Seminars in
RADIATION ONCOLOGY

Image-guided Adaptive Radiotherapy in Cervical Cancer

Li Tee Tan MBBS, MRCP, FRCR, MD,[*] Kari Tanderup PhD,[†] Christian Kirisits PhD,[‡] Astrid de Leeuw PhD,[§] Remi Nout MD, PhD,[‖] Simon Duke MBBS, FRCR,[*] Yvette Seppenwoolde PhD,[‡] Nicole Nesvacil PhD,[‡] Dietmar Georg PhD,[‡] Kathrin Kirchheiner PhD,[‡] Lars Fokdal MD, PhD,[†] Alina Sturdza MD, FRCPC,[‡] Maximilian Schmid MD,[‡] Jamema Swamidas PhD,[¶] Erik van Limbergen MD, PhD,[#] Christine Haie-Meder MD,[**] Umesh Mahantshetty MD,[¶] Ina Jürgenliemk-Schulz MD, PhD,[§] Jacob C. Lindegaard DM, DMSc,[†] and Richard Pötter MD[‡]

This paper reviews the conceptual, methodological, and technical innovations underpinning strategies for adaptive target volume selection and risk-adapted dose prescription in cervical cancer. An adaptive target volume concept has been developed which reflects tumor shrinkage at the end of initial chemo-radiation, which serves for an image-guided boost delivered through brachytherapy, with a risk-adapted dose prescription to different gross tumor- and clinical target volumes defined at diagnosis and after 40-50Gy external beam radiotherapy, and adaptation of the treatment technique according to the topography of the tumor after response and adjacent organs at risk. Clinical results of these innovations are presented based on prospective and retrospective multi-center trials (IntErnational study on MRI-based BRachytherapy in locally Advanced CErvical cancer [EMBRACE], retroEMBRACE) with large patient cohorts (n = 1416, n = 731). The potential benefit of applying these strategies and using a specific multi-parametric dose prescription protocol are explored (EMBRACE-II) and overall current and future research strategies are outlined. The challenges of dissemination and implementation of these complex new techniques into clinical practice are discussed.
Semin Radiat Oncol 29:284–298

[*]Department of Oncology, Cambridge University Hospitals NHS Trust, United Kingdom
[†]Department of Oncology, Aarhus University Hospital, Denmark
[‡]Department of Radiation Oncology, Medical University of Vienna, Vienna, Austria
[§]Department of Radiation Oncology, University Medical Centre, Utrecht, the Netherlands
[‖]Department of Radiation Oncology, Leiden University Medical Center, the Netherlands
[¶]Department of Radiation Oncology, ACTREC, Tata Memorial Centre, Mumbai, India
[#]Department of Radiation Oncology, University Hospital Gasthuisberg, Leuven, Belgium
[**]Institute Gustave Roussy, Villejuif, Paris, France
Financial Disclosure: The EMBRACE studies have been supported by Varian Medical Systems, Elekta, Danish Cancer Society, R108-A6854-14-S31 and R150-A10177 and the Christian Doppler Laboratory for Medical Radiation Research for Radiation Oncology (Medical University of Vienna, Austria).
Conflict of Interest: None.
Address reprint requests to Richard Pötter MD, Professor Emeritus, Department of Radiation Oncology, Comprehensive Cancer Center, Medical University of Vienna, Waehringer Guertel 18-20, A-1090 Vienna, Austria.
E-mail: Richard.Poetter@akhwien.at

Introduction

Cervical cancer is one of the most common malignancies in women worldwide and the second most common cause of female cancer death. The survival rate for cervical cancer is 60%-70% in Western Europe and North America, compared to only 40%-50% in Central/Eastern Europe, and even lower in low and middle income countries. The lower survival rate in less affluent countries is largely due to more advanced disease at presentation because of the lack of systematic screening programmes.

The standard treatment for locally advanced cervical cancer is external beam radiotherapy (EBRT) with concomitant cisplatin-based chemotherapy followed by brachytherapy. For many decades, technological developments in cervix cancer brachytherapy have been limited and treatment planning has been based on X-rays and approaches originally developed by the classical brachytherapy schools in the early 20th century. The most commonly used system is the Manchester point A system which involves standard doses

https://doi.org/10.1016/j.semradonc.2019.02.010
1053-4296/© 2019 Published by Elsevier Inc.

prescribed to a fixed point regardless of tumor size, topography, and response to EBRT, and doses to organs at risk (OAR). This has resulted in a double penalty of suboptimal local control and survival, particularly for patients with large tumors, and significant treatment-related morbidity, particularly affecting the bowel, bladder, and vagina, with a major impact on health-related quality of life in survivors.

Advanced imaging has become an important research field in radiation oncology. The ever-increasing information obtained from advanced imaging has evoked an increasing interest in the potential benefit of adapting the dose to different target volumes according to the risk of recurrence, for example, with simultaneous integrated boost strategies. Examples include head and neck cancer where the high-risk gross tumor volume (GTV) may receive 65Gy in 30 fractions, the intermediate-risk uninvolved nodal regions 60Gy in 30 fractions, and the low-risk uninvolved nodal regions 54Gy in 30 fractions. Similarly, in prostate cancer, different doses may be delivered to the seminal vesicles, the whole prostate and the GTV within the prostate as identified on PET/CT imaging.[1,2] There is also interest in adaptive radiotherapy where the radiation treatment plan delivered to a patient is modified during a course of radiotherapy to account for temporal changes in anatomy due to weight loss (eg, head and neck[3]), internal motion (eg, lung[4]), and tumor shrinkage.[5] Diagrammatic representations of the ICRU89/GEC-ESTRO tumor response-adapted target concepts are shown in Figure 1. For cervix cancer, the power of morphologic imaging based on magnetic resonance imaging (MRI) has given rise to the development of response assessment and image-guided brachytherapy while multimodality imaging has been additionally explored for tissue characterization.[6-10]

For most tumor sites, strategies for prescribing variable dose levels to different target volumes are applied to the clinical situation at diagnosis when the GTV is relatively large, which limits the maximum dose that can be delivered. In contrast, adaptive strategies usually involve modification of the treatment plan to account for organ motion or shrinkage of target volumes only. Uniquely, these 2 strategies have been combined in cervical cancer treatment—an adaptive target volume concept has been developed which reflects tumor shrinkage and the topography of OAR at the end of initial chemo-radiation (after 45-50Gy), which serves for a brachytherapy boost with a risk-adapted dose prescription to different GTV and clinical target volume (CTV) volumes defined at diagnosis and at the end of chemo-radiation and constraints for OAR.

This paper reviews the conceptual, methodological, and technical innovations underpinning strategies for adaptive target volume selection and risk-adapted dose prescription for image-guided brachytherapy after chemo-radiation for cervical cancer. Clinical results of these innovations are presented. The potential benefits of extending these strategies to initial chemo-radiation for cervical cancer are explored. The challenges of dissemination and implementation of these complex new techniques are discussed.

Response-adaptive Target Concept: ICRU and GEC-ESTRO Recommendations

In 2000, the GEC-ESTRO GYN Working Group was established to support and shape the emerging field of gynecological image-guided adaptive brachytherapy (IGABT). Clinicians from a few pioneering European IGABT centers (Leuven, Paris, Vienna) with different historical traditions met to discuss and agree on a common language for prescribing, recording, and reporting IGABT for cervix cancer. This culminated in the publication of 2 recommendations on contouring and dose reporting in 2005 and 2006.[11,12] In 2005, the GEC-ESTRO GYN Working Group founded a network to promote collaboration between the increasing number of institutions with research and development activities in IGABT. The group launched the “IntErnational study on MRI-based BRachytherapy in locally Advanced CErvical cancer” (EMBRACE, www.embracestudy.dk, NCT00920920) to evaluate the outcome of IGABT in a multicenter setting in 2008. In 2010 and 2012, the GEC-ESTRO GYN network published a further 2 recommendations on applicator reconstruction and imaging.[13,14] The Gyn GEC-ESTRO Recommendations I-IV have been used as the conceptual framework for the implementation of IGABT worldwide and are embedded into the new ICRU Report 89 “Prescribing, Recording, and Reporting Brachytherapy for Cancer of the Cervix.”[15]

The ICRU89/GEC-ESTRO recommendations are based on repetitive tumor assessment through clinical examination and imaging, preferably MRI, with adaptation of dose according to the tumor extent at diagnosis, and the response to EBRT at the time of brachytherapy. A common terminology for different target volumes with different risks of recurrence at different time points has been defined.

At time of diagnosis the following volumes are defined (Fig. 2a):

- Initial GTV-T_{init}—the GTV-T_{init} is the primary tumor at diagnosis as assessed by clinical examination and imaging. The clinical and imaging volumes may be different, and a composite GTV-T should be delineated in these situations.
- Initial high-risk CTV-T_HR_{init}—the CTV-T_HR_{init} is the volume bearing the highest risk of recurrence at diagnosis. For cervical cancer, this includes the whole cervix as a minimum in addition to the GTV-T_{init}.
- Initial low-risk CTV-T_LR_{init}—the CTV-T_LR_{init} represents compartments at risk for potential microscopic spread from the primary tumor. In locally advanced cervical cancer, the CTV-T_LR_{init} comprises the whole parametria, the whole uterus, the upper part of the vagina, and the anterior/posterior spaces towards the bladder and rectum.

An adaptive CTV for the primary tumor (CTV-T_{adapt}) can in principle be defined after any treatment phase. The CTV-T_{adapt} takes into account the morphology and topography of the

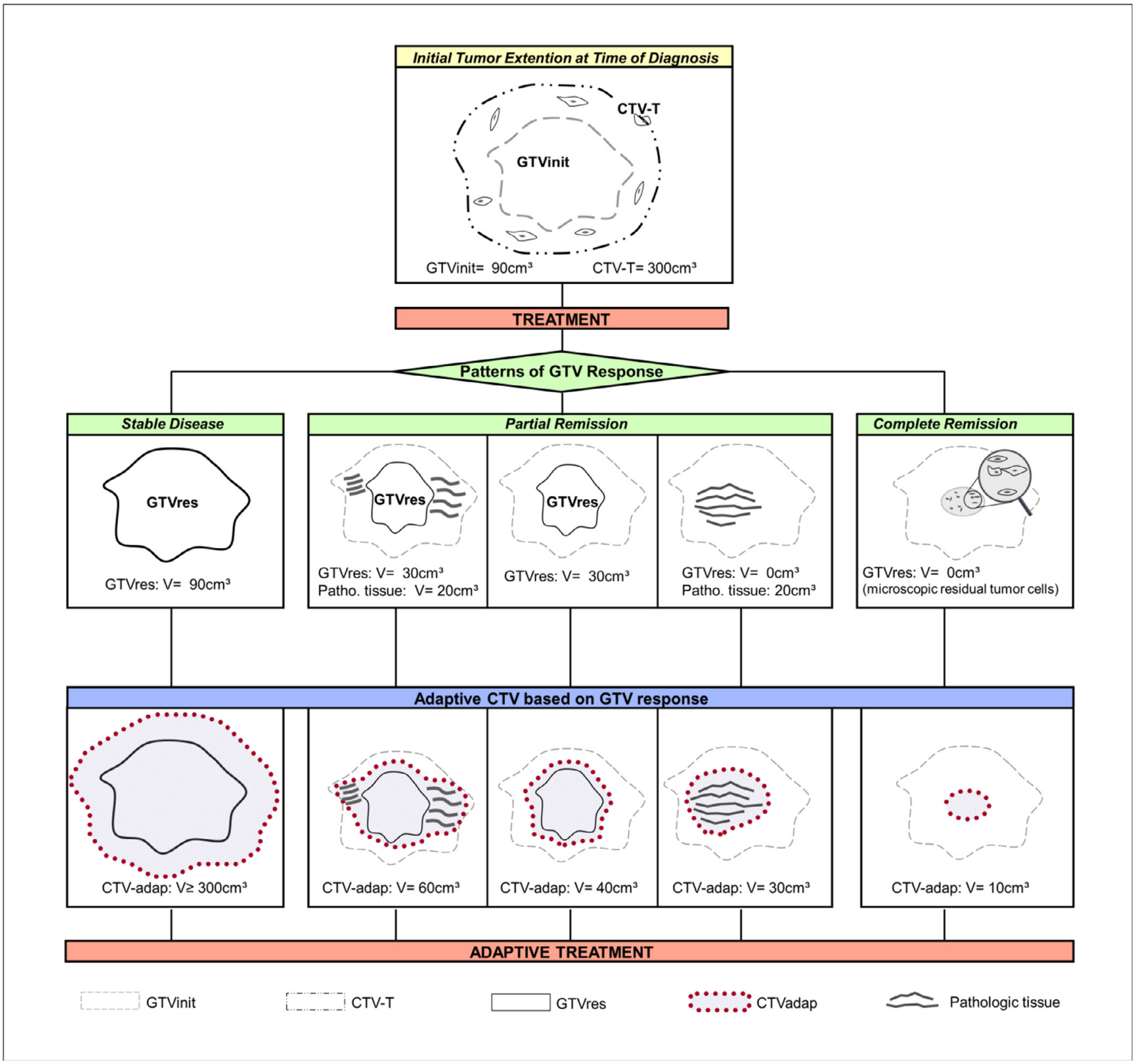


Figure 1 General adaptive target concept with a CTV-T_{init} based on the GTV-T_{init}, and an individualised CTV-T_{adapt} based on the GTV-T_{init} response after treatment and assessment of GTV-T_{res} (ICRU 89). (Color version of figure is available online.)

GTV-T_{init} (eg, expansive vs infiltrative) and the morphologic and/or functional response to treatment. For locally advanced cervical cancer, the adaptive volumes are usually defined at the end of initial chemo-radiation with 40-50Gy which is assumed sufficient to control microscopic disease, that is, at the time of brachytherapy. The relevant volumes are (Fig.2b):

- Residual GTV-T_{res}—the GTV-T_{res} is the residual tumor at the time of brachytherapy.
- Adaptive high-risk CTV (CTV-T_HR_{adapt})—the CTV-T_HR_{adapt} is the volume bearing the highest risk for recurrence. For cervical cancer, this includes the GTV-T_{res}, the whole cervix, and adjacent residual pathologic tissue, if present.
- Adaptive intermediate-risk CTV (CTV-T_IR_{adapt})—the CTV-T_IR_{adapt} represents the GTV-T_{init} as superimposed on the topography at the time of brachytherapy, together with a margin surrounding the CTV-T_HR_{adapt}.

Adaptive Treatment Planning

Adaptive treatment planning takes into account the changes during treatment and prescribes specific (boost) doses to the various volumes of interest. For definitive cervical cancer radiotherapy, these volumes are boosted through brachytherapy in order to achieve very high

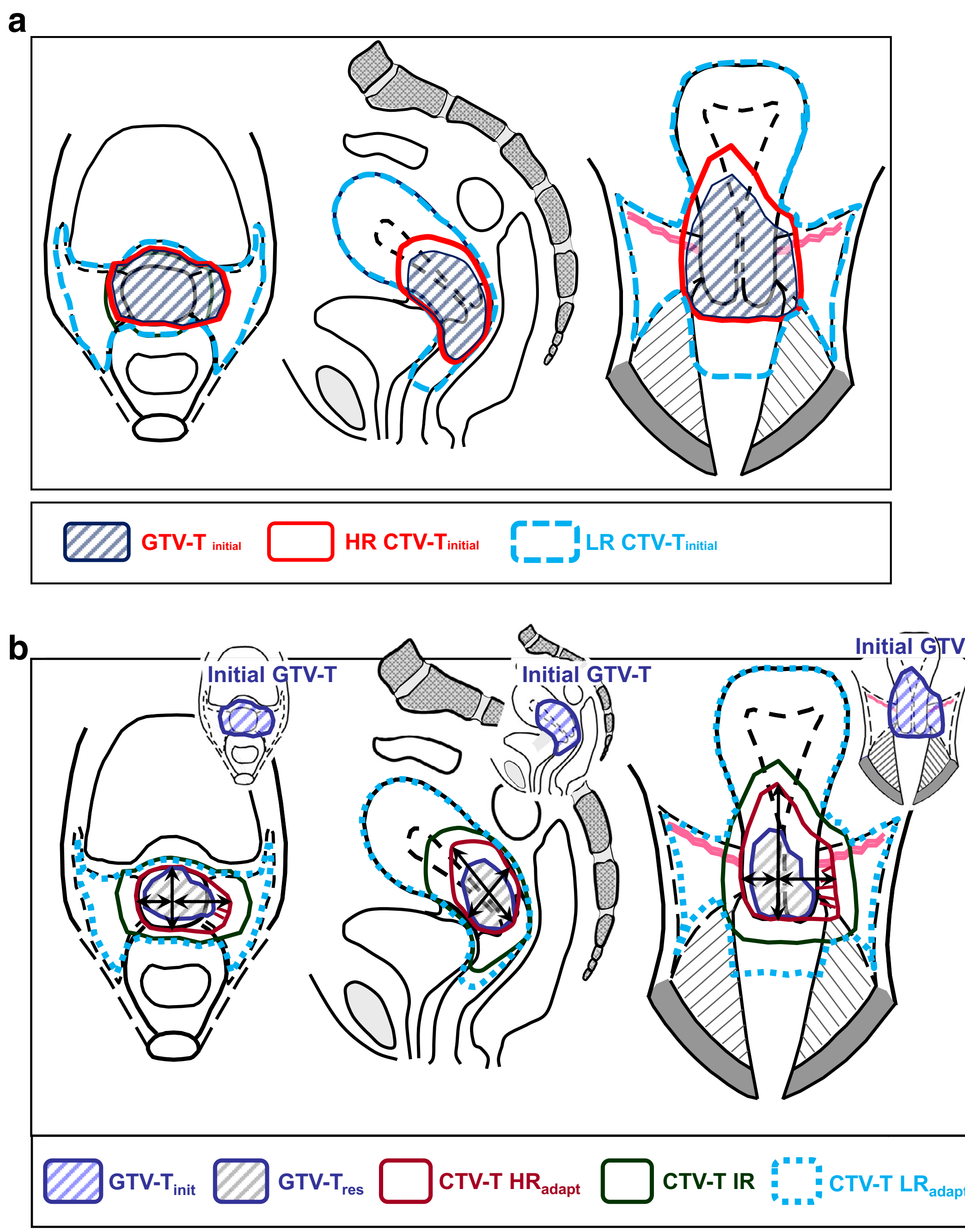


Figure 2 Initial and adaptive target concepts for a stage IIB bulky cervical cancer. (a) Initial GTV-T and CTV-T: large GTV-T_{init}, initial CTV-T HR, and initial CTV-T LR: coronal, transversal, and sagittal view. (protocol EMBRACE II, www.embracestudy.dk). (b) Adaptive target volumes at time of brachytherapy: CTV-T_HR_{adapt} based on the tumour burden after chemo-radiation ,that is, the GTV-T_{res} and any residual pathologic tissue (stripes), and a CTV-T_IR_{adapt} based on the tumor burden at diagnosis, that is, the GTV-$T_{init.}$ The CTV-T_LR_{init} represents the compartments of potential tumor spread at diagnosis. (modified from ICRU 89).

doses in defined small volumes, for example, the CTV-T_HR_{adapt}, the GTV-T_{res}, and the CTV-T_IR_{adapt}. In principle, such adaptive treatment planning may be used for any clinical scenario which may benefit from differential doses to different volumes at different risk of recurrence (eg, vagina,[16,17] ano-rectal,[18,19] oesophagus,[20] or head and neck [nasopharynx][21]), using any form of high-dose boost technique (eg, brachytherapy, stereotactic photon boosts, or protons and other heavy particles) (Fig. 1).

The regression of cervical cancer during chemo-radiation has been investigated in several studies.[22] The overall reduction in volume is around 80%-90% at the time of brachytherapy.[23] A comprehensive analysis of the different response patterns and the resulting CTV-T HR_{adapt} has been performed for a subcohort of EMBRACE I (n = 481), taking into account volumetric changes as well as changes in pattern of spread, for example, in the parametria.[24-26] These analyses confirm the overall excellent response rate, but also provide detailed qualitative and quantitative information on the various response patterns, which is essential for adaptive treatment planning based on the adaptive target volume concept. Only 75 of 481 patients (16%) with a mean GTV_{init} of 79 cc were classified as poor (volumetric) responders with residual distal parametrial disease at brachytherapy and a large CTV-T HR_{adapt} of 60 cc, whereas 147 of 481 patients (31%) with a comparable mean GTV_{init} of 73 cc were classified as moderate responders without residual distal parametrial disease at brachytherapy and a CTV-T HR_{adapt} volume of 39 cc (Fig. 3).[26]

The inherent advantage of brachytherapy is its steep dose gradient which allows high doses to be delivered to the tumor while limiting the dose to surrounding OAR (Fig. 4). For many decades, this advantage has not been fully exploited as with conventional X-ray-based brachytherapy the dose distribution is largely determined by the configuration of the applicators (eg, the pear-shaped distribution of tube and ring/ovoids applicators) while the source configuration is kept largely uniform.

With the advent of modern afterloading equipment, it is now possible to modify individual source positions and dwell times to shape the dose distribution to the tumor topography while avoiding adjacent OAR. This has given rise to the need for new applicators with greater flexibility for source placement which would allow better adaptation of dose distributions to create complex shapes. Some examples of new applicators developed for cervix cancer IGABT are shown in Figure 5. In general, these applicators combine conventional intracavitary applicators (ring or ovoids) with a single plane of interstitial needles,[27-29] a double plane of interstitial needles (straight and oblique),[30] straight, oblique, and perineal needles[31] or highly individualized applicators based on 3D printing.[32] These new applicators take into account the patient and tumor specific situation.

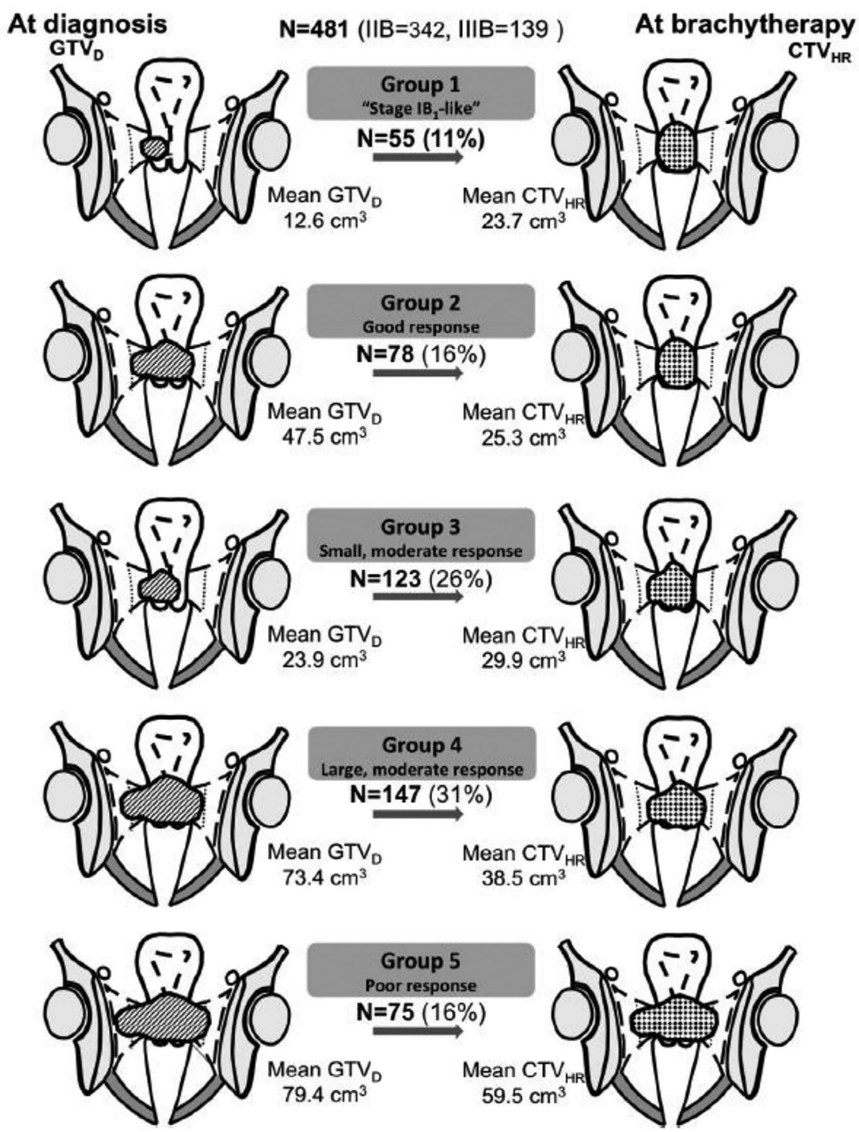
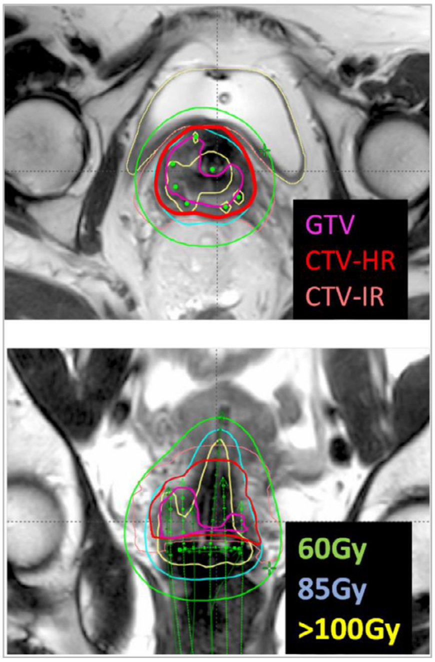


Figure 3 MRI-based volume and response characteristics of FIGO stage IIB and IIIB cervical cancer evaluated at diagnosis and at brachytherapy classified into 5 major groups. The striped volume represents the GTV-T_{init} and the dotted volume the CTV-T_$HR_{adapt.}$[32]



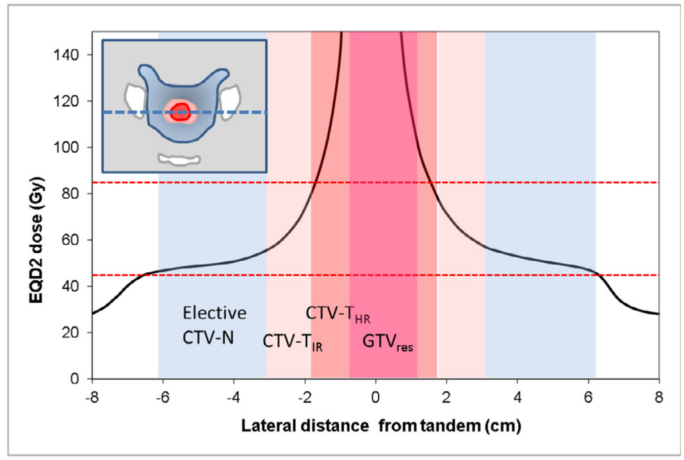


Figure 4 Left panel: paratransaxial and coronal MRI with applicator in place. Isodose levels of 60Gy (green), 85Gy (cyan), and 100Gy (yellow) are indicated in relation to CTV-T_IR$_{adapt}$, CTV-T_HR$_{adapt}$, and GTV-T$_{res}$.

Right panel: The transverse pelvic dose profile at the level of point A is based on combined EBRT and intracavitary brachytherapy total dose in EQD2. The horizontal dashed lines indicate 45Gy and 85Gy. The steep dose gradient facilitates the risk-adapted dose prescription with >60Gy to CTV-T_IR$_{adapt}$, >85Gy to CTV-T_HR$_{adapt}$, and >95Gy to GTV-T$_{res}$. (modified from ICRU 89).

The full potential of these new applicators is critically dependent on the use of MRI for improved delineation of tumor, targets and OAR, and an understanding of the ICRU/GEC-ESTRO target concepts of different risk-volumes. These volumes reflect tissue with different burdens of macroscopic and microscopic tumor at diagnosis and at the time of brachytherapy. As the risk of recurrence is related to tumor burden, the dose prescription is adapted to each target volume and varies widely from 60Gy at the edge of the CTV-T_IR$_{adapt}$ (which in turn is adapted to the extent of

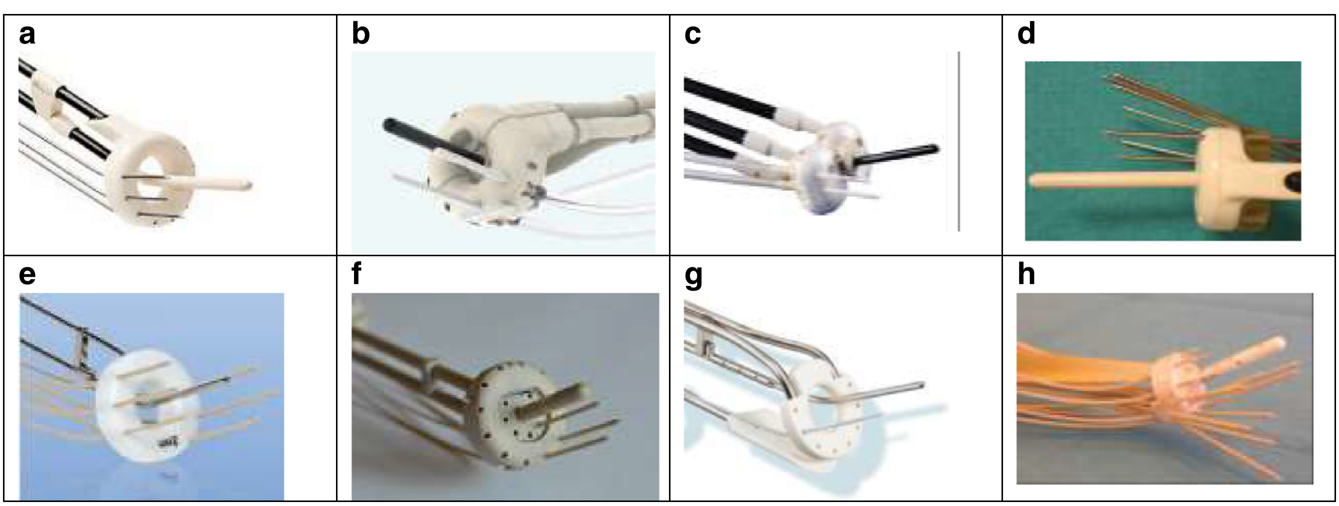


Figure 5 Examples of combined intracavitary-interstitial applicators: (a) Vienna applicator based on tandem-ring with parallel needles (Elekta), (b) Venezia applicator with split ring and option for double plane parallel and oblique needles (Elekta), (c) Utrecht applicator based on tandem-ovoid with parallel needles (Elekta), (d) Vienna II applicator based on tandem-ring with double plane of parallel and oblique needles (in-house, Medical University of Vienna), (e) Vienna-style ring applicator in titanium with parallel needles (Varian Medical Systems), (f) Vienna-style applicator in plastic with double plane parallel needles (Varian Medical Systems), (g) Interstitial Ring applicator with parallel needles (Bebig), (h) 3D printed individualized template (in-house, Aarhus University Hospital) with tandem, parallel, and oblique needles (Varian). (Color version of figure is available online.)

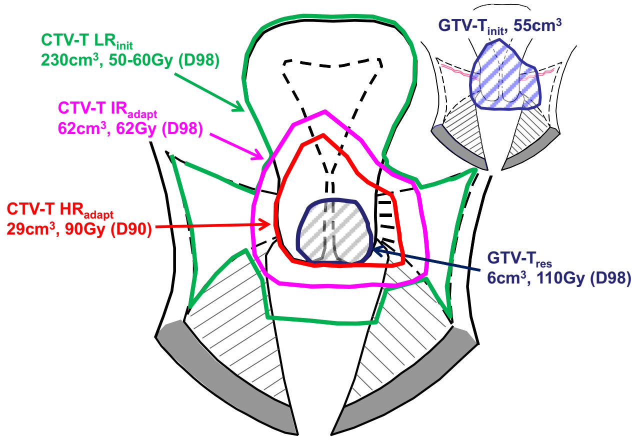


Figure 6 Median volumes and mean doses (D90 for CTV-T HR_{adapt}, D98 for CTV-T IR_{adapt} and GTV-T_{res}) for adaptive radiotherapy/IGABT in cervical cancer (unpublished data from the EMBRACE studies (EMBRACE I, n = 1300 and EMBRACE II (CTV-T LR_{init}, n = 168)). Initial median GTV-T in EMBRACE II is 55 cm^3. The anatomical location of the GTV-T_{init} at the time of diagnosis is reflected in the CTV-T_IR_{adapt} defined at brachytherapy; this region received a median near-minimum dose of 62Gy in EMBRACE I. In good-responding tumors, the dose at the limits of the GTV-T_{init} is 60-70Gy, while in poor-responding tumors the region of GTV_{init} may receive doses similar to the CTV-T HR_{adapt} (eg, around 80Gy).

tumor at diagnosis, that is, the GTV-T_{init}), 85Gy at the edge of the CTV-T_HR_{adapt} (volume at high risk of recurrence after chemo-radiation) and >90Gy to the GTV-T_{res} (macroscopic disease on MRI at the time of brachytherapy).

Several monoinstitutional studies[33,34] and the prospective multicenter EMBRACE study have demonstrated that a highly differential dose distribution with significant dose escalation is clinically feasible with IGABT in cervical cancer (Fig. 6]. It is particularly noteworthy that this has been achieved without breakdown in tissue as has been observed in adaptive studies in other clinical sites.[35] This is because with IGABT, the "super-high" doses are only administered to small volumes as shown in Figure 6. The response-adaptation of volume is the key factor to identify volumes which are small enough to tolerate such high doses.

The dose adaptation according to response with IGABT represents a considerable change of practice compared to classical point A based brachytherapy.[36] The individualized dose prescription in EMBRACE-I resulted in improved target dose coverage while the isodose surface volumes (V85Gy) [ICRU 89] decreased by 23% overall compared to the standard plans used with point A based brachytherapy.[37] There was volume de-escalation for the V85Gy in 41% of patients and escalation in 21% of patients.

Clinical Results—Retro-EMBRACE and EMBRACE

The first EMBRACE study (EMBRACE-I) was a prospective observational study of chemo-radiation and MRI-based IGABT. Quality assurance was carried out to ensure uniform target definition and dose reporting of IGABT according to GEC-ESTRO recommendations,[38] but institutions could follow different practices regarding EBRT and brachytherapy techniques and dose prescription. Launched in 2008, the study closed at the end of 2015 with the accrual of 1416 patients. In 2010, the GEC-ESTRO GYN network launched Retro-EMBRACE, a retrospective study of patients treated with CT or MRI-based IGABT before the start of EMBRACE-I. Data on 852 patients from 12 centers worldwide were collected.

Retro-EMBRACE demonstrated that IGABT results in excellent local and pelvic control.[39] The 3-year actuarial pelvic control rate was 96% for stage IB disease, 89% for stage IIB disease, and 73% for stage IIIB disease. These results are superior to those reported in large mono and multicenter historical cohorts involving radiotherapy alone.[40,41] as well as more recent reports of chemo-radiation in cohort studies[42] and randomized trials[43] with an overall increase in pelvic control of around 10% (Table 1). The beneficial effect of IGABT on pelvic control was most pronounced in advanced disease. The overall survival was similar to those reported in randomized trials of chemo-radiation[43-45] but around 12% better than large population-based cohorts treated with chemo-radiation.[43,46,47] At the same time, major morbidity (grades 3-5) was limited after IGABT (3%-6% per organ). The prospective French STIC trial also reported a 50% reduction of grade 3 and 4 morbidity for 3D IGABT compared to 2D brachytherapy.[48]

The inter-institution and inter-patient dose variations in Retro-EMBRACE have provided a unique opportunity to investigate the dose and volume effects for tumor targets and OAR. There was a significant correlation between local control and dose, volume, and overall treatment time (OTT) for all target volumes at the time of brachytherapy: GTV-T_{res}, CTV-T_HR_{adapt}, and CTV-T_IR_{adapt}.[49] A D90 dose of ≥85Gy to CTV-T_HR_{adapt} delivered in 7 weeks results in a 3-year local control rate of ≥94% in small targets (CTV-T_HR_{adapt} <20cc), >93% in intermediate size targets (CTV-T_HR_{adapt} 20-30 cc), and >86% in large targets (CTV-T_HR_{adapt} 31-70 cc). For the CTV-T_IR_{adapt} and GTV-T_{res}, D98 doses of ≥60Gy and ≥95Gy respectively, are required to assure similar levels of local control. The ability to achieve adequate dose to target volumes depended on the brachytherapy technique used; for large tumors, use of combined intracavitary/interstitial brachytherapy significantly increased local control without increasing morbidity.[50]

30% of Retro-EMBRACE patients experienced treatment failure; 9% had local failure, 6% regional (nodal) failure, and 13% pelvic failure (local and/or regional). 24% of patients had distant failure (systemic and/or paraaortic nodes); of these, 21% had systemic metastases and 9% had para-aortic node failure. Six percent of patients had pelvic failure without distant failure while 17% had distant failure without pelvic failure. Overall, 6% of patients had pelvic failure alone, 17% had distant failure alone, and 7% had both pelvic and distant failure.[51]

Table 1 5-year pelvic failure in Retro-EMBRACE (IGABT) compared with mono- and multicenter historical cohorts[1] and meta-analysis from 2008 on chemoradiation[2] and selected chemoradiation trials[3], all treated with conventional brachytherapy. Crude data are shown for all cohorts (except for Eifel 2004 for IB/IIB and IIIB). For the TATA trials, data are available only for IIIB and IB2/IIB (eligible for surgery), respectively according to the design of these trials. [4]For comparison of the overall pelvic failure rates the different composition of the cohorts in regard to stage has to be taken into account

	n	Stage	IB	IIB	IIIB	Overall[4]	Concomitant Chemotherapy
RetroEMBRACE 2016	731	IB: 17% IIB: 50% IIIB: 20%	4%	11%	25%	13%	77%
Perez 1998[1]	1499	IB: 33% IIB: 29% IIIB: 23%	12%	21%	41%	23%	0%
Barillot 1997[1]	1875	IB: 26% IIB: 29% IIIB: 25%	13%	24%	49%	NA	0%
Vale 2010[1]	471	IB: 11% IIB: 51% IIIB: 23%	NA	NA	NA	22%	100%
Vale 2008[2]	3.128	IB: <24% IIB: 36% IIIB: 38%	NA	NA	NA	23%	50%
Rose 1999[3]	176	IIB: 58% IIIB: 39%	NA	NA	NA	19%	100%
Whitney 1999[3]	169	IIB: 61% IIIB: 34%	NA	NA	NA	>25%	100%
Eifel 2004[3]	195	IB2: 33% IIB: 36% IIIB: 25%	IB2 + IIB: 13%		29%	17%	100%
TATA 2018[3]	317	IB2: 18% IIB: 57%	IB2 + IIB: 14%		-	14%	100%
TATA 2018[3]	424	All IIIB	–	–	29%	29%	100%

NA, not available.

Preliminary analysis of the pattern of failure in the EMBRACE-I study showed that 51% of local failures occurred in the CTV-T_HR$_{adapt}$ alone, 17% in the CTV-T_IR$_{adapt}$ alone, and 30% in both the CTV-T_HR$_{adapt}$ and the CTV-T_IR$_{adapt}$. Only 2% of local failures were unrelated, a finding which further validates the response-adapted ICRU/GEC-ESTRO target volume concepts.[52] Eleven percent of patients experienced nodal failures; for node-negative and node-positive patients at presentation, this was 7% and 16%, respectively. At diagnosis, 99% of node-positive patients had pathological nodes in the pelvis and 14% in the para-aortic region. In contrast, 55% of patients with nodal failures recurred in the pelvis, while 68% recurred in the para-aortic region. Of the patients with nodal failure, 41% developed nodal recurrence outside the irradiated elective nodal volume (39% in the para-aortic region), 40% inside the elective nodal volume, and 35% inside the nodal boost target.[51] There were significantly more systemic relapses in node-positive and advanced stage patients who received ≤4 chemotherapy cycles compared with those who received ≥5 cycles.[53]

EMBRACE-I has also provided descriptive evaluations of morbidity-time patterns as well as analyses of risk factors including dose. While major morbidity was limited, mild morbidity reported by patients and physicians was frequent and had an adverse impact on quality of life.[54] Vaginal morbidity, particularly stenosis, was prevalent[55] and correlated with the prescribed EBRT pelvic dose as well as the brachytherapy dose at the ICRU recto-vaginal point.[56] The overall volume irradiated to 43Gy (V43Gy) during EBRT was shown to be associated with acute and late bowel morbidity.[57-59] Dose-effect relationships have also been demonstrated for rectal morbidity[60-65]; limiting the rectal D2cc to ≤65Gy reduced the incidence of G2 or greater bleeding and proctitis to ≤5%, while limiting the rectal D2cc to ≤75Gy reduced the incidence of fistulae to ≤3%.[65] Intermediate doses to larger volumes of the rectum (eg, V55Gy) were also predictive of rectal morbidity.[66] Dose-effect relationships for the bladder have been demonstrated in mono-institutional analyses,[62,64] and preliminary findings from EMBRACE-I suggest an advantage in limiting the bladder D2cc to ≤80Gy. The use of combined intracavitary/interstitial brachytherapy results in less OAR morbidity compared to intracavitary brachytherapy alone in patients with parametrial infiltration.[67]

Current Research Questions—EMBRACE-II

In 2016, the GEC-ESTRO GYN network launched EMBRACE-II (www.embracestudy.dk, NCT03617133), a prospective interventional study with specific treatment interventions derived from the evidence collected from the

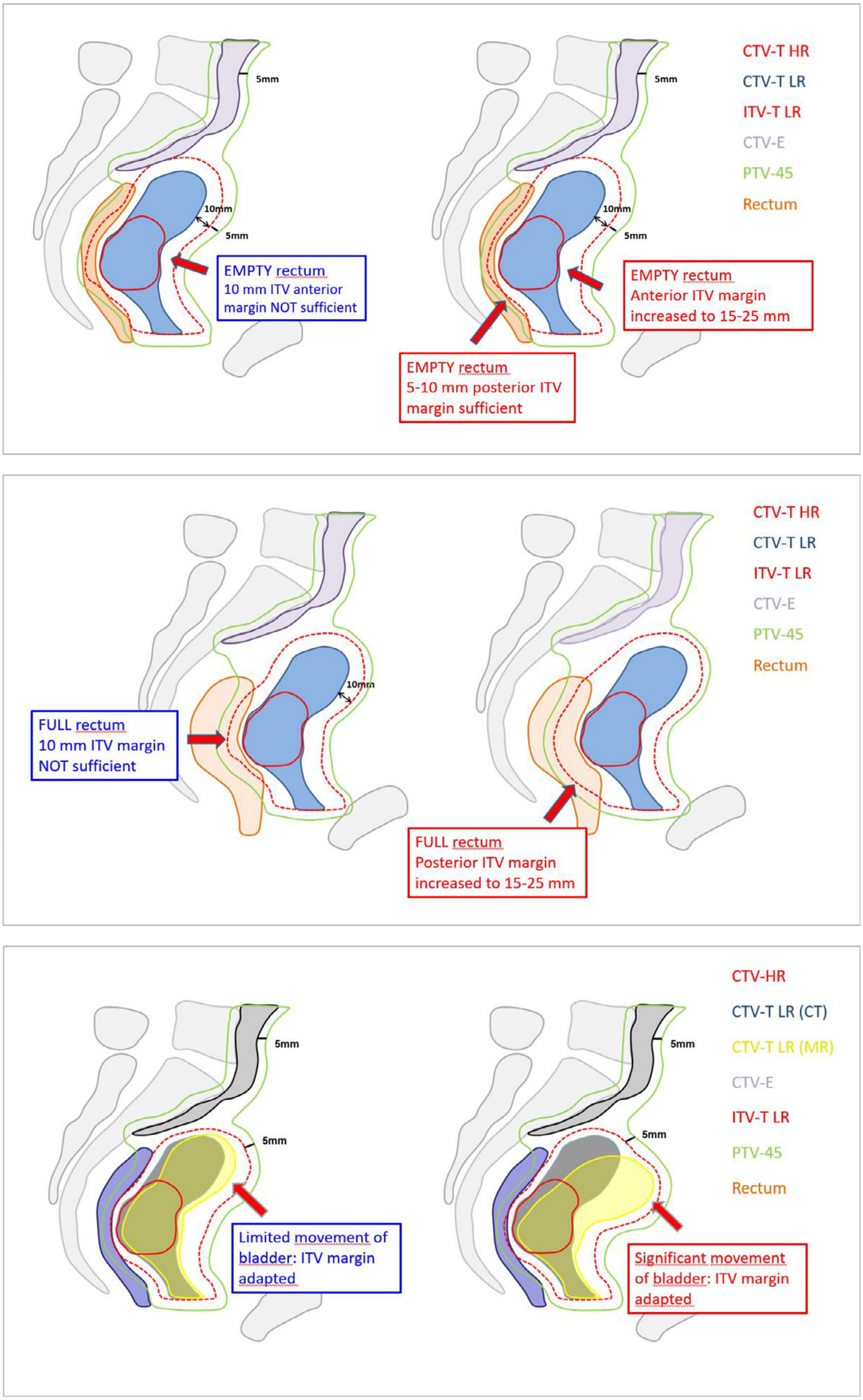


Figure 7 Examples of individualized CTV-T to ITV-T margins for 3 scenarios—empty rectum, full rectum, and mobile bladder (modified from protocol EMBRACE II, www.embracestudy.dk). (Color version of figure is available online.)

first 2 EMBRACE studies.[68] EMBRACE-II combines the most advanced techniques currently available for EBRT and brachytherapy in cervix cancer, that is, intensity-modulated radiotherapy (IMRT/VMAT) and MRI-based IGABT, with the delivery of concomitant chemotherapy to the highest standard. The aims of the study are to prospectively validate the findings of Retro-EMBRACE and EMBRACE-I, and to benchmark an excellent overall survival, based on improved local, nodal, and systemic control, as well as reduction of morbidity and improvement of quality of life.

For IMRT, the ICRU89 tumor-related target concepts of GTV-T_{init}, CTV-T_HR_{init}, and CTV-T_LR_{init} have been systematically applied (Fig. 2a). A commonly-expressed concern about the use of IMRT for definitive radiotherapy for cervical cancer is the large day-to-day movement of the target, particularly the fundus of the uterus, which can require margins of up to 4cm to be applied for full coverage.[69] By implementing a risk-adapted target concept, it is possible to apply specific margins for uncertainties which ensures that GTV-T_{init} and CTV-T_HR_{init}, which is at greatest risk of recurrence, receives the full prescription dose of 45Gy, while the uninvolved fundus of the uterus, which is part of the CTV-T_LR_{init}, is allowed to receive 40Gy from EBRT in addition to the dose delivered through brachytherapy (the total EBRT + BT dosimetric aim is 45Gy for this volume with microscopic disease only). Similarly, a risk-adapted strategy has been applied to involved lymph nodes (GTV-N). A margin around the GTV-N is applied to create the CTV-N—this margin varies from 0-3mm taking into account extra-capsular extension and possible progression during treatment planning.

Systematic application of the internal target volume (ITV) concept is mandated to compensate for organ motion (Fig. 7). Two approaches are described:

- Individualized CTV-T to ITV-T margins based on multiple pretreatment imaging series that allow the assessment of the individual range of internal target motion, both for CTV-T_HR_{init} and CTV-T_LR_{init}.
- A "plan of the day" approach in which multiple library plans with different ITV-T margins applied are created for each patient.

Daily monitoring of target position is necessary to decide if replanning would be an advantage according to the motion patterns observed.

In addition, a risk-adapted protocol for irradiation of the elective lymph node CTV (CTV-E) has been implemented (Fig. 8). Retro-EMBRACE and EMBRACE-I showed that para-aortic failure is the major challenge for nodal control. The CTV-E for the pelvis is therefore extended at the cranial border to systematically include the nodes at the aortic bifurcation, a frequent area of nodal recurrence.[70] In addition, patients at higher risk of para-aortic and distant relapse (3 or more involved nodes or any common iliac node) will receive prophylactic para-aortic irradiation. At the same time, in patients at low risk for nodal recurrence (node-negative stage IA, IB1, or IIA1 squamous cell carcinomas with no uterine invasion), the CTV-E is reduced to exclude the nodes above the common iliac bifurcation to limit toxicity.

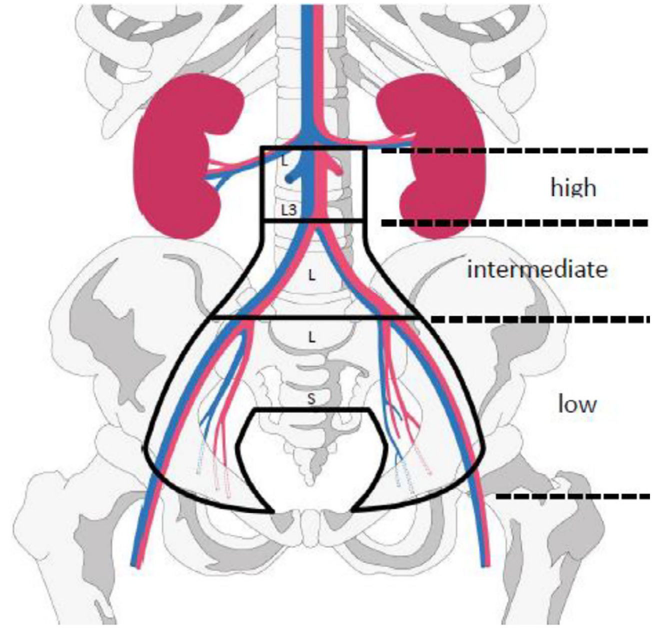


Figure 8 Risk-adapted elective lymph node CTV for cervix cancer EBRT (protocol EMBRACE II, www.embracestudy.dk). (Color version of figure is available online.)

Image-guided radiotherapy (IGRT), with daily in-room imaging and couch correction based on bony image fusion, is also mandatory. This has been shown to allow the planning target volume (PTV) margin to be reduced to 5mm without compromising target coverage. The combination of IMRT, IGRT, a 5mm PTV margin, and dose planning with relaxed target coverage criteria, has been shown to reduce the mean V43Gy from 2500 cc to ~1500 cc for patients undergoing pelvic irradiation in EMBRACE-I and the initial cohort of EMBRACE-II respectively, and from 3200 cc to ~2200 cc for patients receiving pelvic + para-aortic irradiation. Furthermore, the conformality index (V43Gy/PTV volume) was reduced from 1.54 to 1.02 for pelvic patients, and 1.51 to 1.03 for pelvic + para-aortic patients. In order to achieve the goals for EMBRACE II, targets for volumes (eg, V43 Gy) and conformality indices have also been set in addition to delineation guidelines and dose volume constraints for OAR (EMBRACE II protocol).

For combined brachytherapy and EBRT, a specific dose prescription protocol has been developed which balances the aim for high local control with acceptable morbidity (Table 2). The ability to reach the conflicting dose constraints for targets and OAR relies on increased use of intracavitary/interstitial brachytherapy. At the same time, EMBRACE-I patients with small tumors at the time of brachytherapy were treated to high doses which did not appear to translate to improved local control; EMBRACE II aims at de-escalating the brachytherapy dose in these patients to reduce morbidity.

Evidence from EMBRACE-I suggests that limiting the dose to the ICRU recto-vaginal point to less than 65Gy and the

Table 2 Risk-adapted brachytherapy dose prescription protocol for EMBRACE-II

Target	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 $EQD2_{10}$
Planning aim	>90 Gy <95 Gy	>75 Gy	>95 Gy	>60 Gy	>65 Gy
Limits for prescribed dose	>85 Gy	–	>90 Gy	–	–
OAR this whole headline is to be in the same format as the headline with target: bold, size etc.	Bladder D_{2cm3} $EQD2_3$	Rectum D_{2cm3} $EQD2_3$	Recto-vaginal point $EQD2_3$	Sigmoid D_{2cm3} $EQD2_3$	Bowel D_{2cm3} $EQD2_3$
Planning aim	<80 Gy	<65 Gy	<65 Gy	<70 Gy*	<70 Gy*
Limits for prescribed dose	<90 Gy	<75 Gy	<75 Gy	<75 Gy*	<75 Gy*

* For the sigmoid/bowel structures, these dose constraints are valid in case of non-mobile bowel loops resulting in the situation that the most exposed volume is located at a similar part of the organ.

EBRT dose to 45Gy will reduce the incidence of G2 or greater vaginal stenosis from 21% to 14%.[56] In typical brachytherapy standard loading patterns[71] and most clinical practices,[72] the relative vaginal loading is usually around 50%. There is potential to decrease the vaginal loading to 33% which should reduce the ICRU recto-vaginal dose significantly without compromising CTV-T_HR_{adapt} and GTV-T_{res} doses.[72] There are also differences between institutions regarding the definition of the lower border of the EBRT field which has impact on the volume of vagina included. A vaginal target concept for EBRT, and a specific vaginal dose reporting system referring to the posterior-inferior border of the symphysis,[73,74] have been specified in EMBRACE-II to reduce the EBRT ± brachytherapy dose to the lower and mid vagina.

Retro-EMBRACE showed that increasing OTT by 1 week is equivalent to a loss of 5Gy in the CTV-T_HR_{adapt} D90. The EMBRACE-II protocol has therefore set a target of ≤50 days for OTT in at least 80% of the patients[49]. To achieve this, efficient organization of the whole multimodality treatment is required, including delivering EBRT in a maximum of 25 fractions, use of simultaneous integrated boost in patients with lymph node involvement, minimizing treatment interruptions as much as possible and planning the timing of brachytherapy carefully. In EMBRACE-I, 70% of the patients received ≥5 cycles of chemotherapy, but there was a large variation between centers ranging from 15% to 85%. For optimal outcome particularly in high risk patients (stage III/IV, node positive[75]), the EMBRACE-II protocol therefore emphasizes administration of adequate doses of chemotherapy.

Training and Dissemination

There are numerous educational activities which have been developed to support the implementation of IGABT and IMRT/VMAT for cervical cancer. These include traditional face-to-face teaching courses and workshops conducted by radiotherapy professional organizations (eg, the ESTRO and ABS schools), national organizations (eg, the Dutch Cancer Society), individual institutions (eg, Vienna, Aarhus), and equipment manufacturers (eg, ELEKTA, Varian), as well as relatively new online courses such as the ESTRO FALCON contouring workshops and the UK e-Learning for Healthcare program for advanced radiotherapy techniques (www.e-lfh.org.uk/radiotherap-e).

Clinical trials of cervical cancer involving IGABT and/or IMRT/VMAT (eg, EMBRACE-I, INTERLACE) also require centers to undertake a radiotherapy quality assurance (RTQA) process before study participation. For EMBRACE-II, accreditation for each center involves positive evaluation by the study coordinators of: (1) a compliance questionnaire documenting clinical practice and infrastructure, (2) contouring and dose planning dummy runs for the principal investigator and physicist, and (3) registration and submission of 5 patient cases. Centers that have previously contributed to EMBRACE-I are required to complete the RTQA process for IMRT/VMAT and IGRT. New centers must undergo RTQA for both IGABT and IMRT/VMAT and IGRT.

Uniquely, EMBRACE-II has implemented a continuous medical education (CME) programme for all study participants to support RTQA. The RTQA and CME programmes are hosted on the Cambridge Cancer Medicine Online platform (www.ccmo.co.uk) which is linked to a bespoke online contouring tool (the Addenbrooke's Contouring Tool, ACT). Contouring CME content included questionnaires on previous experience, 2 practice cases with reference contours for self-learning, quizzes on key aspects of the protocol, and a contouring atlas.

A preliminary analysis of the contouring dummy run for IMRT/VMAT was presented at the 2018 ESTRO 37 meeting in Barcelona.[76] The regions of interest (ROIs) assessed were GTV-T_{init}, CTV-T_HR_{init}, CTV-T_LR_{init}, CTV-E, CTV-N, and ITV45. ROIs were scored as 2 (excellent), 1 (fair), or 0 (revision required). A total score of ≥9 (out of 12) was needed to pass. To date, 78 oncologists (including 9 non-principal investigators) from 67 centers have submitted contours for evaluation. 32 (41%) passed at the first attempt and a further 34 (42%) at the second attempt after individualized feedback. A further 5 (6%) passed on their third attempt. The ROIs that received the lowest scores were the CTV-E (1.01) and the ITV45 (1.06).

While difficulty with the ITV-T had been anticipated by the study coordinators as it was an unfamiliar concept, difficulty with the CTV-E was more surprising and change in practice to a risk-adapted nodal volume may have contributed. Uptake of contouring practice cases was moderate, probably because of the time necessary to contour. Quizzes may be a quick way of identifying areas of difficulty and reinforcing key aspects of the protocol. Analysis of participant responses has spurred development of targeted more time-efficient CME content, including a detailed ITV-T step-by-step guide and an online contouring learning tool ("Mini-Contour") for use in the annual update meetings to highlight key contouring issues.

For dose planning, the CME content included 3 training cases with different levels of complexity and quizzes for self-learning. 67 centers participated in the dose planning dummy run. Twenty-four (36%) centers passed after their first submission, while 23 (34%) and 10 (15%) needed one or more revisions, respectively.[77] The most common reasons for revisions were low conformality, relatively high OAR doses or insufficient lymph node coverage. Individual feedback improved plan quality considerably, resulting in a median V43Gy reduction of 133 cc from first plan submission to approved plan, and an improvement in conformality from 1.12 to 1.03. Further CME resources have been created in response to identified difficulties including planning "tricks and tips" advice and mini-quizzes for discussion at the annual update meetings.

The accreditation experience in EMBRACE-II has highlighted the challenges involved in implementing new radiotherapy techniques, especially if they involve a change of practice and/or unfamiliar concepts and skills. For physicians in EMBRACE-II, these include the risk-adapted target volumes for EBRT and brachytherapy, the use of image fusion (CT + MRI ± PET-CT) for contouring, and the ITV-T concept. For physicists and dosimetrists, there are "new" planning concepts of improved conformality through relaxed coverage criteria for all target volumes, and coverage probability planning for lymph node boosting. For radiation treatment technologists, there is the mandate to match on bony fusion only and the need to assess differential motion of the target on daily imaging. There is therefore a need to adapt training and education activities according to the experience of individual centers and staff groups.

Future Research Questions

Overall, IGABT has resulted in significant improvements in local control for cervical cancer patients of all stages. However, there is potential for further improvement for patients with advanced local disease (eg, IIIB) and for patients with large or asymmetric CTV-T_HR$_{adapt}$ at the time of brachytherapy through the use of more sophisticated applicators for combined intracavitary/interstitial brachytherapy. For node-positive patients, there is the potential to adapt treatment strategy according to the estimated risk of microscopic nodal spread through selecting appropriate targets (para-aortic, small pelvis) and according to nodal response during EBRT in patients with significantly enlarged lymph nodes. Moreover, 10%-30% of patients will still succumb to distant metastases depending on local and nodal stage. Currently, systemic adjuvant treatment does not have an established role in the treatment of cervical cancer and the results of adjuvant and neo-adjuvant chemotherapy are awaited from the OUTBACK (NCT01414608) and INTERLACE (NCT01566240) studies, respectively. There is also potential to reduce treatment-related morbidity and improve quality of life through IGABT respecting well defined dose constraints and through the use of IMRT and IGRT— these aims are being assessed specifically in EMBRACE II.

There is also considerable interest in exploring the potential of novel agents such as targeted therapy, immunotherapy, or vaccines for preventing systemic metastases in locally advanced cervical cancer. Examples include the ATEZOLACC study (NCT03612791), evaluating the clinical benefit of adding atezolizumab, a programmed cell death ligand 1 (PD-L1) immune checkpoint inhibitor, to standard chemo-radiation, and a similar study AIM2CERV (NCT02853604), evaluating the benefit of adding ADXS-HPV immunotherapy. A challenge is to identify better predictive factors to select those patients who will benefit from intensification of systemic therapy, and critical biological characteristics which can potentially be targeted through specific drugs.

The ultimate adaptive goal is to develop personalized treatment for cervix cancer patients with different risks of local, nodal, and systemic recurrence, as well as late morbidity. A multicenter pilot study of selected immunohistochemistry markers is being planned in a subset of EMBRACE-I patients to identify the most promising biomarkers which will then be validated prospectively within the unique cohort of EMBRACE-II patients treated with a uniform state-of-the-art protocol.[68] EMBRACE-II will also implement an imaging sub-study to evaluate the value of multiparametric quantitative MRI as a biomarker for identifying patients at increased risk of local, nodal, and systemic recurrence.[68]

It is important to remember that cervical cancer is largely a disease of low and middle income countries. Lack of brachytherapy equipment, imaging scanners, and qualified personnel are barriers to implementation of IGABT in these countries and there is therefore a need to investigate the health economics of different techniques and workflows and to adapt resources to those patients most likely to benefit. Examples include optimal combination of MRI and CT imaging, development of ultrasound-based IGABT[78,79] and use of skills mix. These issues are currently the focus of further GEC ESTRO recommendations and of the GEC-ESTRO BrachyHERO (Health Economics in Radiation Oncology) project in conjunction with the International Atomic Energy Agency and the World Health Organisation.

The outstanding clinical results of the tumor response-adaptive strategies described in this paper for cervical cancer could also serve as a template for improving clinical outcome in other tumor sites commonly treated with definitive radiotherapy. A key feature is identifying the various small adaptive volumes which would benefit from additional very high differential boost doses, and the optimum method of delivering these doses (eg, brachytherapy, photons, or heavy particles). Initial experience is being collected for some tumor sites, such as vaginal, anal, rectal, lung, nasopharyngeal, and esophageal cancer.

Conclusion

In cervical cancer, the implementation of adaptive target volume selection, adapted treatment technique, and risk-adapted dose prescription through image-guided brachytherapy boost has resulted in a significant improvement in pelvic control across all stages, while reducing serious morbidity. Current and future research will focus on additional adaptive strategies for both EBRT and brachytherapy to maximize the therapeutic ratio in individual patients.

References

1. Chang JH, Lim Joon D, Lee ST, et al: Intensity modulated radiation therapy dose painting for localized prostate cancer using (1)(1)C-choline positron emission tomography scans. Int J Radiat Oncol Biol Phys 83: e691-e696, 2012
2. Zamboglou C, Thomann B, Koubar K, et al: Focal dose escalation for prostate cancer using (68)Ga-HBED-CC PSMA PET/CT and MRI: A planning study based on histology reference. Radiat Oncol 13:81, 2018
3. Zhang P, Simon A, Rigaud B, et al: Optimal adaptive IMRT strategy to spare the parotid glands in oropharyngeal cancer. Radiother Oncol 120:41-47, 2016
4. Toftegaard J, Keall PJ, O'Brien R, et al: Potential improvements of lung and prostate MLC tracking investigated by treatment simulations. Med Phys 45:2218-2229, 2018
5. Geets X, Tomsej M, Lee JA, et al: Adaptive biological image-guided IMRT with anatomic and functional imaging in pharyngo-laryngeal tumors: Impact on target volume delineation and dose distribution using helical tomotherapy. Radiother Oncol 85:105-115, 2007
6. Haack S, Pedersen EM, Jespersen SN, et al: Apparent diffusion coefficients in GEC ESTRO target volumes for image guided adaptive brachytherapy of locally advanced cervical cancer. Acta Oncol 49:978-983, 2010
7. Andersen EK, Hole KH, Lund KV, et al: Pharmacokinetic parameters derived from dynamic contrast enhanced MRI of cervical cancers predict chemoradiotherapy outcome. Radiother Oncol 107:117-122, 2013
8. Park JJ, Kim CK, Park SY, et al: Assessment of early response to concurrent chemoradiotherapy in cervical cancer: Value of diffusion-weighted and dynamic contrast-enhanced MR imaging. Magn Reson Imaging 32:993-1000, 2014
9. Daniel M, Andrzejewski P, Sturdza A, et al: Impact of hybrid PET/MR technology on multiparametric imaging and treatment response assessment of cervix cancer. Radiother Oncol 125:420-425, 2017
10. Georg P, Andrzejewski P, Baltzer P, et al: Changes in tumor biology during chemoradiation of cervix cancer assessed by multiparametric MRI and hypoxia PET. Mol Imaging Biol 20:160-169, 2018
11. Haie-Meder C, Potter R, Van Limbergen E, et al: Recommendations from Gynaecological (GYN) GEC-ESTRO Working Group (I): Concepts and terms in 3D image based 3D treatment planning in cervix cancer brachytherapy with emphasis on MRI assessment of GTV and CTV. Radiother Oncol 74:235-245, 2005
12. Potter R, Haie-Meder C, Van Limbergen E, et al: Recommendations from Gynaecological (GYN) GEC ESTRO Working Group (II): Concepts and terms in 3D image-based treatment planning in cervix cancer brachytherapy-3D dose volume parameters and aspects of 3D image-based anatomy, radiation physics, radiobiology. Radiother Oncol 78:67-77, 2006
13. Hellebust TP, Kirisits C, Berger D, et al: Recommendations from Gynaecological (GYN) GEC-ESTRO Working Group: Considerations and pitfalls in commissioning and applicator reconstruction in 3D image-based treatment planning of cervix cancer brachytherapy. Radiother Oncol 96:153-160, 2010
14. Dimopoulos JC, Petrow P, Tanderup K, et al: Recommendations from Gynaecological (GYN) GEC-ESTRO Working Group (IV): Basic principles and parameters for MR imaging within the frame of image based adaptive cervix cancer brachytherapy. Radiother Oncol 103:113-122, 2012
15. International Commission on Radiation Units and Measurements. Prescribing, Recording, and Reporting Brachytherapy for Cancer of the Cervix (ICRU report 89). Bethesda; 2013
16. Fokdal L, Tanderup K, Nielsen SK, et al: Image and laparoscopic guided interstitial brachytherapy for locally advanced primary or recurrent gynaecological cancer using the adaptive GEC ESTRO target concept. Radiother Oncol 100:473-479, 2011
17. Dimopoulos JC, Schmid MP, Fidarova E, et al: Treatment of locally advanced vaginal cancer with radiochemotherapy and magnetic resonance image-guided adaptive brachytherapy: Dose-volume parameters and first clinical results. Int J Radiat Oncol Biol Phys 82:1880-1888, 2012
18. Dresen RC, Beets GL, Rutten HJ, et al: Locally advanced rectal cancer: MR imaging for restaging after neoadjuvant radiation therapy with concomitant chemotherapy. Part I. Are we able to predict tumor confined to the rectal wall? Radiology 252:71-80, 2009
19. Sun Myint A, Lee CD, Gerard JP: Rectal brachytherapy. In: van Limbergen E, Potter R, Hoskin P, Baltas D, eds. GEC ESTRO brachytherapy handbook (ed 2) www.estro.org: GEC ESTRO, 2014
20. Galalae R, Pötter R, van Limbergen E: Oesophageal cancer. In: van Limbergen E, Pötter R, Hoskin P, Baltas D, eds. GEC ESTRO brachytherapy handbook (ed 2): GEC ESTRO; 2014
21. Bacorro WR, Agas RAF, Cabrera SMR, et al: A novel applicator design for intracavitary brachytherapy of the nasopharynx: Simulated reconstruction, image-guided adaptive brachytherapy planning, and dosimetry. Brachytherapy 17:709-717, 2018
22. Mayr NA, Wang JZ, Lo SS, et al: Translating response during therapy into ultimate treatment outcome: A personalized 4-dimensional MRI tumor volumetric regression approach in cervical cancer. Int J Radiat Oncol Biol Phys 76:719-727, 2010
23. Schmid MP, Mansmann B, Federico M, et al: Residual tumour volumes and grey zones after external beam radiotherapy (with or without chemotherapy) in cervical cancer patients. A low-field MRI study. Strahlenther Onkol 189:238-244, 2013
24. Schmid MP, Fidarova E, Potter R, et al: Magnetic resonance imaging for assessment of parametrial tumour spread and regression patterns in adaptive cervix cancer radiotherapy. Acta Oncol 52:1384-1390, 2013
25. Yoshida K, Jastaniyah N, Sturdza A, et al: Assessment of parametrial response by growth pattern in patients with International Federation of Gynecology and Obstetrics Stage IIB and IIIB cervical cancer: Analysis of patients from a prospective, multicenter trial (EMBRACE). Int J Radiat Oncol Biol Phys 93:788-796, 2015
26. Jastaniyah N, Yoshida K, Tanderup K, et al: A volumetric analysis of GTVD and CTVHR as defined by the GEC ESTRO recommendations in FIGO stage IIB and IIIB cervical cancer patients treated with IGABT in a prospective multicentric trial (EMBRACE). Radiother Oncol 120:404-411, 2016
27. Dimopoulos JC, Kirisits C, Petric P, et al: The Vienna applicator for combined intracavitary and interstitial brachytherapy of cervical cancer: Clinical feasibility and preliminary results. Int J Radiat Oncol Biol Phys 66:83-90, 2006
28. Kirisits C, Lang S, Dimopoulos J, et al: The Vienna applicator for combined intracavitary and interstitial brachytherapy of cervical cancer: Design, application, treatment planning, and dosimetric results. Int J Radiat Oncol Biol Phys 65:624-630, 2006
29. Nomden CN, de Leeuw AA, Moerland MA, et al: Clinical use of the Utrecht applicator for combined intracavitary/interstitial brachytherapy treatment in locally advanced cervical cancer. Int J Radiat Oncol Biol Phys 82:1424-1430, 2012
30. Berger D, Pötter R, Mahantshetty U, et al. Vienna-II ring applicator for distal parametrial/pelvic wall disease in cervical cancer brachytherapy; Concept, design, technical feasibility, treatment planning, and dosimetric results. Radiother Oncol submitted.
31. Walter F, Maihofer C, Schuttrumpf L, et al: Combined intracavitary and interstitial brachytherapy of cervical cancer using the novel hybrid

applicator Venezia: Clinical feasibility and initial results. Brachytherapy 17:775-781, 2018
32. Lindegaard JC, Madsen ML, Traberg A, et al: Individualised 3D printed vaginal template for MRI guided brachytherapy in locally advanced cervical cancer. Radiother Oncol 118:173-175, 2016
33. Potter R, Georg P, Dimopoulos JC, et al: Clinical outcome of protocol based image (MRI) guided adaptive brachytherapy combined with 3D conformal radiotherapy with or without chemotherapy in patients with locally advanced cervical cancer. Radiother Oncol 100:116-123, 2011
34. Lindegaard JC, Fokdal LU, Nielsen SK, et al: MRI-guided adaptive radiotherapy in locally advanced cervical cancer from a Nordic perspective. Acta Oncol 52:1510-1519, 2013
35. Olteanu LAM, Duprez F, De Neve W, et al: Late mucosal ulcers in dose-escalated adaptive dose-painting treatments for head-and-neck cancer. Acta Oncol 57:262-268, 2018
36. Tanderup K, Nielsen SK, Nyvang GB, et al: From point A to the sculpted pear: MR image guidance significantly improves tumour dose and sparing of organs at risk in brachytherapy of cervical cancer. Radiother Oncol 94:173-180, 2010
37. Serban M, Kirisits C, Potter R, et al: Isodose surface volumes in cervix cancer brachytherapy: change of practice from standard (Point A) to individualized image guided adaptive (EMBRACE I) brachytherapy. Radiother Oncol 129:567-574, 2018
38. Kirisits C, Federico M, Nkiwane K, et al: Quality assurance in MR image guided adaptive brachytherapy for cervical cancer: Final results of the EMBRACE study dummy run. Radiother Oncol 117:548-554, 2015
39. Sturdza A, Potter R, Fokdal LU, et al: Image guided brachytherapy in locally advanced cervical cancer: Improved pelvic control and survival in RetroEMBRACE, a multicenter cohort study. Radiother Oncol 120:428-433, 2016
40. Barillot I, Horiot JC, Pigneux J, et al: Carcinoma of the intact uterine cervix treated with radiotherapy alone: A French cooperative study: Update and multivariate analysis of prognostics factors. Int J Radiat Oncol Biol Phys 38:969-978, 1997
41. Perez CA, Grigsby PW, Chao KS, et al: Tumor size, irradiation dose, and long-term outcome of carcinoma of uterine cervix. Int J Radiat Oncol Biol Phys 41:307-317, 1998
42. Vale CL, Tierney JF, Davidson SE, et al: Substantial improvement in UK cervical cancer survival with chemoradiotherapy: Results of a Royal College of Radiologists' audit. Clin Oncol (R Coll Radiol) 22:590-601, 2010
43. Vale C, Tierney JF, Stewart LA, et al: Reducing uncertainties about the effects of chemoradiotherapy for cervical cancer: A systematic review and meta-analysis of individual patient data from 18 randomized trials. J Clin Oncol 26:5802-5812, 2008
44. Shrivastava S, Mahantshetty U, Engineer R, et al: Cisplatin chemoradiotherapy vs radiotherapy in FIGO stage IIIB squamous cell carcinoma of the uterine cervix: A randomized clinical trial. JAMA Oncol 4:506-513, 2018
45. Gupta S, Maheshwari A, Parab P, et al: Neoadjuvant chemotherapy followed by radical surgery versus concomitant chemotherapy and radiotherapy in patients with stage IB2, IIA, or IIB squamous cervical cancer: A randomized controlled trial. J Clin Oncol 36:1548-1555, 2018
46. Han K, Milosevic M, Fyles A, et al: Trends in the utilization of brachytherapy in cervical cancer in the United States. Int J Radiat Oncol Biol Phys 87:111-119, 2013
47. Gill BS, Lin JF, Krivak TC, et al: National Cancer Data Base analysis of radiation therapy consolidation modality for cervical cancer: The impact of new technological advancements. Int J Radiat Oncol Biol Phys 90:1083-1090, 2014
48. Charra-Brunaud C, Harter V, Delannes M, et al: Impact of 3D image-based PDR brachytherapy on outcome of patients treated for cervix carcinoma in France: Results of the French STIC prospective study. Radiother Oncol 103:305-313, 2012
49. Tanderup K, Fokdal LU, Sturdza A, et al: Effect of tumor dose, volume and overall treatment time on local control after radiochemotherapy including MRI guided brachytherapy of locally advanced cervical cancer. Radiother Oncol 120:441-446, 2016
50. Fokdal L, Sturdza A, Mazeron R, et al: Image guided adaptive brachytherapy with combined intracavitary and interstitial technique improves the therapeutic ratio in locally advanced cervical cancer: Analysis from the retroEMBRACE study. Radiother Oncol 120:434-440, 2016
51. Tan LT, Kirchheiner K, Sturdza A, et al: OC-0392: Impact of image-guided brachytherapy on pattern of relapse in the RetroEMBRACE cervical cancer study. Radiother Oncol 127:S201, 2018
52. Schmid M, Haie-Meder C, Mahanshetty U, et al: OC-0055: Local failures after radiochemotherapy and MR-image-guided brachytherapy in cervical cancer patients. Radiother Oncol 123:S26, 2017
53. Nomden C, Potter R, de Leeuw A, et al. Nodal failure after chemo-radiation and MRI guided brachytherapy in cervical cancer: Patterns of failure in the EMBRACE study cohort. Radiother Oncol. submitted.
54. Kirchheiner K, Potter R, Tanderup K, et al: Health-related quality of life in locally advanced cervical cancer patients after definitive chemoradiation therapy including image guided adaptive brachytherapy: An analysis from the EMBRACE study. Int J Radiat Oncol Biol Phys 94:1088-1098, 2016
55. Kirchheiner K, Nout RA, Tanderup K, et al: Manifestation pattern of early-late vaginal morbidity after definitive radiation (chemo)therapy and image-guided adaptive brachytherapy for locally advanced cervical cancer: An analysis from the EMBRACE study. Int J Radiat Oncol Biol Phys 89:88-95, 2014
56. Kirchheiner K, Nout RA, Lindegaard JC, et al: Dose-effect relationship and risk factors for vaginal stenosis after definitive radio(chemo)therapy with image-guided brachytherapy for locally advanced cervical cancer in the EMBRACE study. Radiother Oncol 118:160-166, 2016
57. Letschert JG, Lebesque JV, Aleman BM, et al: The volume effect in radiation-related late small bowel complications: Results of a clinical study of the EORTC radiotherapy cooperative group in patients treated for rectal carcinoma. Radiother Oncol 32:116-123, 1994
58. Stanic S, Mayadev JS: Tolerance of the small bowel to therapeutic irradiation: A focus on late toxicity in patients receiving para-aortic nodal irradiation for gynecologic malignancies. Int J Gynecol Cancer 23:592-597, 2013
59. Sondergaard J, Holmberg M, Jakobsen AR, et al: A comparison of morbidity following conformal versus intensity-modulated radiotherapy for urinary bladder cancer. Acta Oncol 53:1321-1328, 2014
60. Koom WS, Sohn DK, Kim JY, et al: Computed tomography-based high-dose-rate intracavitary brachytherapy for uterine cervical cancer: Preliminary demonstration of correlation between dose-volume parameters and rectal mucosal changes observed by flexible sigmoidoscopy. Int J Radiat Oncol Biol Phys 68:1446-1454, 2007
61. Kang HC, Shin KH, Park SY, et al: 3D CT-based high-dose-rate brachytherapy for cervical cancer: Clinical impact on late rectal bleeding and local control. Radiother Oncol 97:507-513, 2010
62. Georg P, Potter R, Georg D, et al: Dose effect relationship for late side effects of the rectum and urinary bladder in magnetic resonance image-guided adaptive cervix cancer brachytherapy. Int J Radiat Oncol Biol Phys 82:653-657, 2012
63. Chopra S, Dora T, Engineer R, et al: Late rectal toxicity after image-based high-dose-rate interstitial brachytherapy for postoperative recurrent and/or residual cervical cancers: EQD2 predictors for grade >/=II toxicity. Brachytherapy 14:881-888, 2015
64. Mazeron R, Maroun P, Castelnau-Marchand P, et al: Pulsed-dose rate image-guided adaptive brachytherapy in cervical cancer: Dose-volume effect relationships for the rectum and bladder. Radiother Oncol 116:226-232, 2015
65. Mazeron R, Fokdal LU, Kirchheiner K, et al: Dose-volume effect relationships for late rectal morbidity in patients treated with chemoradiation and MRI-guided adaptive brachytherapy for locally advanced cervical cancer: Results from the prospective multicenter EMBRACE study. Radiother Oncol 120:412-419, 2016
66. Ujaimi R, Milosevic M, Fyles A, et al: Intermediate dose-volume parameters and the development of late rectal toxicity after MRI-guided brachytherapy for locally advanced cervix cancer. Brachytherapy 16. 968-975. e2, 2017
67. Fortin I, Tanderup K, Haie-Meder C, et al: Image guided brachytherapy in cervical cancer: A comparison between intracavitary and combined intracavitary/interstitial brachytherapy in regard to doses to HR CTV, OARs and late morbidity—Early results from the EMBRACE study in 999 patients. Brachytherapy 15:S21, 2016

68. Potter R, Tanderup K, Kirisits C, et al: The EMBRACE II study: The outcome and prospect of two decades of evolution within the GEC-ESTRO GYN working group and the EMBRACE studies. Clin Transl Radiat Oncol 9:48-60, 2018
69. Jadon R, Pembroke CA, Hanna CL, et al: A systematic review of organ motion and image-guided strategies in external beam radiotherapy for cervical cancer. Clin Oncol 26:185-196, 2014
70. Beadle BM, Jhingran A, Yom SS, et al: Patterns of regional recurrence after definitive radiotherapy for cervical cancer. Int J Radiat Oncol Biol Phys 76:1396-1403, 2010
71. Nkiwane KS, Potter R, Tanderup K, et al: Single line source with and without vaginal loading and the impact on target coverage and organ at risk doses for cervix cancer stages IB, II, and IIIB: Treatment planning simulation in patients treated with MRI-guided adaptive brachytherapy in a multicentre study (EMBRACE). Brachytherapy 12:317-323, 2013
72. Mohamed S, Lindegaard JC, de Leeuw AA, et al: Vaginal dose de-escalation in image guided adaptive brachytherapy for locally advanced cervical cancer. Radiother Oncol 120:480-485, 2016
73. Westerveld H, Potter R, Berger D, et al: Vaginal dose point reporting in cervical cancer patients treated with combined 2D/3D external beam radiotherapy and 2D/3D brachytherapy. Radiother Oncol 107:99-105, 2013
74. Westerveld H, de Leeuw A, Kirchheiner K, et al: Multicentre evaluation of a novel vaginal dose reporting method in 153 cervical cancer patients. Radiother Oncol 120:420-427, 2016
75. Schmid MP, Franckena M, Kirchheiner K, et al: Distant metastasis in patients with cervical cancer after primary radiotherapy with or without chemotherapy and image guided adaptive brachytherapy. Gynecol Oncol 133:256-262, 2014
76. Duke S, Jensen N, Rumpold T, et al: PO-0809: Implementing a novel online education programme to support RTQA – the EMBRACE-II experience. Radiother Oncol 127:S421-S422, 2018
77. Seppenwoolde Y, Assenholt M, Georg D, et al: Importance of training in external beam treatment planning for locally advanced cervix cancer: Report from the EMBRACE II dummy run. Radiother Oncol 133:149-155, 2019
78. Nesvacil N, Schmid MP, Potter R, et al: Combining transrectal ultrasound and CT for image-guided adaptive brachytherapy of cervical cancer: Proof of concept. Brachytherapy 15:839-844, 2016
79. Schmid MP, Nesvacil N, Potter R, et al: Transrectal ultrasound for image-guided adaptive brachytherapy in cervix cancer—An alternative to MRI for target definition? Radiother Oncol 120:467-472, 2016