5.

Lower GI symptoms after radiotherapy are caused by multifactorial processes involving the immune, enzyme and hormonal systems, and muscular and neurological functions. Inflammatory changes including activations of cytokines, edema, loss of stem cells, and obliterative endarteritis that can lead to ischemia, necrosis and progressive fibrosis.[4,5] Systemic conditions affecting the small and large intestines include diarrhea, flatulence, bloating, abdominal pain, and cramps, which may be present as single symptoms, or might reveal an underlying condition of enteritis/colitis. Diarrhea is one of the most frequent late GI symptoms (≥G2; 10%).[6] Diarrhea can have multiple systemic or local causes such as small bacterial overgrowth, altered GI transit and motility, malabsorption syndrome with, eg, bile acid malabsorption that is partly due to local injury of the ileum. Strictures can occur in the small intestine (≥G3; 1%), colon (≥G3; 0.3%), sigmoid (≥G3; 0.8%), or anorectum (≥G3; 0.3%), and can predispose for symptoms such as diarrhea, bloating, pain,

and cramps, the latter due to subocclusion or ileus. Anorectal symptoms such as proctitis (≥G2; 4.5%), anal incontinence (≥G2; 3.2%),[7] and urgency of defecation, are related to the anorectal wall, the surrounding musculature with the anal sphincters and levator ani and neurological innervation.[8] Other symptoms include bleeding (most often anorectum: ≥G2; 4.7%) and fistulas involving rectum (≥G3; 0.8%) or sigmoid-colon-small bowel (≥G3; 1.1%).[6]

The urinary function is regulated by a complex system composed by: an elastic smooth muscle responsible for bladder compliance; the involuntary (sympathetic and parasympathetic) nervous system that inhibits or activates the voiding reflex; the voluntary (somatic) nervous system that activates the voiding reflex; and the urethra that ensures closure during bladder filling and relaxation during voiding. Radiation-induced damage to different substructures of the lower urinary tract can lead to different dysfunctions. The most frequent urinary side effects are: frequency, incontinence, cystitis, bleeding, and fistula which occur with incidence (≥G2) of 14%, 12%, 9.4%, 2.8%, and 1.8%, respectively.[9] Ureter stenosis (≥G3) is rare in patients with stage I and II disease (1%), while parametrial infiltration to the pelvic wall or hydronephrosis at diagnosis increases the incidence to 4% and 11%, respectively.[10] Patients with tumor infiltration in the bladder at time of diagnosis have significantly higher incidence of urinary morbidity,[9] which may be a combined effect of disease regression and larger bladder volumes treated to higher doses.

The vagina wall consists of 4 layers: (1) the mucosa at the inner side of the vaginal cavity; (2) the lamina propria, consisting of loose connective tissue with blood vessels and lymphatic tissue; (3) a smooth muscle layer, and (4) the adventitia, consisting of a dense layer of connective tissue with blood vessels, lymphatic tissue, and nerves. The vaginal mucosa and Bartholin glands facilitate lubrication. These different parts of the vagina and its surrounding tissues will inevitably receive a high dose of irradiation, especially in the cranial part of the vagina which may cause vaginal morbidity and sexual problems. Late vaginal symptoms are frequent with ≥G2 incidence of 29%.[11] Stenosis caused by adhesions which occluded or fibrosis of the connective tissue is most frequently observed, followed by vaginal dryness caused by destruction of the epithelium and diminished lubrication.[11] Vaginal bleeding and mucositis are in general mild late side effects, but could be severe, especially when a large part of the vagina is irradiated to a high dose (eg, in case of T-stage 3A). In addition, although robust evidence is missing, damage of the small nerves in the vaginal wall and of the large clitoral nerve might cause less sensation. Finally, in some cases, severe radionecrosis, presumably caused by irreversible damage to, eg, the vessels, can lead to ulcer or fistula.

Fatigue is a common side effect after radiotherapy, and cancer-related fatigue is often perceived as more persistent and distressing, compared to noncancer-related fatigue.[12] G1 persistent fatigue is experienced by over one third of patients while 7% suffer from G2 persistent fatigue after treatment (persistency defined according to the LAPERS methodology as presence of fatigue in more than half of the follow-up visits[13]). Recent evidence suggests radiation-induced fatigue may be mediated by activation of the proinflammatory cytokine network, but requires further investigation.[14] Fatigue may also be related to psychological factors or may be a secondary symptom caused by the burden of other organ-related side effects, such as GI problems or menopausal symptoms.

Radiation-induced fibrosis is mediated by fibrogenic cytokine expression, and inflammatory and vascular alterations. Clinical manifestations include cutaneous/mucosal induration, lymphedema, joint motion restrictions, muscle weakness, and stiffness.[15] Preliminary and unpublished crude incidence rates of fibrosis from the EMBRACE I study are 8.5% and 0.9% for G2 and G3, respectively.

Contouring of Organs at Risk

The ICRU report 89 recommends contouring of OARs on 3D images with the BT applicator in situ. This should include contouring of the outer wall of bladder, rectum, sigmoid, and bowel.[3] Further anatomical structures under investigation at the moment and of interest for urinary morbidity are the bladder trigone and urethra, which may play an important role for treatment-related endpoints such as urinary urgency and incontinence.[16] Ureters can be identified on 3D imaging,[17] although there is so far limited experience with prospective contouring and dose assessment. For GI function, it may additionally be relevant to consider the anal canal and pelvic floor muscles, which could be important for fecal urgency and incontinence. 3D contouring of the vagina and assessment of dose to this structure is related with considerable uncertainties,[18] and therefore it is currently recommended to assess vaginal dose through reference points in the upper, mid and lower vagina (see Reporting of Dose for Target Volumes and OARs Section). Additionally, upcoming efforts are evaluating the potential role of vagina dose surface maps.[19]

Reporting of Dose for Target Volumes and OARs

Recommendations for dose and volume reporting of 3D image-guided BT in LACC are outlined in the ICRU89 report.[3] The 3D dose distribution in radiotherapy of LACC is characterized by exposure of larger tissue volumes to intermediate dose levels from EBRT and exposure of smaller volumes to high doses in the region of the BT boost. EBRT and BT doses are converted into equieffective dose according to the linear quadratic (LQ) model to facilitate dose accumulation across the 2 modalities. The current standard for reporting equieffective dose in cervix BT is equivalent dose in 2 Gy fractions (EQD2) using α/β ratios of 10 Gy for tumor volumes and 3 Gy for OARs.[3] For pulse dose rate BT a repair half time of 1.5 hours is the current standard. Uncertainties related to the LQ model increase at larger doses per fraction, eg, >5-10 Gy.[20] The characteristics of the combined EBRT and BT dose distribution are highly dependent on the weighting between EBRT and BT dose. The relevance of

different parts of the DVH depends therefore on the dose and fractionation schedule. The principles presented in this paper are based on schedules with 45-50 Gy whole pelvis EBRT and 40-45 Gy of BT applied either by high dose or pulsed dose rate.

The BT dose distribution is characterized by significant dose heterogeneities throughout the target, and it is preferable to record DVH parameters which reflect the dose to both the inner and outer parts of the target volume. With regard to local control, low-dose regions in the target volumes are assumed to be critical, and reporting of the near minimum dose (D98) is recommended for GTV_{res}, CTV-T_{HR}, and CTV-T_{IR}. The D98 reflects the dose in the outermost periphery of the target (typically 2% of the target volume represents <1 cm^3 of tissue), and further reporting of the dose delivered to 90% of the CTV-T_{HR} (D90) is therefore recommended, to include a measure which is less dependent on contouring uncertainties and which is more representative for a larger portion of the target. Finally, the median dose (D50) reflects the high dose delivered to the central part of the CTV-T_{HR}, which may presumably also have importance for local control.

With regard to morbidity, the high-dose regions play a significant role. Dose to hotspots in the organ walls are best described through reporting of the dose to small absolute volume such as 0.1 cm^3 and 2 cm^3. For bladder and rectum, the location of hotspots is rather stable between fractions, and addition of $D_{0.1cm3}$ and D_{2cm3} (in EQD2) across BT fractions represents the total dose with sufficient accuracy.[21,22] For sigmoid and bowel, significant organ movement[23,24] induce uncertainties in estimation of total hotspot dose.[25] In case of bowel adhesions, the anatomy is more stable, and the risk associated with high D_{2cm3} and $D_{0.1cm3}$ doses is potentially higher as the hotspot is more likely to be situated in the same part of the sigmoid/bowel. A further challenge is that D_{2cm3} and $D_{0.1cm3}$ do not reflect the anatomical location of the hot spots. This is a shortcoming when radiosensitivity varies across an organ, as, eg, for large and small bowel.[26] For the bladder, there is a different clinical effect from D_{2cm3} being located in the superior part of the bladder wall as compared to in the trigone region.[27] Such limitations can be circumvented by contouring subvolumes of organs as, eg, the bladder trigone and reporting dose accordingly.[16,28] Furthermore, the ICRU bladder point has a specific anatomic location related to the trigone region and is a better surrogate of trigone dose than the bladder D_{2cm3}.[28–30] Finally, additional points have been suggested to reflect the dose to the urethra and the urethral sphincters: Internal-Urethral-Ostium and Posterior-Inferior Border of Symphysis -Urethra (PIBS-U).[16,28]

3D contouring and dose reporting for the vagina have uncertainties.[18] Furthermore, fractional hot spot doses such as D_{2cm3} may be high (>10 Gy per fraction), which makes it difficult to use dose-effect relations across different fractionation schedules due to EQD2 calculation uncertainties.[24] For these reasons, the ICRU89 report could not recommend 3D metrics for routine vaginal dose reporting, although developments in this area including dose surface metrics are encouraged for research-oriented reporting. To overcome the difficulties with 3D dose reporting, a reporting method was developed and validated based on points positioned at the level of the PIBS, plus 2 points (±2 cm) in mid vagina and at the introitus.[31,32] The PIBS points are recommended by the ICRU89 report together with the rectovagina reference point.[3] Furthermore, lateral points at 5 mm depth from the surface of the applicator can be reported.[3] The vaginal reference length (VRL) is defined from the center of the vaginal sources to the PIBS plane.[31] The VRL does not represent the entire vaginal length, but a well-defined reference length. Finally, the total TRAK (total reference air kerma) delivered from the vaginal sources (ring or ovoids) is related to the overall dose delivered in the upper vagina.[33]

In addition to reporting high doses to small volumes (D_{2cm3} and $D_{0.1cm3}$), further characterization of normal tissue volumes irradiated to low and intermediate dose levels such as 15-60 Gy can add to the comprehensiveness of dose reporting.[3] It is therefore recommended to report EBRT dose volume parameters reflecting these dose levels. Ideally, accumulated EBRT and BT low and intermediate doses should be assessed. However, this is currently challenging as commercial technologies are not available for providing reliable dose addition in this region of steep gradients.[25]

The overall treated volume can be evaluated through several parameters. The most direct measure is isodose surface volumes evaluated at clinically relevant dose levels, such as V85Gy, V75Gy, or V60Gy.[3] Furthermore, the Point A dose correlates with V85Gy, V75Gy, or V60Gy[34] and it is therefore useful as a surrogate for the overall intensity of a treatment. Point A dose can be reported for purely intracavitary BT and is also useful as anchorage to clinical experience in the era without 3D image-guided adaptive brachytherapy (IGABT). In particular, in cases with small residual CTV-T_{HR}, high D90 may occur while point A dose and V85 Gy are low as compared to a standard plan with point A dose of, eg, 75-85 Gy $EQD2_{10}$.[35] In such cases, point A is useful to monitor the magnitude of dose de-escalation.

Clinical Evidence for Correlation Between Dose-Volume Parameters and Local Control and Morbidity

There is an obvious relation between dose and the chance of eradication of the primary tumor, which has been evidenced for most malignancies. The dose-effect relationship for local control is further modulated by characteristics of the individual tumor such as tumor volume, histology, microenvironment (including hypoxia), repopulation (overall treatment time [OTT]), and radiosensitivity. Concomitant delivery of drugs, eg, cisplatin, may also impact the tumor dose-effect relationship. For morbidity, there is an underlying causality between delivered dose/volume and effect, although specific dose-effect relations may be complex. A given symptom may be caused by radiation damage of several types of tissue with different tolerance to dose—eg, stenosis can be caused by submucosal vascular endothelial and/or fibroblast damage.

Furthermore, a given symptom or condition can originate from damage of different organ substructures—eg, urinary frequency can be caused by reduced capacity of the whole bladder and/or or damage to substructures as the trigone or the bladder neck.[36] On top of this complexity, patient-related factors such as smoking and comorbidity strongly impact the risk of toxicity.

The quality and reliability of morbidity reporting is often the weakest link when establishing dose-effect evidence for morbidity. In particular, the assessment of mild and moderate morbidity endpoints requires specific efforts and prospective recording. Furthermore, clinical studies traditionally focus on severe or life-threatening endpoints, thus not reporting mild-moderate symptoms.[37] Each endpoint needs to be systematically assessed through quantitative measurement, clinical examination, or dialogue with the patient, or underreporting may occur.[38] Both mild and moderate morbidity may produce substantial bother to the patient[6,9] and has been shown to deteriorate quality of life in head and neck cancer patients.[39] In particular, persisting mild and moderate morbidity may cause significant distress for cancer survivors. It is essential that dose-effect models and related dose planning aims reflect not only severe but also mild and moderate morbidity and, preferably, duration of morbidity. Clinical evidence for dose effect is of higher quality when based on prospective assessment of mild, moderate and severe morbidity and complemented by patient-reported outcomes.

This section describes the clinical evidence that is currently available for dose effect and volume effect for both local control and morbidity which is related to BT delivered on top of EBRT and chemotherapy. An overview of the evidence is summarized in Table 1. The level of clinical evidence is scored according to the principles for prognostic studies, where the highest level of evidence is achieved with prospective studies with "adequate power."[40,41] Furthermore, models that are validated in independent patient cohorts have increased reliability. "Adequate power" or "adequate cohort size" of a clinical study depends on the size of the hazard ratio of a given risk factor as well as the number of events. Furthermore, the predictive accuracy of dose-effect models relies on the ability to include multiple explanatory factors in the statistical regression analysis. Identification of, eg, 4 risk factors in multivariable analysis requires around 40 morbidity events,[42] which requires patient cohorts of 270 or 200 patients for endpoints with frequency of 15% or 20%, respectively. In the present review, the level of evidence is defined as high when: (1) identification of risk factors are revealed based on multivariable analysis, (2) patient cohorts are sufficiently large to identify risk factors of intermediate and high hazard (eg, >300 patients), (3) relevant dose reporting is available, and (4) prospective assessment of morbidity is available. The level of evidence is scored as intermediate when multivariable analysis is available in intermediate cohort sizes (eg, 100-300 patients) with prospective morbidity assessment. "Under investigation" is indicated when research efforts are ongoing, but when high or intermediate evidence is not available to the knowledge of the authors. "No correlation" is indicated when "high evidence" material is available, but when correlation between a certain endpoint and a dose reporting parameter was not found.

The relation between dose and local failure or morbidity is often modeled through logarithmic dose-response curves based, eg, on Cox or logistic regression models. With dose-effect modeling it is possible to quantify the increased risk per Gray. This facilitates the translation of evidence on dose effect into clinical proposals for dose constraints. Figure 1 shows examples of dose-response curves for vaginal stenosis, diarrhea, cystitis and urinary incontinence.

Dose Effect for Local Control

The target structures proposed through the GEC ESTRO recommendations were the result of a conceptual development and initially not based on experience with mature clinical outcome. The subsequent demonstration of dose-effect relations in several studies proved that these target volumes are indeed relevant for controlling local disease. The major clinical series providing this evidence were the data from the Medical University of Vienna[44] and Institute Gustave Roussy[45] as well as the multi-institutional data from retroEMBRACE.[43] These 3 studies support similar dose-effect relations.

In the largest series from retroEMBRACE, it was reported that escalation of CTV-T_{HR} D90 from 75 Gy to 85 Gy resulted in increased local control by 3% in limited to intermediate size (20-30 cm^3) CTV-T_{HR} and by 7% in large size (70 cm^3) CTV-T_{HR}. The steepness of the dose-effect relation depended significantly on stage and histology (squamous cell vs adeno/adenosquamous carcinoma). A CTV-T_{HR} dose of ≥85 Gy (D90) delivered in 50 days provided 3-year local control rates of >94% in limited size CTV-T_{HR} (20 cm^3), >93% in intermediate size (30 cm^3), and >86% in large size (70 cm^3) CTV-T_{HR}. CTV-T_{IR} and GTV_{res} D98 of ≥60 Gy and ≥95 Gy, respectively, resulted in a similar level of local control. Furthermore, the CTV-T_{HR} D98 and in particular inspection of the spatial dose distribution within and at borders of the target volumes are relevant for plan evaluation and the detection of low-dose regions not reflected by the above mentioned DVH parameters.[51] The use of combined intracavitary interstitial applicators significantly correlates with local tumor control for CTV-T_{HR} volumes ≥30cm^3.[52] Other large mono-institutional series with application of MRI based IGABT have confirmed high levels of local control (>90%) at mean CTV-T_{HR} doses around 90 Gy.[53–58]

Impact of OTT on local control has been demonstrated in the era prior to chemotherapy and prior to the introduction of IGABT.[59,60] The retroEMBRACE study found that an additional dose of 5 Gy (CTV-T_{HR} D90) is required to compensate for an increase of OTT by 1 week.[43] A larger detrimental effect on local control of increased OTT was found in a cohort treated with MRI-guided BT applied with lower doses than in retroEMBRACE.[45] These results emphasize that OTT is still relevant in the era of chemotherapy and IGABT.

Table 1 Evidence for Dose-Effect and Volume-Effect Relationships for Endpoints Relevant for Brachytherapy

Target/OAR	Dose	Endpoint	Source of Clinical Data	# Patients	Level of Evidence*
CTV-T_{HR}	D90	Local control	retroEMBRACE[43] MUW[44] IGR[45]	488 141 225	High
CTV-T_{HR}	D98#	Local control	retroEMBRACE[43]	488	High
GTV_{res}	D98#	Local control	retroEMBRACE[43]	267	Intermediate
CTV-T_{IR}	D98#	Local control	retroEMBRACE[43]	345	Intermediate
Bladder	D_{2cm3}	Bleeding, cystitis, fistula	EMBRACE	1340	High
Bladder	ICRU bladder point	Incontinence	EMBRACE IGR[46]	1340 297	High
Ureters	No reporting system	Ureter stenosis			Under investigation
Rectum	D_{2cm3}	Bleeding, proctitis, fistula	EMBRACE[7]	960	High
Rectum	ICRU rectovaginal point	Bleeding, proctitis, fistula	EMBRACE[7]	960	High
Anus	?	Incontinence			Under investigation
Sigmoid	D_{2cm3}	Diarrhea, fistula, strictures, bleeding	EMBRACE	1340	No correlation / Under investigation
Bowel	D_{2cm3}	Diarrhea	EMBRACE	1340	High
Bowel	D_{2cm3}	Fistula, strictures, incontinence, bleeding	EMBRACE	1340	High
Vagina	ICRU rectovaginal point	Vaginal stenosis	EMBRACE[47]	630	High
Vagina	PIBS	Vaginal stenosis	EMBRACE	301	High
Vagina	Dose surface maps	Stenosis	UMCU[19]	31	Under investigation
Normal tissue	V60Gy	Cystitis	EMBRACE	1340	High
Normal tissue	V60Gy	Pooled diarrhea + flatulence + bowel fistula & stenosis	EMBRACE IGR[48]	1340 260	High
Normal tissue	V60Gy	Fatigue	EMBRACE	1177	High

Abbreviations: IGR, Institute Gustave Roussy; MUW, Medical University of Vienna; UMCU, University Medical Center Utrecht.

* Based on size of cohort and quality of reporting for morbidity endpoints (see further explanation in the text).

\# In the retroEMBRACE study, D98 was not reported for GTV_{res}, CTV-T_{HR}, and CTV-T_{IR}. However, D98 can be interpolated from D90 and D100 with high accuracy[35] for which dose effect was established.

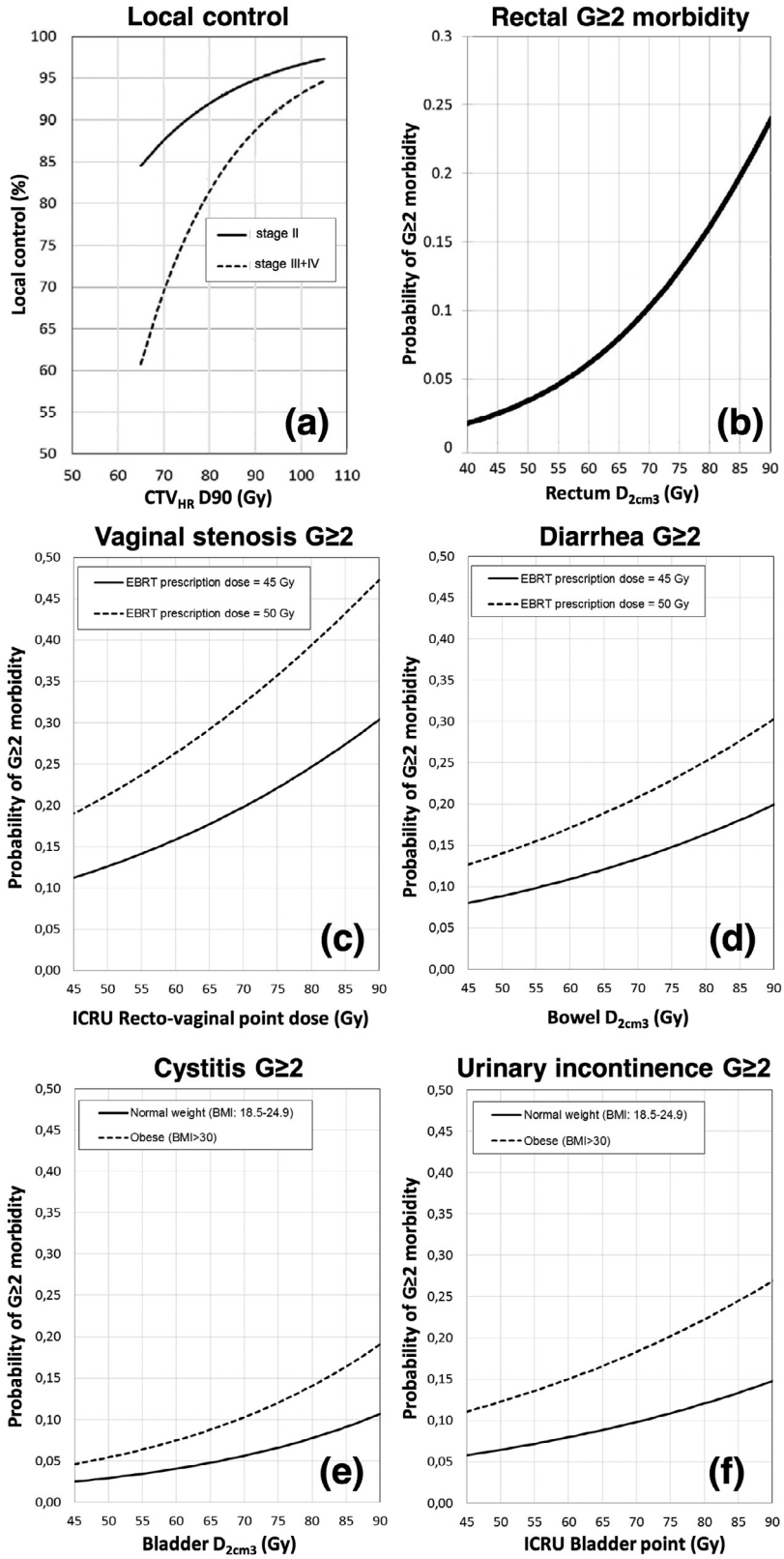


Figure 1 Dose-effect curves for: (A) Local control at 3 years vs CTV-T_{HR} D90 for FIGO stage II and stage III+IV (adapted from Tanderup et al[43]). (B) CTCAE ≥G2 rectal morbidity (crude incidence) vs rectum D_{2cm3} (adapted from Mazeron et al[7]). (C) CTCAE ≥ G2 vaginal stenosis at 2 years vs rectovaginal point dose for 2 EBRT dose prescription protocol (45 and 50 Gy) (reproduced from data in Kirchheiner et al[47]). (D) CTCAE ≥G2 diarrhea at 3 years vs bowel D_{2cm3} for 2 EBRT dose prescription protocol (45 and 50 Gy) (reproduced from data in Jensen et al[50]). (E) CTCAE ≥G2 cystitis at 3 years vs bladder D_{2cm3} for patients with normal and high body mass index (BMI) (reproduced from data in Spampinato et al[50]). (F) CTCAE ≥G2 urinary incontinence at 3 years vs ICRU bladder point dose for patients with and normal and high BMI (reproduced from data in Spampinato et al[27]).

Dose Effect for Genitourinary Morbidity

Two mono-institutional studies[7,61] in populations of approximately 200 LACC patients have shown correlation between bladder D_{2cm3} and urinary side effects. Both studies pooled different urinary endpoints in their analysis, whereas there is growing awareness that different side effects may be associated with different functional substructures of the bladder. For this reason, attempts were made to connect dose hotspots to an anatomical position considering the ratio between bladder D_{2cm3} and the ICRU bladder point dose.[29,30] Recently, one study found a correlation between hotspots in the bladder base and incontinence.[62] These results were confirmed in another study where late urinary morbidity was related to trigone dose.[46] An analysis on late urinary morbidity is furthermore carried out in the EMBRACE I study cohort. By analyzing both physician and patient-reported outcome, it has been shown that a high bladder D_{2cm3} is an important risk factor for moderate to severe grade bladder fistula, bleeding and cystitis.[50] Whereas, it was not possible to identify a relation between D_{2cm3} and urinary incontinence, the dose to the ICRU bladder point, being positioned in close anatomical proximity to substructures responsible for continence (trigone, bladder neck, and urethra)[16] was significantly related to urinary incontinence.[27] Finally, D_{2cm3} or ICRU bladder point was not found to be predictive for urinary frequency whereas factors related to EBRT volume and dose were of importance, together with patient-related risk factors (smoking, overweight, and baseline frequency; ongoing EMBRACE analysis).

For ureter stenosis, the EMBRACE study did not show any increased risk of ureter stenosis with the application of combined intracavitary/interstitial (IC/IS) needles.[10] However, an effect of needles/dose in close proximity to ureters cannot be ruled out, as there are no large scale studies available with systematic recording of ureter dose.

Dose Effect for Gastrointestinal Morbidity

There is long term evidence that dose to the ICRU rectum point is associated with endpoints such as rectal bleeding and fistula.[61] This was confirmed in the EMBRACE study, which also evaluated the predictive role of the ICRU rectum point dose on proctitis.[7] Utilization of 3D dose reporting has provided evidence that D_{2cm3} is also a predictor for rectal bleeding, fistula and proctitis.[7,61]

A recent systematic review on dose-volume predictors and constraints for late bowel toxicity following pelvic radiotherapy summarized evidence on the impact of EBRT dose on bowel morbidity.[63] Whereas the impact of BT on rectal side effects has been well known for decades, the evidence for the effect of BT on small bowel and sigmoid morbidity has been lacking. However, current analysis of the EMBRACE cohort shows that risk factors for diarrhea are bowel D_{2cm3}, rectum D_{2cm3} as well as EBRT components such as prescribed dose, para-aortic irradiation as well as high-dose regions related to lymph node boosts.[49] Furthermore, pooled ≥G3 bowel morbidity (bleeding, fistula, stenosis, diarrhea, necrosis, and perforation) correlates with bowel D_{2cm3}. Finally, the isodose surface volume irradiated to 60 Gy (V60Gy) is related to ≥G3 rectum morbidity as well as ≥G3 (ongoing analysis EMBRACE) and ≥G2 bowel morbidity.[48] Sigmoid D_{2cm3} has not been found to correlate with bowel morbidity (EMBRACE ongoing analysis,[49]).

Risk factors related to BT (such as, eg, rectum D_{2cm3}) have not been identified for fecal incontinence. This observation likely point toward inadequate reporting of dose to the anal region, as there is currently no specific methodology recommended.

Dose Effect for Vaginal Morbidity

Uncertainties related to 3D dose reporting for the vagina may explain the fact that several retrospective mono-center reports have reported partly conflicting results on dose effect for the vagina.[64–68] Murakimi et al found that patients with a D_{2cm3} of >145 Gy EQD2 had significantly higher risk of developing vaginal ulcers.[65] A D_{2cm3} cut-off value of 108 Gy has been reported for ≥G1 morbidity.[67] Dose effect for late ≥G2 vaginal morbidity has also been reported with V70Gy and D5% being the most important dosimetric factors while other DVH parameters, such as D_{2cm3}, were also significantly associated with ≥G2 vaginal toxicity.[68] While these studies are positive, others failed to find dose-effect relationships between the D_{2cm3} of the vaginal wall and vaginal toxicity.[68,66] In addition, the vagina seems to have variation in radiosensitivity, as the proximal part is less vulnerable to irradiation than the distal.[69,70]

A dose-effect relationship between the dose at the ICRU rectovagina reference point and vaginal stenosis has been established in EMBRACE I data, and doses of >65 Gy $EQD2_3$ were significantly associated with a higher risk of ≥G2 vaginal stenosis.[71] Furthermore, 50 Gy EBRT was also found to be associated with more stenosis as compared to 45 Gy schedules. Finally, preliminary results of a prospective substudy of EMBRACE I in ~300 patients showed a significant dose-effect relation between ≥G2 vaginal stenosis for doses to the PIBS points.[72]

Preliminary results from vaginal dose surface maps in a small patient cohort of 31 patients have shown that dose-surface metrics correlates with ≥G2 stenosis.[19] A threshold for the D_{20cm2} to the outer vaginal wall (2 mm width) of around 80 Gy $EQD2_3$ was found between patients with G ≤ 1 and ≥G2 stenosis, and the surface area irradiated to more than 60 Gy (S_{60Gy} in %) was also significantly correlated to ≥G2 stenosis.

Dose Effect for Fatigue

While patient-related risk factors for fatigue have been reported by several studies,[73–75] there has been limited understanding of the role of pelvic radiotherapy. The EMBRACE study has contributed with novel insights into treatment-related risk factors for fatigue through the analysis of both incidence and persistent presence of fatigue. Multivariable analyses confirmed that patient-related factors such as younger age, higher body-mass index, baseline fatigue and chronic disease were risk factors for fatigue.[76]

Treatment-related risk factors for late persistent ≥G2 fatigue were large high-dose volumes related to EBRT (lymph node boosts) as well as a large isodose surface volume treated with total EBRT and BT dose of ≥60 Gy (V60Gy $EQD2_3$). Median and interquartile range of V60Gy was 223 cm^3 and [177-289 cm^3]. Patients treated with V60Gy below and above the median of 223 cm^3 had an incidence of 4% and 6% ≥G2 persistent fatigue, when no lymph node boost was given. The impact of the BT boost volume (V60Gy) on fatigue increased in patients with lymph node boosts, as the incidence of persistent fatigue increased from 9% to 15% with V60Gy below and above the median. For comparison, V60Gy for typical standard BT plans are 268 cm^3 and 200 cm^3 with point A dose of 85 Gy and 75 Gy, respectively.[35]

Dose Effect for Other Tissue Types

Further structures adjacent to or even inside the high-dose region of BT are nerves, vessels, and connective tissue. Evidence of dose effect is scarce for these structures, which are not routinely contoured, except that the risk of fibrosis in connective and vascular tissues has been described to increase with higher doses (>60 Gy) and larger treated volumes.[15]

Evidence for Correlation Between Dose-Volume Parameters and Brachytherapy Technique

The ability to achieve dose constraints depends both on the patient anatomy as well as the BT technique including type of applicator/application, fractionation and dose optimization. The combined IC/IS technique, using a transvaginal approach for needle insertion, developed progressively over the last 2 decades both in terms of frequency of application as well as in terms of complexity/efficacy. The requirement for needle application is typically for large tumors involving parametria and vaginal tissues at the time of BT.[77–79] However, small tumors (eg, CTV-T_{HR} volumes <30 cm^3) can also benefit from IC/IS technique when OARs are in close proximity to the applicator or due to asymmetric tumor extension relative to the tandem.[78,79] Depending on the extent of tumor infiltration, parallel needles for proximal parametria and oblique needles for distal parametria and/or far into vaginal tissues (>2-3 cm) are typically applied.[80]

The use of MRI-guided BT and IC/IS technique in EMBRACE I improved target coverage and conformality as compared to classical standard loading; eg, median V85Gy $EQD2_{10}$ was 23% smaller than average standard V85Gy $EQD2_{10}$ with 85 Gy at Point A.[35] Dosimetric studies on the IC/IS technique from the Vienna experience and retro-EMBRACE study reported a dose increase in CTV-T_{HR} D90 of 9 Gy $EQD2_{10}$ and similar OARs doses when compared to patients treated with the IC technique alone.[52,77,81] Systematic dose re-planning studies, comparing the dosimetric outcomes of the IC vs IC/IS techniques, pairwise, in the same patients, reported an increased therapeutic window of 4-8 Gy EQD2 with the IC/IS technique.[79,82,83]

The EMBRACE I study showed that different applicator types and implantation methods were related to different dose distribution characteristics (eg, shape, dose fall-off, etc).[80] Patients treated with tandem & ring (T&R) applicators had a more favorable therapeutic ratio and more conformal dose distributions compared to patients treated with the tandem & ovoids (T&O) applicators. For IC implants, bladder and rectum doses (D_{2cm3} and ICRU points) were 5-7 Gy $EQD2_3$ higher for T&O as compared to T&R. Differences between the 2 applicators were reduced in IC/IS implants; however, rectovaginal ICRU point dose and bladder D_{2cm3} remained 4-5 Gy $EQD2_3$ higher for T&O as compared to T&R. Vaginal point doses situated 5 mm lateral with respect to the vaginal applicator were 20-22 Gy $EQD2_3$ higher for T&R as for both IC and IC/IS techniques.

The applicator insertion, including vaginal packing, is also important for the dosimetric quality of the implant. The VRL reflects the insertion depth of the applicator, and large VRL leads to less dose to the lower parts of the vagina (as reflected by the PIBS and PIBS -2 cm points)[32,84] and to urethra and anal canal.[28]

Dose Planning Aims and Dose Prescription Protocols Including Aims for Overall Treatment Time

Dose planning aims are primarily based on clinical evidence for dose-effect relations. In addition, the practical feasibility of adhering to a given dose planning aim in a typical patient cohort needs to be considered. The feasibility of adhering to dose constraints is limited by quality of the implant, tumor size/topography, and OAR proximity. Small symmetric tumors imply large therapeutic windows as high target doses can be achieved with limited organ doses, whereas large tumors in combination with poor implant quality imply a more limited therapeutic window and potential need to compromise target and/or organ dose planning aims. Dose planning aims depend furthermore on the clinical environment including availability of applicator types (IC as well as IC/IS) and availability of imaging (eg, MRI vs CT). In general, higher quality of BT implant (availability of advanced applicators including IC/IS) and higher confidence in target and OAR delineation (availability of MRI) allows for more ambitious dose planning aims. Dose prescription protocols should be considered as under continuous development as new clinical evidence, new BT applicators, and new technology for implant guidance become available.

Dose planning aims are expressed as total EBRT and BT dose (each converted to EQD2) and are defined in terms of hard and soft constraints. Hard constraints should be achieved in the far majority of patients—eg, at least 90-95% of patients (per parameter), whereas soft constraints should be achieved in at least 70-80% of patients (per parameter). The priorities and balance between different DVH

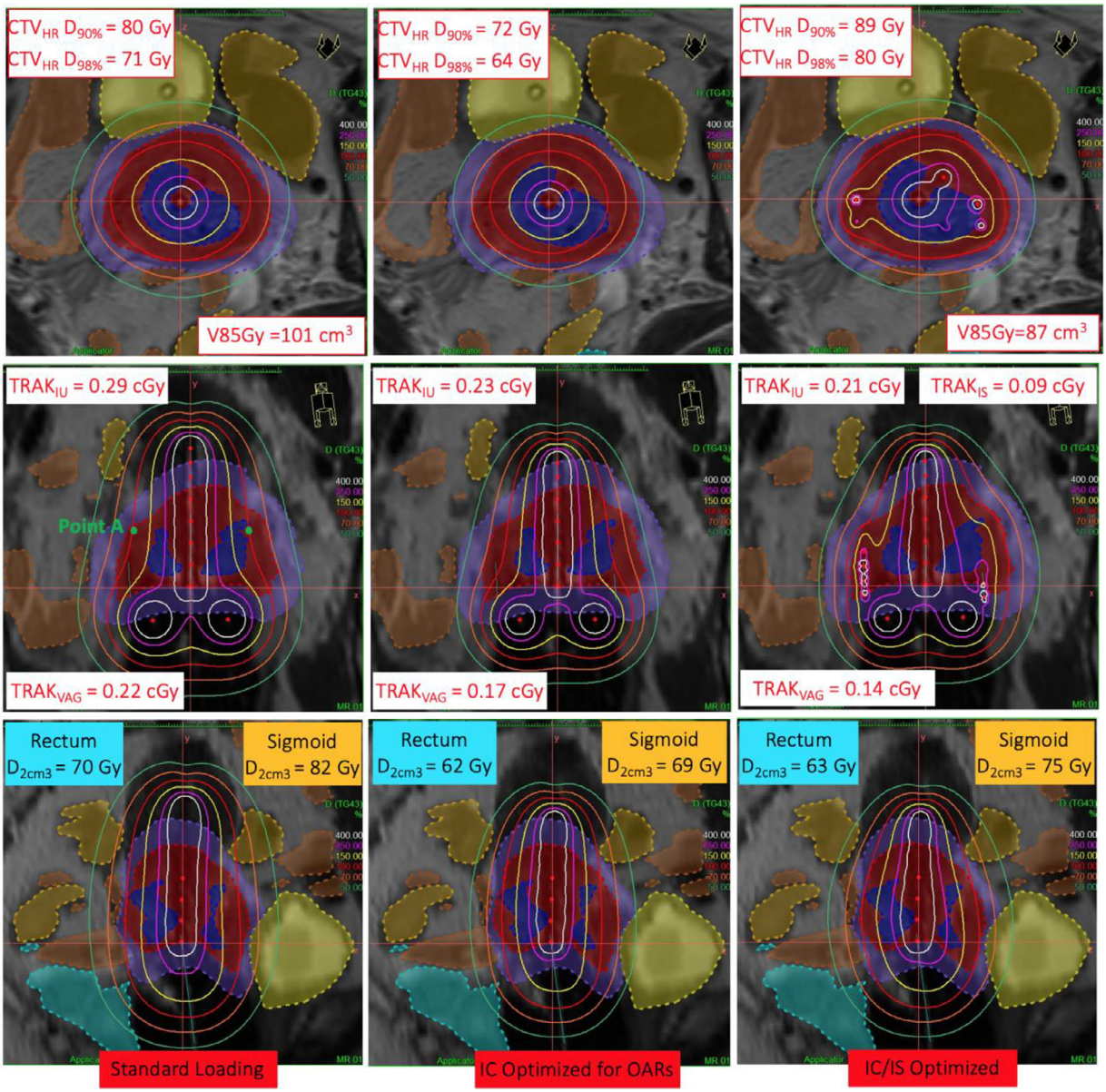


Figure 2 Example of dose optimization workflow in a large tumor at time of brachytherapy (BT). The case is a stage IIIB tumor with distal parametrium and upper one-third vagina involvement at BT. The CTV_{HR} volume is 49 cm^3. First, second, and third rows show paratransverse, coronal, and sagittal MRI with combined intracavitary/interstitial (IC/IS) applicator in situ. First column is the starting point in dose optimization: IC standard loading with 85 Gy $EQD2_{10}$ at point A. Second column is the second step in dose optimization: de-escalated IC loading to meet OARs dose soft constraints. Third column is the final result of dose optimization: combined IC/IS loading respecting both target and OARs dose constraints. GTV, CTV_{HR}, CTV_{IR} are shown in dark blue, red, and violet, respectively. Bladder, rectum, sigmoid, and bowel are shown in yellow, cyan, brown, and orange, respectively. Isodose lines are displayed relative to 100% = 85 Gy $EQD2_{10}$. Vaginal ($TRAK_{VAG}$), intrauterine ($TRAK_{IU}$), and needle ($TRAK_{IS}$) loadings, V85Gy $EQD2_{10}$ and CTV_{HR}/OARs doses are indicated for the 3 dose optimization steps. (Color version of figure is available online.)

parameters are based on the therapeutic priorities (chance of tumor control vs risk of morbidity) as well as the level of evidence of dose effect for a given endpoint. In general, the highest priority is the hard constraint of the CTV-T_{HR} (D90 and then D98) and thereafter hard constraints for OARs and GTV. When hard constraints for targets and OARs are achieved, the priorities are, in general, to aim for reaching/approaching soft constraints for CTV-T_{HR} and GTV and thereafter reaching/approaching soft constraints for OARs and CTV-T_{IR}. However, these priorities are not general principles and are not applicable in all patients. For example, there are cases where it is simply not possible to respect the hard target constraints due to large size or difficult topography of the target or due to challenges to place applicators and/or needles, and in such cases the OAR constraints will limit the prescribed target dose. Furthermore, there may be specific considerations for individual patients such as patient age, performance status, comorbidities, patient's own

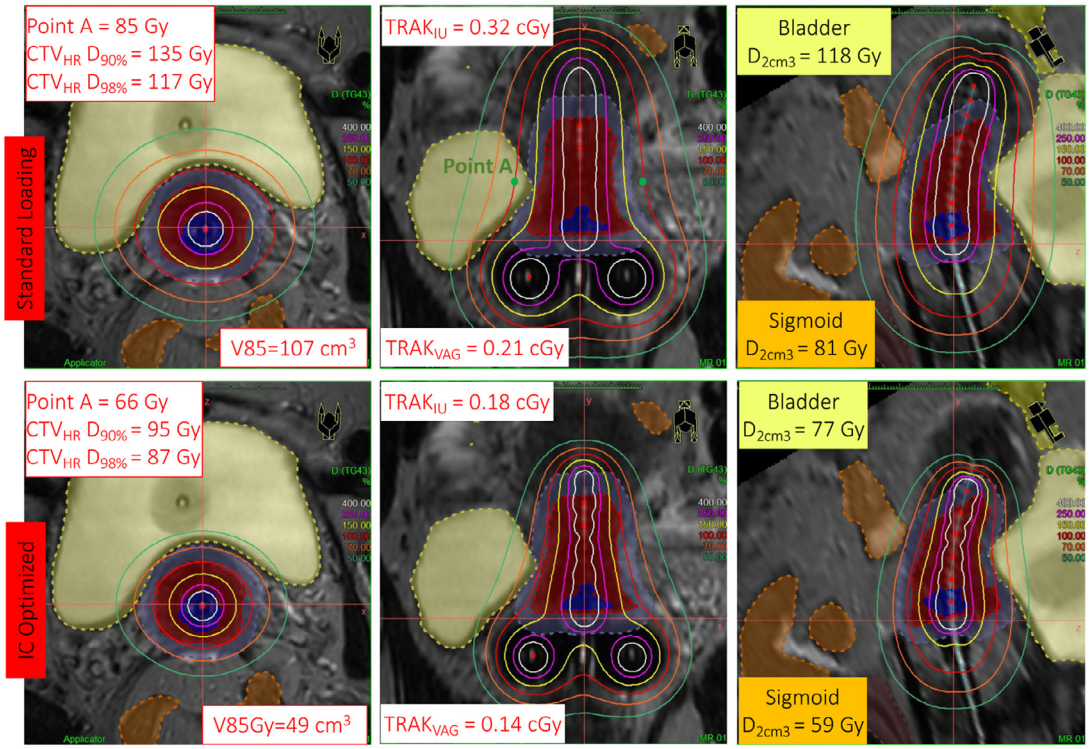
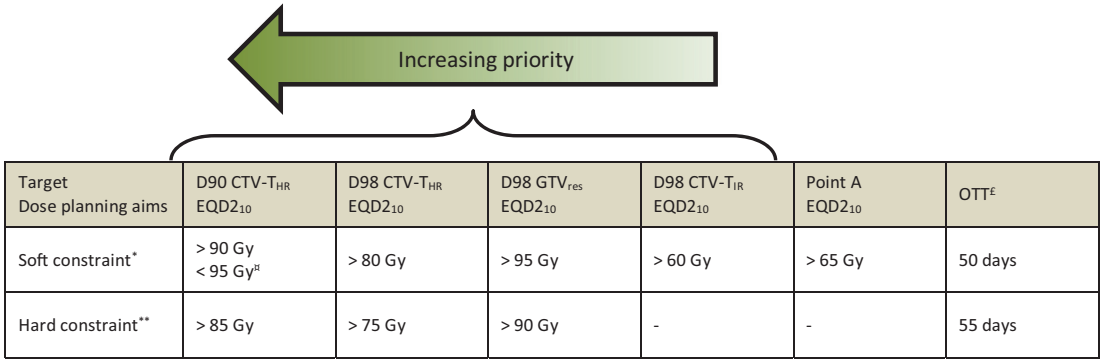


Figure 3 Example of dose optimization workflow in small tumors where overall dose de-escalation, including vaginal dose de-escalation, is performed. The case is a stage IB2 tumor with CTV_{HR} volume of 17cm^3. First, second, and third columns show paratransverse, coronal, and sagittal MRI with intracavitary (IC) applicator in situ. First row is the starting point in dose optimization: IC standard loading with 85 Gy $EQD2_{10}$ at point A. Second row is the final step in dose optimization: de-escalation of the intrauterine and vaginal loadings to respect target and OARs dose constraints. GTV, CTV_{HR}, CTV_{IR} are shown in dark blue, red, and purple, respectively. Bladder and sigmoid are shown in yellow and orange, respectively. Isodose lines are displayed relative to 100% = 85 Gy $EQD2_{10}$. Vaginal ($TRAK_{VAG}$), intrauterine ($TRAK_{IU}$), and needle ($TRAK_{IS}$) loadings, Point A/CTV_{HR}/OARs doses and V85Gy $EQD2_{10}$ are indicated for the standard loading and the optimized dose distributions. (Color version of figure is available online.)

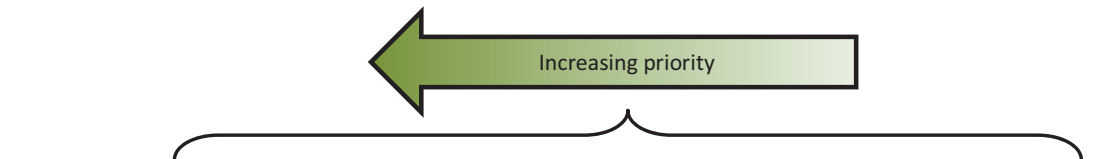
priority, etc. Figures 2 and 3 shows 2 typical scenarios of dose optimization and adherence to dose constraints for small and large residual tumor volumes at time of BT.

Figure 4 shows an example of a dose prescription protocol which is based on MRI-based treatment planning and availability of IC/IS applicators. The dose prescription protocol is modified from the EMBRACE II protocol and has been updated according to clinical evidence which has emerged since the EMBRACE II study was launched. Furthermore, the protocol is based on experience with the dosimetric performance of the EMBRACE I and II studies. Finally, expert experience and opinion was taken into account when clinical evidence was limited or not available. The dose prescription protocol is based on OTT of ~50 days. If the OTT is significantly extended, the delivered dose to the tumor target is less efficient due to tumor repopulation. Each week of OTT extension beyond 50 days is currently estimated to be equivalent to a loss of 5 Gy $EQD2_{10}$ in CTV-T_{HR} dose.[43] A "planning aim" for maximum OTT of 50 days is therefore advised (soft constraint), and the large majority of patients (>90%) should preferentially be treated with OTT of <55 days (hard constraint). The LQ model and EQD2 calculations do not take tumor repopulation into account. Therefore, in case of OTTs beyond 50-55 days, it may be considered to increase the target dose planning aim beyond 85 Gy or 90 Gy in order to compensate for the loss of efficiency of dose. The specific impact of OTT on morbidity remains unknown for morbidity endpoints in LACC, and there are currently no recommendations to adjust OAR planning aims based on variations in OTT.

The soft dose constraint indicated for point A dose should be considered a safety measure. For small targets, the point A dose can be low (eg, <70 Gy), while CTV-T_{HR} dose can be high (eg, >90 Gy $EQD2_{10}$). Contouring uncertainties may have significant impact on target dose, and under-contouring of small targets can lead to an "undesirable collapse" of the V85Gy and V60Gy isodose surface volumes.[35] With MRI-based BT, the contouring of limited size tumors confined to the cervix is usually precise and a point A dose of 65 Gy is currently considered a lower threshold for the majority of patients. In the current experience of the EMBRACE II study (453 patients) and in the EMBRACE I study, 96% and 95% of patients were treated with point A dose >65 Gy, respectively, and 83% and 86% of patients were treated with point A dose >70 Gy, respectively. CT-based BT usually leads to larger contouring uncertainties, compared to MRI, and a higher safety threshold on point A should be considered, such as 70 Gy.



Target Dose planning aims	D90 CTV-T_{HR} $EQD2_{10}$	D98 CTV-T_{HR} $EQD2_{10}$	D98 GTV_{res} $EQD2_{10}$	D98 CTV-T_{IR} $EQD2_{10}$	Point A $EQD2_{10}$	OTT[£]
Soft constraint*	> 90 Gy < 95 Gy[¤]	> 80 Gy	> 95 Gy	> 60 Gy	> 65 Gy	50 days
Hard constraint**	> 85 Gy	> 75 Gy	> 90 Gy	-	-	55 days



OAR Dose planning aims	Rectum D_{2cm3} $EQD2_3$	Bladder D_{2cm3} $EQD2_3$	ICRU Recto-vaginal point $EQD2_3$	ICRU bladder point $EQD2_3$	Bowel D_{2cm3} $EQD2_3$	Sigmoid D_{2cm3} $EQD2_3$
Soft constraint*	< 65 Gy	< 80 Gy	< 65 Gy	< 75Gy	< 65 Gy[$]	< 70 Gy[$]
Hard constraint**	< 75 Gy	< 85 Gy[#]	< 75 Gy	< 85Gy	< 75 Gy[$]	< 75 Gy[$]

Figure 4 Dose planning aims for a clinical environment with MRI-based brachytherapy and availability of IC/IS applicators (based on clinical evidence and the dosimetric performance in the EMBRACE studies).

*Soft constraints are expected to be achieved in at least ~70-80% of patients.

**Hard constraints are expected to be achieved in at least ~90-95% of patients. In patients with involvement of bladder or rectum at time of brachytherapy (BT), the hard constraints may be exceeded for the respective organs. For advanced parametrial involvement at time of BT, it may also not be possible to achieve the hard constraints on target dose.

¤The soft constraint of <95 Gy to CTV-T_{HR} is not of highest priority as it may often be exceeded in tumors which are of limited size at time of BT.

£OTT: overall treatment time.

#In the EMBRACE II protocol a hard constraint on bladder D_{2cm3} of 90 Gy was used. Due to new clinical evidence, a lower hard constraint is proposed. However, in cases with large CTV-T_{HR} volume at time of BT it may be difficult to achieve 85 Gy. Furthermore, in patients with bladder involvement, this constraint should not be prioritized.

$For the sigmoid/bowel structures the dose constraints are particularly relevant in case of nonmobile bowel loops resulting in the situation that the most exposed volume is located in the same part of the organ in each BT fraction.

With the growing clinical evidence that higher PIBS doses are related to a higher incidence of vaginal toxicity,[72] a next logical step is to transport this knowledge into dose planning aims. The dose to the PIBS point is affected by the EBRT lower target border and therefore awareness of the location of this border is essential. In the EMBRACE II protocol the CTV-T_{LR} includes uninvolved vagina with a 20 mm margin measured from the most inferior position of the initial CTV-T_{HR}, along the vaginal axis. The PIBS+2cm point usually receives the full prescribed EBRT dose plus a considerable contribution from BT. The PIBS+2cm dose can therefore mainly be modulated by decreasing vaginal BT loading when possible without violating hard constraints of higher priority. The dose to the PIBS-2cm point normally receives a very low dose, and in the EMBRACE II protocol a dose constraint for PIBS-2cm of <5 Gy (EBRT dose) has been introduced based on the rationale that recurrences in the lower vagina are very rare.[85] It is likely that ongoing research will soon provide evidence for dose constraints for the PIBS points.[72] Furthermore, the EMBRACE II protocol advises for vaginal dose de-escalation when possible without compromising target dose.[33,86] Vaginal dose de-escalation involves as first priority the adherence to the ICRU rectovaginal dose constraints and as second priority the lowering of the vaginal TRAK to, eg, 30-40% of the total TRAK applied in a typical standard loading plan with around 50%-50% distribution of TRAK between tandem and vaginal sources. Vaginal dose de-escalation can be further evaluated with dose assessment at the 5mm lateral dose points and visual inspection of the 140% isodose curve as described in the EMBRACE II protocol.[91]

Fractionation and Weighting between EBRT and BT Dose

The dose and fractionation pattern and balance between EBRT and BT dose prescription should facilitate as large a

therapeutic window as possible for tumor control and morbidity while also considering OTT as well as the burden for the patient in terms of number of BT implantations/fractions. Administration of higher EBRT doses leads to considerably larger volumes being irradiated to intermediate dose levels. The 60 Gy isodose surface volume around the BT applicator is typically 30-50% larger for 50 Gy schedules as compared to 45 Gy schedules,[35] and further boosting with EBRT to 60 Gy or more to the primary tumor volume leads to significant increase of intermediate dose volumes.[3,87–89] In general, high EBRT doses have not demonstrated higher disease control, but rather increased morbidity.[54,90] Specifically, EBRT schedules with prescription dose of 50 Gy as compared to 45 Gy have not evidenced higher lymph node control (ongoing EMBRACE analysis), but are related to more morbidity.[71,91,27,49] Therefore, it can be considered beneficial to restrict the EBRT dose to 45 Gy. Schedules with 45 Gy EBRT require larger BT dose contribution, potentially more BT fractions, and higher demands on the BT quality (such as, eg, the availability of IC/IS). A future perspective may be to consider even lower elective target dose levels and higher BT contribution depending on the risk profile of the patient as well as the assessment of nodal disease.[92]

The therapeutic window and the ability to reach dose constraints increases with more BT fractions, whereas more fractions also represent an increased burden for the patient in terms of anesthesia, applicator insertion, and/or additional overnight stays with the BT applicator in place.[93] This requires more resources from the hospital with potential increased load on operating theatre and imaging devices (MRI or CT) as well as the need for additional hospitalization. A frequently used fractionation schedule for image-guided BT includes 45 Gy EBRT combined with 4 fractions of high-dose rate BT, which may be delivered in 2 applicator insertions. Reduction from 4 to 2-3 fractions may be feasible for small tumors or tumors with good response applying sufficient dose to the limited size CTV-T_{HR}, without violating OAR dose constraints. Large residual tumor volumes with large size CTV-T_{HR} will benefit from 4 fractions in order to achieve the highest possible tumor control with acceptable morbidity.

Conclusion

The introduction of image-guided BT and 3D reporting has significantly improved the understanding of the relation between treatment-related parameters on local control/morbidity. As IGABT has now been broadly available for more than a decade, there are now mature outcomes available from mono-institutional series as well as from prospective multicenter studies. This has given rise to significant insights into dose and effect relations for both local tumor control and risk of morbidity. It has been demonstrated that local control is related to the doses delivered to the adaptive target volumes introduced by the GEC ESTRO recommendations. This confirms that these target volumes are indeed clinically relevant. For morbidity, clinical evidence of dose-effect relations is available for rectal, bladder, vaginal, and bowel toxicity as well as for fatigue. This has made it possible to provide evidence-based dose planning aims and dose prescription protocols, which can be used in clinical practice in image-guided BT.

While new clinical evidence for dose effects for many disease and morbidity-related endpoints has been a significant step forward, there are many topics that deserve further research and development. There is a need for more comprehensive modeling of risk factors for multiple disease-related endpoints (local, nodal, and systemic). Risk factors should include treatment-related factors including dose/volume parameters, but also factors that can facilitate further understanding of patient-related factors (eg, age, smoking, and comorbidity) and disease-related factors (eg, histology, tumor invasion/infiltration,[94] and tumor regression[95–97]), which interplay with the effect of treatment. Furthermore, biomarkers that can predict which patients can benefit from further treatment intensification or de-intensification are needed. In the context of the EMBRACE II study, substudies are investigating the predictive value of biomarkers and quantitative MRI for disease outcome.

Developments are also needed for enhanced normal tissue sparing. Research efforts should be prioritized to improve assessment of dose to OARs and organ substructures should be considered, eg, for vagina, clitoris, bladder neck/trigonum, urethra, ureters, anal canal, and different parts of the bowel. Improved assessment of dose to these structures may increase the understanding of treatment-related risk factors for development of several morbidity endpoints and help to introduce new dose constraints for relevant organ structures. Also, further analysis of the combined effect of large volumes irradiated to intermediate dose levels (30-60 Gy) and small volumes irradiated to high-dose levels (hotspots to >60 Gy) could produce insights into development of morbidity. Finally, in order to help individualization of treatment, it is essential to evaluate the impact of patient and disease-related factors on the risk of morbidity.

Specific for BT (as compared to EBRT) is that imaging, contouring, dose planning and dose delivery are carried out in a compressed workflow within 1 day. The complexity of the process in terms of the number of structures to be contoured and the amount of dose planning aims to be considered during dose optimization needs therefore to be carefully balanced against time resources in daily routine. New methods for automatic segmentation[98] and planning may considerably accelerate the BT workflow and may also facilitate the introduction for additional structures in dose evaluation and dose planning.

While dose-effect models may demonstrate correlations between dose-volume parameters and local control or morbidity, the models do not explain the underlying mechanisms. More detailed understanding of the causal relationship between dose and effects can be reached through studies that are designed to measure physiological function in more detail, eg, through imaging, biopsies, functional measures etc. Such studies can also support the development of strategies for management of morbidity, as they

reveal the causal pathways and therefore offer treatment strategies.[5]

The current evidence for dose and volume effects is a good starting point for future research efforts focusing on development of individualized and risk adaptive radiotherapy approaches in LACC. Risk adapted radiotherapy is a pathway for improving local, nodal and systemic control in patients with high risk of recurrence while reducing treatment-related morbidity in intermediate- and low-risk patients. With such strategy, modulations of radiotherapy target, dose and treated volume are applied according to risk of disease failure and risk of morbidity. Risk group factors should include both status at diagnosis as well as tumor response, and may be based on a variety of assessments such as clinical parameters, imaging and biomarkers. Radiotherapy modulations could include changes in prescribed dose, fractionation, conformality, and OTT, and could also include combinations with new drug therapies including immunotherapy. Current dose and volume constraints are applicable within our current clinical frame and needs continuous development if the treatment is modulated. Future clinical studies exploiting risk adaptation should therefore also aim to empower the next generation of evidence on dose and volume effects for disease control and morbidity.

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