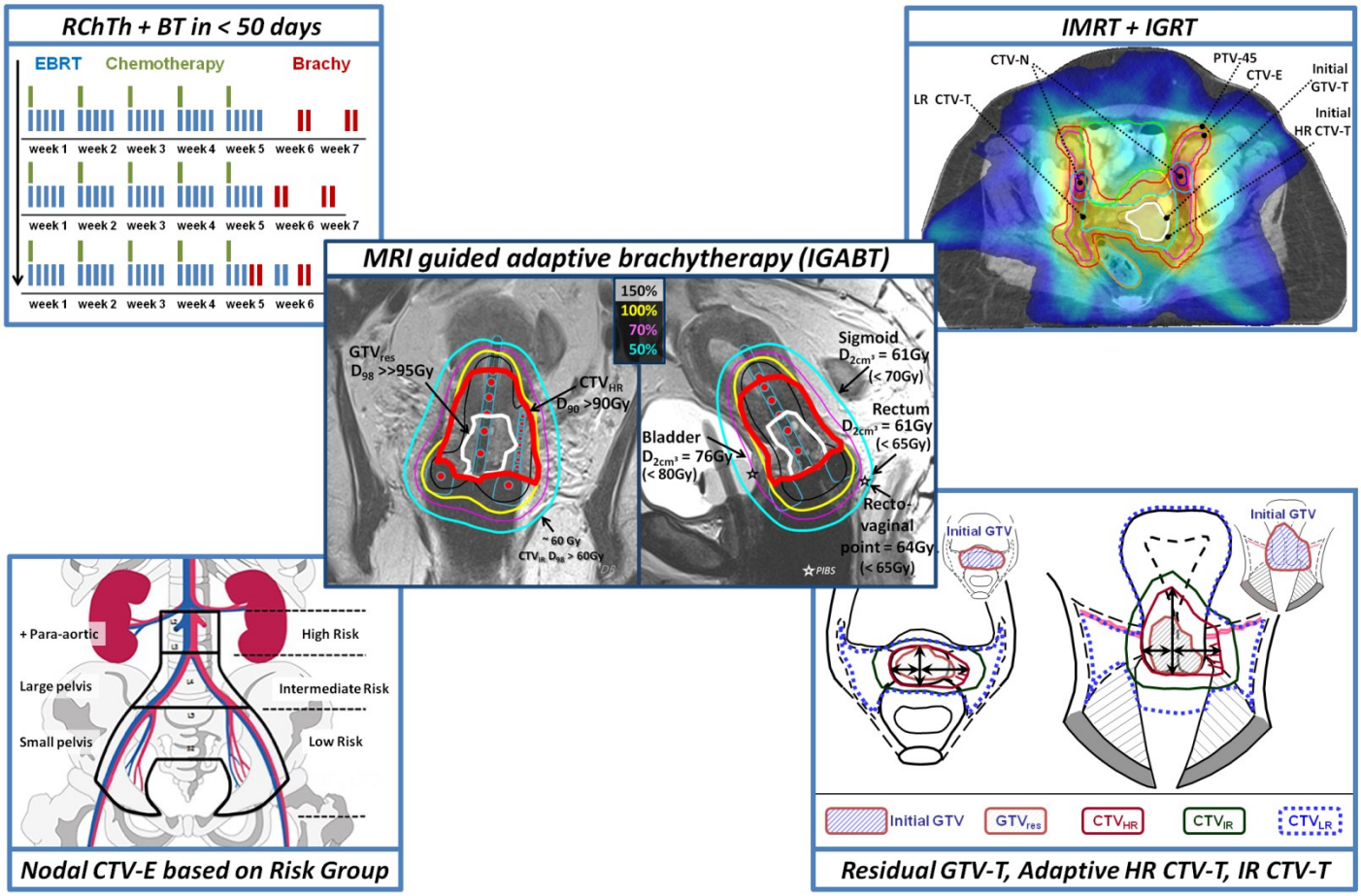
Image guided intensity modulated External beam radiochemotherapy and MRI based adaptive BRAchytherapy in locally advanced CErvical cancer

EMBRACE-II



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CONTENTS

1 ABBREVIATIONS

^{18}F-FDG	Fluorine 18 - Fluorodeoxyglucose
2/3/4D	Two/Three/Four-dimensional
ACT	Addenbrooke's Contouring Tool
ATRAB	Applied and Translational Radiobiology (Medical University Vienna)
AUC	Area Under the Curve
BL	Baseline
BT	Brachytherapy
CBCT	Cone beam computed tomography
CHT	Chemotherapy
COP	Coverage Probability
CR	Complete Remission
CRF	Case Report Form
CRT	Conformal Radiotherapy
CSS	Cancer Specific Survival
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTV	Clinical Target Volume
CuSO4	Copper sulphate
D90	The isodose that includes 90% of the target
D100	The isodose that includes 100% of the target
D2cm^3	Minimum dose in the most exposed 2 cm3 of an OAR
DFS	Disease Free Survival
DNA	Deoxyribonucleic acid
DVH	Dose Volume Histogram
EANM	European Association of Nuclear Medicine
EBRT	External Beam Radiotherapy
EMBRACE	The European and International study on MRI-guided Brachytherapy in locally Advanced Cervical Cancer
EORTC	European Organisation for Research and Treatment of Cancer
EPID	Electronic Portal Imaging Device
ESTRO	European Society for Therapeutic Radiology and Oncology
EQD2	Equivalent dose in 2 Gy fractions
FIGO	Fédération Internationale de Gynécologie et d' Obstétrique
FTE	Full Time Equivalent
Fx	Fraction
G	(Morbidity) Grade
GEC	Groupe Européen de Curiethérapie
GFR	Glomerula Filtration rate
GI	Gastro-Intestinal
GTV	Gross Tumor Volume
Gy	Gray
HDR	High Dose Rate
HPV	Human Papilloma Virus
HR	High Risk
IC	Intracavitary

ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICRU	International Commission on Radiation Units and Measurements
IMRT	Intensity Modulated Radiotherapy
IGRT	Image Guided Radiotherapy
IR	Intermediate Risk
IS	Interstitial
ITV	Internal Target Volume
IV	Intravenous
kV	Kilovoltage
LACC	Locally Advanced Cervical Cancer
LN	Lymph Nodes
LR	Low Risk
MRI	Magnetic Resonance Imaging
MVCT	Megavoltage Computed Tomography
N0/N-	Lymph Node Negative
N1/N+	Lymph Node Positive
OAR	Organs at Risk
OS	Overall Survival
OTT	Overall Treatment Time
PAN	Para-Aortic Lymph Nodes
PDR	Pulsed Dose Rate
PET-CT	Positron Emission Tomography- Computed Tomography
PFS	Progression Free Survival
PI	Principal Investigator
PIBS	Posterior-Inferior Border of Symphysis
PTV	Planning Target Volume
QoL	Quality of Life
RT	Radiotherapy
SD	Standard Deviation
SIB	Simultaneous Integrated Boost
SPSS	Statistical Package for Social Sciences
SUV_{max}	Maximum Standardized Uptake Value
TNM	Tumor (Lymph)Nodes Metastasis
TPS	Treatment Planning System
TRAK	Total Reference Air Kerma
uCR	Uncomplete Remission
US	Ultrasound
VMAT	Volumetric Modulated Arc Therapy
WHO	World Health Organization

2 SUMMARY

2.1 BACKGROUND

The standard treatment of locally advanced cervical cancer is radio-chemotherapy including external beam radiotherapy (EBRT), brachytherapy (BT) and concomitant chemotherapy with weekly Cisplatin. Image Guided Adaptive Brachytherapy (IGABT), with repetitive MRI regarded as gold standard, is increasingly recognized as the new paradigm replacing 2D BT and spreading throughout the world. This spread is at present predominantly in Europe, North America and in many places in Asia. The Gyn GEC ESTRO Recommendations I-IV have been used as the conceptual frame for these developments during the last decade and are now embedded into the new ICRU/GEC ESTRO report 88 which is being published in 2015.

Beside increasing mono-institutional clinical experience – also reported in literature – there is increasing clinical evidence and analyses from multi-institutional studies, in particular RetroEMBRACE (n=731) and EMBRACE (n>1350) about dose volume effects and outcome. The mature RetroEMBRACE clinical outcome data and dose volume effect analysis for disease outcome show an improved excellent local and pelvic control and survival and significant dose volume effects for IGABT. Overall treatment time was found to have significant impact on local control, and in addition, volume effects of EBRT were found (IMRT vs. 3D CRT) with impact on morbidity and quality of life. Furthermore, dose effects of chemotherapy (≥5 cycles) were found to have impact on survival in advanced disease. Comprehensive analyses from both large patient cohorts reveal further relevant treatment parameters with major impact on disease outcome, morbidity and quality of life. In the international community the results from the EMBRACE studies are regarded as benchmark for future clinical research in this field.

Based on the large success of the RetroEMBRACE and EMBRACE studies, the EMBRACE study and research group decided to continue the clinical research work and to initiate a consecutive EMBRACE II study with interventions derived from the evidence collected within the EMBRACE studies.

2.2 INTERVENTIONS, AIMS AND HYPOTHESES

The EMBRACE II interventions address local, nodal and systemic treatment as well as exposure of organs at risk:

- Increased use of IC/IS technique in BT
- Reduction of vaginal source loading
- Systematic utilisation of IMRT
- Utilisation of daily IGRT (set-up according to bony structures)
- EBRT target concept related to the primary tumour; concepts for OAR contouring
- EBRT dose prescription and reporting
- Adaptation of EBRT nodal elective CTV according to risk of nodal and systemic recurrence
- Systematic application of simultaneous chemotherapy
- Reduction of overall treatment time

The general aims of the EMBRACE II study are:

- To systematically apply IMRT with daily IGRT as well as advanced image guided adaptive BT in a prospective multi-centre setting
- To systematically implement a dose prescription protocol for IGABT
- To implement systematic contouring, prescription and reporting for EBRT CTV and OARs.
- To administer EBRT in different targets which are adapted to the risk of nodal and systemic failure: to improve para-aortic and systemic control in high risk patients and not to decrease lymph node control in low risk and intermediate risk patients

- To systematically administer simultaneous chemotherapy to EBRT to reach prescribed dose in as many patients as possible, in particular in high risk patients
- To benchmark an outstanding high level of local, nodal and systemic control as well as survival with application of advanced EBRT, BT and chemotherapy within limited overall treatment time
- To benchmark a low incidence of intermediate and major morbidity as well as a high level of quality of life with application of advanced EBRT, BT and chemotherapy

Beside these general aims, there is a significant number of specific aims which refer to the prospective validation of dose volume parameters from the EMBRACE analyses (e.g. dose escalation for large tumors with increased application of IC/IS techniques), to explore and evaluate dose volume parameters for EBRT and to identify prognostic parameters.

General and specific hypotheses were formulated for the various interventions (BT, EBRT, chemotherapy) and endpoints (disease, morbidity, quality of life).

2.3 TYPE OF DESIGN

The study is a multicenter prospective interventional study with some areas for observational research (e.g. DVH for IMRT). Reporting on the key patient, tumor, treatment and outcome parameters is mandatory including disease, morbidity and quality of life. Sub-studies as on adaptive IMRT and translational research are optional for cooperation between individual departments. Patient registration and reporting will be performed by the individual investigator via the internet to a central database.

2.4 PATIENTS TO BE INCLUDED

Patients with newly biopsy proven squamous carcinoma, adenocarcinoma or adeno-squamous carcinoma of the uterine cervix, FIGO stage IB, IIA, IIB, IIIA, IIIB and IVA (and nodal status according to TNM) in whom definitive radio-chemotherapy with curative intent is planned are qualified for the study. Treatment has to include IGABT with MRI and IMRT with IGRT and ≥5 cycles of cis-Platin. Patients with para-aortic metastatic nodes (stage IVB) to the level of L2 are also eligible but patients with further dissemination are not (M0).

Patient work up and staging includes as a minimum patient characteristics with performance status and blood tests (e.g. haemoglobin, lymphocytes), tumor status (biopsy), gynaecological examination, MRI of the pelvis, abdominal CT or MRI, whole body FDG PET-CT (preferably) or at least chest CT. Further investigations are applied if necessary (e.g. cystoscopy, rectoscopy) or done according to institutional practice (e.g. laparoscopic lymph node assessment). Baseline morbidity scoring and quality of life questionnaire are mandatory.

2.5 TREATMENT OF PATIENTS IN THE TRIAL

All patients will receive both EBRT and concomitant chemotherapy and BT. Summation of EBRT and BT doses will be performed by calculation of a biologically equivalent dose in 2 Gy per fraction (EQD2) using the linear-quadratic model with α/β = 10 Gy for tumour effects and α/β = 3 Gy for late normal tissue damage. The repair half time is assumed to be 1.5 hrs.

EBRT has to be delivered as IMRT/VMAT with daily cone beam CT (IGRT) in 25 fractions with 1.8 Gy to a total dose of 45 Gy given in 5 weeks. Target definition is MRI based (initial GTV) for the CTV-T with an initial HR and LR CTV-T and an ITV-T. CT or MRI based nodal Target (CTV-E) is according to risk of nodal spread “Small Pelvis”, “Large Pelvis” or “Large Pelvis + Para-aortic Region”. Overall CTV/ITV to PTV margin is 5 mm. Involved nodes are boosted preferably based on PET CT with 10-15 Gy and treated as simultaneous integrated boost within 5 weeks (2.2-2.4 Gy per fraction). A range for DVH parameters for the various OARs - contoured according to specific

protocols - is taken into account for treatment planning. The LR CTV-T and the CTV-E will be treated with 45 Gy by use of EBRT (PTV45). Maximal treatment time including both EBRT and BT is 50 days.

Brachytherapy is prescribed with dose escalation for advanced disease with large adaptive CTV-T_{HR} including IC/IS techniques and dose de-escalation for limited size CTV-T_{HR} to spare organs at risk and in particular the upper vagina. The primary imaging method is MRI with the applicator in place which enables definition of the relevant volumes of interest directly on the images for treatment planning: GTV_{res}, adaptive CTV_{HR}, CTV_{IR} and organ volumes. The applicator and the reference points are reconstructed in the same image series. All treatment plans have to be optimized to achieve defined planning aims for dose and volume parameters for tumor (D98 for GTV_{res}) and target volumes (e.g. D90-95 Gy for adaptive CTV-T_{HR}) and for $2cm^3$ reference volumes for OARs (e.g. <80 Gy for bladder, <65 Gy for rectum) and for vaginal reference points (recto-vaginal point < 65 Gy, PIBS). If the planning aims cannot be achieved, limits for the finally prescribed dose levels are defined for GTV_{res}, CTV_{HR}, CTV_{IR}, point A, bladder, rectum, sigmoid bowel and vagina. Planning aim doses and limits for the finally prescribed dose levels are based on the experience of the previous retroEMBRACE and EMBRACE trials.

For chemotherapy weekly concomitant Cisplatin (40 mg/m2) for 5-6 courses is standard unless chemotherapy is precluded by patient age, co-morbidity and toxicity. Aim is to apply minimum 5 cycles of cis-Platin, in particular in advanced disease.

2.6 QUALITY ASSURANCE

Only approved departments and investigators can enroll patients into the protocol. This approval is the under the responsibility of the study coordinators. The approved departments are at present those that have contributed continuously to EMBRACE in a considerable number of patients. These departments have to go additionally through a QA procedure for IMRT/IGRT.

New departments will have to go through a QA procedure both for IGABT and IMRT/IGRT. Approval requires a compliance questionnaire, successful training, registration and submission of cases and positive evaluation by the study coordinators for each centre.

There is no formal on site monitoring, but patient files and treatment plans must be kept at least until closure of the protocol and final analysis of the results is obtained. Continuous data monitoring is performed through the study offices in Vienna and Aarhus and through Utrecht for the centres in the Netherlands.

Continuous education will be offered through ACT and annual workshops and EMBRACE meetings.

2.7 OUTCOME MEASURES

Local and nodal (pelvic) control within the specific EBRT and BT targets (HR-CTV-T, IR-CTV, LR CTV-T; CTV-E, CTV-N) and morbidity related to OAR in the pelvis and the para-artic region as well as overall survival, cancer specific survival and systemic control are the primary outcome measures. All endpoints will be evaluated by actuarial statistics. Morbidity will be scored by use of the Common Terminology Criteria for Adverse Events (CTCAE v3.0/4.0). QoL will also be systematically recorded in all patients.

2.8 EVALUATION OF OUTCOME MEASURES

Tumor and nodal remission status (complete, uncertain complete, partial, stable & progressive disease) will be evaluated 3 months after treatment by pelvic (para-aortic, CT) MRI and gynaecological examination. Regular follow-up including gynaecological examination will then be instituted with planned appointments 6, 9, 12, 18, 24, 30, 36, 48 and 60 months after treatment. Pelvic (para-aortic, CT)

MRI will be repeated at 12 months after treatment or in case of suspected recurrence. Morbidity and quality of life will be scored systematically at base line and at each time point during follow-up.

2.9 SAMPLE SIZE AND DATA MATURITY

The study aims at recruiting 1000 patients in 4 years and to follow them for at least 5 years to allow for a meaningful assessment of the endpoints by univariate and multivariate analysis.

3 INTRODUCTION

3.1 BACKGROUND

The standard treatment for locally advanced cervical cancer is currently radio-chemotherapy consisting of EBRT, intracavitary BT and concomitant chemotherapy with Cisplatin. During the last decade, the utilisation of MRI guided brachytherapy has grown based on the GEC ESTRO recommendations (Haie-Meder C. et al. 2005, Pötter R. et al. 2006, Hellebust TP. et al. 2010, Dimopoulos JC. et al. 2012) and the cervix is among the first cancer sites where response-adaptive radiotherapy has been successfully implemented in clinical practice. The novel target concepts involved in response-adaptive radiotherapy are described further in section 3.2. Acquisition of MRI at the time of brachytherapy allows the brachytherapy boost to be individually tailored according to the residual tumour volume after typically 40-50 Gy of external beam radiation therapy (EBRT). This approach has changed patterns of clinical practise with regard to dose administration, and significant improvements in clinical outcome have been reported from mono-institutional settings with regard to local control, overall survival and morbidity (Pötter R. et al. 2007, Pötter R. et al. 2011, Lindegaard JC. et al. 2013).

In 2008, the GEC-ESTRO Gyn network initiated the "International Study on MRI-Based Brachytherapy in Cervical Cancer" (EMBRACE, www.embracestudy.dk). EMBRACE has recruited >1300 patients by 2015 from 27 international centers performing MRI-guided brachytherapy. The purpose of the EMBRACE study is to evaluate and benchmark MRI-guided brachytherapy in a prospective multicenter study. In 2010, the GEC-ESTRO Gyn network also initiated the retrospective study retroEMBRACE, in which 852 patients treated with image-guided brachytherapy prior to initiation of EMBRACE accrual have been included to provide long-term outcome data for image-guided brachytherapy while the EMBRACE study data is still maturing (www.retroembrace.com).

Data from retroEMBRACE shows that overall local control is excellent with 89% at 5 years with 98% in stage IB and 91% in IIB tumours. However, in stage IIIB tumours there is still a significant challenge with regard to local control which is 75% at 5 years (Sturdza A. et al. in submission 2015). Nodal and systemic control also remains challenging with levels of 87% and 77% at 5 years, respectively (all stages) (RetroEMBRACE 01/2015 work in progress). Furthermore, treatment related urinary and gastrointestinal late morbidity is still a significant problem with the 3 year actuarial incidence of intermediate to major morbidity ($G \geq 2$) being 30% and 29% for urinary and gastrointestinal side effects, respectively, according to EMBRACE data. Major morbidity ($G \geq 3$) is seen in 7% and 8%, respectively (EMBRACE 2014, work in progress). Patient reported symptoms are equally high with 30-40% of patients reporting significant urinary and gastrointestinal bother according to quality of life data from the EMBRACE study (EMBRACE 2015, work in progress). Sexual side effects are still poorly understood although almost 30% of patients develop significant narrowing and shortening of the vagina (Kirchheiner K. et al. 2014). Further development of both BT and EBRT is needed to improve on local control, regional control as well as on treatment related morbidity and quality of Life.

Adjuvant and neo-adjuvant chemotherapy has been proposed to improve systemic control, and is currently being evaluated in a randomized phase III study (OUTBACK, https://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?study=1174; INTERLACE *www.cancerresearchuk.org*). However, local and nodal disease also has impact on systemic disease, and therefore improvement on loco-regional treatment is equally important. Recent developments in advanced image guidance for both EBRT and BT have potential to improve local as well as nodal and also systemic control. Furthermore, the new technologies has potential to decrease organ doses as well as well as the overall burden of treatment, with the promise to significantly reduce treatment related organ symptoms and overall quality of life.

Advances in image guided adaptive brachytherapy include improved individualisation of brachytherapy applicators as well as individualised dose optimisation. Dose optimisation using intracavitary (IC) applicators has shown to significantly decrease OAR dose and morbidity (Charra-Brunaud C. et al. 2012). Dose optimisation based on IC may be used to improve target dose coverage in tumours of limited size at BT, but for large residual tumours or in case of unfavourable topography, IC BT has limited possibilities to cover the CTV_{HR} to doses larger than e.g. 85Gy (Tanderup K. et al. 2010). Combined intracavitary-interstitial (IC/IS) applicators have been developed for targeting tumours which are not well covered by intracavitary (IC) applicators (Dimopoulos JC. et al. 2006, Kirisits C. et al. 2006). The IC/IS applicators allow for improved dose conformality, and target dose escalation and/or dose de-escalation in organs at

risk can be carried out (Fokdal L. et al. 2013). Furthermore, in the process of moving from standard loading to 3D image guided optimisation there has so far been reluctance to change the loading drastically in ovoids and ring, in order to stay as close as possible to previous clinical practise. However, EMBRACE data have demonstrated that dose to the ICRU recto-vaginal point correlate with the probability of G≥2 vaginal morbidity (Kirchheiner K. et al. in submission 2015). This observation is a strong motivation to explore new approaches to dose optimisation which spare vaginal mucosa and decreases the dose to the ICRU recto-vaginal point.

Pelvic EBRT is currently delivered with different techniques: 3D conformal EBRT, intensity modulated radiotherapy (IMRT), volumetric arc techniques (VMAT), and tomotherapy. Application of IMRT in cervix cancer significantly reduces the volume of tissue irradiated to intermediate doses such as 30-40Gy for bladder, rectum, sigmoid and bowel (Forrest J. et al. 2012). The progress from 3D conformal EBRT to IMRT has demonstrated a reduction of treatment related morbidity in mono-institutional and retrospective settings (Mundt AJ. et al. 2003, Xu KM. et al. 2015). Furthermore, EMBRACE quality of life data has shown a significantly lower incidence of bowel symptoms in patients treated with IMRT as compared to 3D conformal EBRT with the four-field box technique (see Figure 3.6 and 3.7).

During the last decade, a variety of techniques, such as kV x-ray, cone beam CT (CBCT) or megavolt CT (MVCT), have been developed to improve the possibilities to perform on board image guidance in EBRT. With imaging devices mounted on or in a fixed relationship to the accelerator, it is now possible to perform daily imaging with the patient in the treatment position. The on-board images can be fused with the treatment planning scan and a couch correction can be applied to correct for translational setup errors. In the case of cervix cancer the daily imaging can be used for visualisation and fusion of bony anatomy. By using daily image guided set-up in cervix cancer, the precision of the elective lymph node clinical target volume (CTV-E) can be significantly improved (Laursen LV. et al. 2012), and thereby planning target volume (PTV45 Gy) margins can be reduced. A further step is to use daily image guidance (CBCT) to visualise soft tissue such as bladder and uterus in order to further reduce the PTV-T margins which are applied to take into account the motion of the primary gross tumour volume (GTV), the CTV-T and the uterus (see chapter 9). Such approaches have been developed and involve adaptive EBRT where daily library plans are applied (Heijkoop ST. et al. 2014). Decrease of PTV margins as well as implementation of IMRT has potential to reduce morbidity, in particular bowel morbidity.

The primary aim of EMBRACE II is to implement a risk adaptive dose prescription protocol in locally advanced cervical cancer. The individualised dose prescription is based on evidence of dose and effect relationships for target and OARs from the EMBRACE and retroEMBRACE studies and involves a set of new dose planning aims. The ability to reach these dose planning aims is based on interventions in terms of advanced BT and EBRT technology. Advanced BT involves increased utilisation of IC/IS applicators as well as vaginal dose de-escalation. Advanced EBRT involves IMRT as well as daily image guidance utilising margin reduction. This approach will enable delivery of increased focal doses to gross disease (primary tumour and positive lymph nodes) as well as reduction of high and intermediate dose to OARs. The improved dose administration is hypothesised to benchmark an outstanding high level of local, nodal control, and systemic control as well as a low incidence of intermediate and major morbidity. Through this well-controlled prospective interventional study we aim to achieve the composite aims listed in section 4.2.

3.2 TUMOR AND TARGET CONCEPTS FOR RESPONSE ADAPTED RADIOTHERAPY IN CERVIX CANCER: RESIDUAL GTV-T, ADAPTIVE CTV-T_{HR} AND CTV-T_{IR}

The target concept for response-adapted radiotherapy is focussed on the primary tumour change (GTV-T) and the change of the CTV-T during upfront chemo-radiation. These changes are essential for selecting the appropriate target for brachytherapy (see chapter 5.4, ICRU report 88). Therefore new terms and concepts have been introduced as compared to ICRU 50, 62 and 83 which correspond to those of the Gyn GEC ESTRO Recommendations I and II (Haie-Meder C. et al. 2005, Pötter R. et al. 2006). These terms and concepts are further elaborated in the ICRU/GEC ESTRO report 88. Therefore, in the following, a short summary is given, taken from the recent ICRU/GEC ESTRO report 88 (chapter 5):

"**Residual GTV-T (GTV-T_{res})** is defined as the residual macroscopic tumor at the time of (brachytherapy) boost after treatment assumed sufficient to control microscopic disease. GTV-T_{res} still bears clinical and/or imaging characteristics similar to the initial GTV-T_{init} and may represent macroscopic and/or microscopic and/or even no residual disease.

Residual pathologic tissue may surround the residual GTV-T and bears different clinical and/or imaging characteristics (e.g. edema, fibrosis) compared to the initial GTV-T. It is always located within the region of the initial GTV-T.

Adaptive CTV-T (CTV-T_{adapt}) can be defined after any treatment phase and includes in any case the GTV-T_{res} and the residual surrounding pathologic tissue, if present. The adaptive CTV-T is a sub-volume of the initial CTV-T, except in case of tumor progression.

Adaptive High Risk CTV-T (CTV-T HR_{adapt}) is defined as a specific form of the adaptive CTV-T for cervix cancer radiotherapy following the GEC ESTRO recommendations. CTV-T HR_{adapt} includes the GTV-T_{res} and the whole cervix and adjacent residual pathologic tissue, if present. It is the volume bearing the highest risk for recurrence. The CTV-T HR_{adapt} for cervix cancer is selected by clinical examination and imaging at the time of brachytherapy, after 40-45 Gy EBRT plus chemotherapy in advanced cervical cancer.*

Intermediate Risk CTV-T (CTV-T IR) represents the area of the GTV_{init} as superimposed on the topography at the time of brachytherapy and a margin surrounding the anatomical cervix borders (CTV-T HR_{adapt}) in areas without an initial GTV-T. The CTV-T IR therefore always includes the CTV-T HR_{adapt} and margins as appropriate.

Adaptive Low Risk CTV-T (CTV-T LR_{adapt}) represents compartmental areas at risk for potential contiguous or incontiguous microscopic spread from the primary tumor. CTV-T LR_{adapt} comprises in advanced cervix cancer the whole parametria, the whole uterus, the upper part of the vagina and the anterior/posterior spaces towards bladder and rectum. This CTV-T LR always includes the CTV HR/IR, respectively. The CTV-T LR is defined at diagnosis (initial CTV-T LR) and maybe adapted during EBRT and also at brachytherapy (adaptive CTV-T LR).*" (ICRU 88, 2015)

* in EMBRACE II an initial CTV-T HR (CTV-T HR_{init}) and an initial CTV-T LR (CTV-T LR_{init}) are defined for EBRT which correspond to the adaptive CTV-Ts as defined for brachytherapy (see chapter 9).

Examples, variations and uncertainties for selection and contouring of the initial and residual GTV-T and the initial and adaptive CTV-T are described in detail in ICRU 88, in chapter 9 and 10, and in the appendix. Most research work has focussed so far on the adaptive CTV-T. Uncertainties vary with method of investigation (e.g. imaging modality such as MRI, CT, US) with MRI and clinical examination at present regarded as gold standard. For this reason, MRI and clinical examination are mandatory tools for EMBRACE II at diagnosis and during treatment, in particular at the time of brachytherapy.

In the following, typical examples for contouring are given for brachytherapy in schematic diagrams for contouring of GTV-T_{res}, adaptive CTV-T HR, CTV-T IR and adaptive CTV-T LR taking into account various disease extensions and stages at diagnosis and various forms of response (taken from ICRU report 88). The 9 comprehensive examples in the Appendix of ICRU 88 are also of major interest.

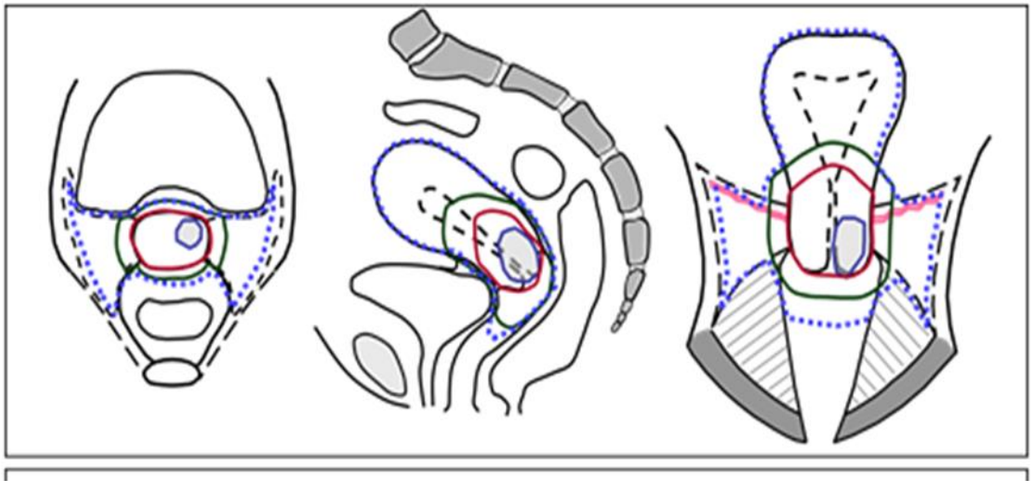


Figure 3.1 (compare figure 9.4 for EBRT). “Schematic diagram for cervical cancer, limited disease, stage IB1, with initial GTV-T, initial CTV-THR (cervix) and initial CTV-TIR (margins around cervix)* and initial CTV-TLR (margins for whole parametria, whole uterine corpus, upper third of vagina, utero-bladder and cervix-rectum space) for initial brachytherapy combined with EBRT: coronal, transversal and sagittal view (see also Appendix example 1, Paris)” (Fig. 5.8 from ICRU report 88 in press). *only considered for brachytherapy in EMBRACE II.

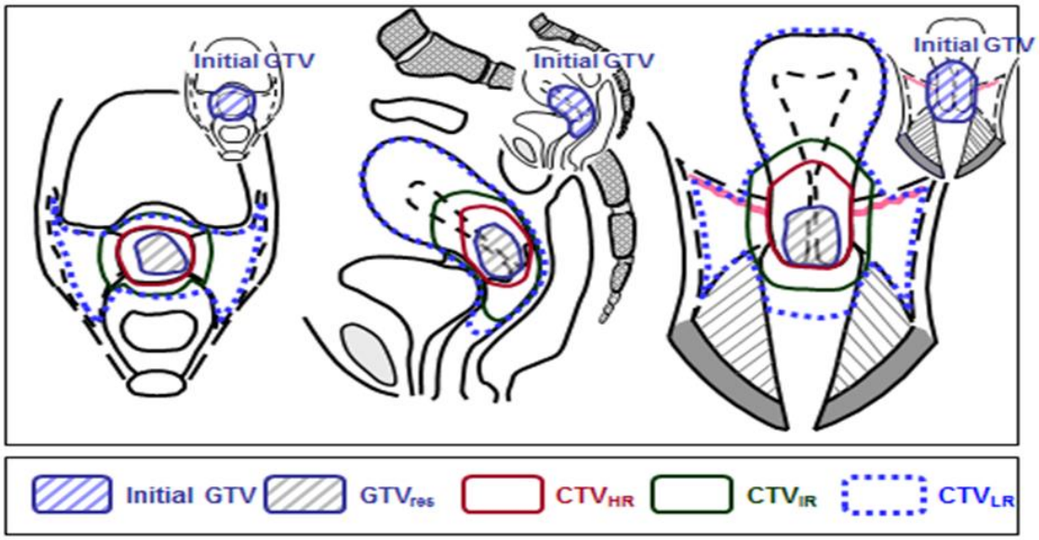
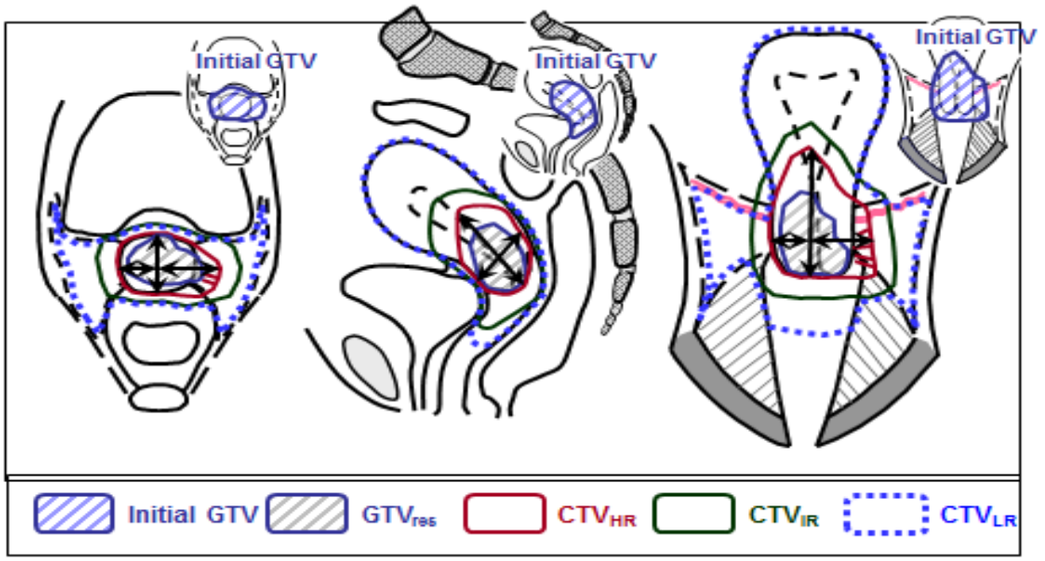


Figure 3.2 (compare figure 9.5 for EBRT). “Schematic diagram for cervical cancer, stage IB2 (bulky disease), good response after chemo-radiotherapy: residual GTV-T (GTV-T_{res}), adaptive CTV-T HR (CTV-T HR_{adapt}), initial GTV-T (GTV-T_{init}), intermediate risk CTV-T (CTV-T IR) (GTV-T_{init} plus margins around the CTV-T HR_{adapt}) and CTV-T LR_{adapt} for adaptive brachytherapy: coronal, transversal and sagittal view (see also Appendix example 2)” (figure 5.9 from ICRU report 88 in press).



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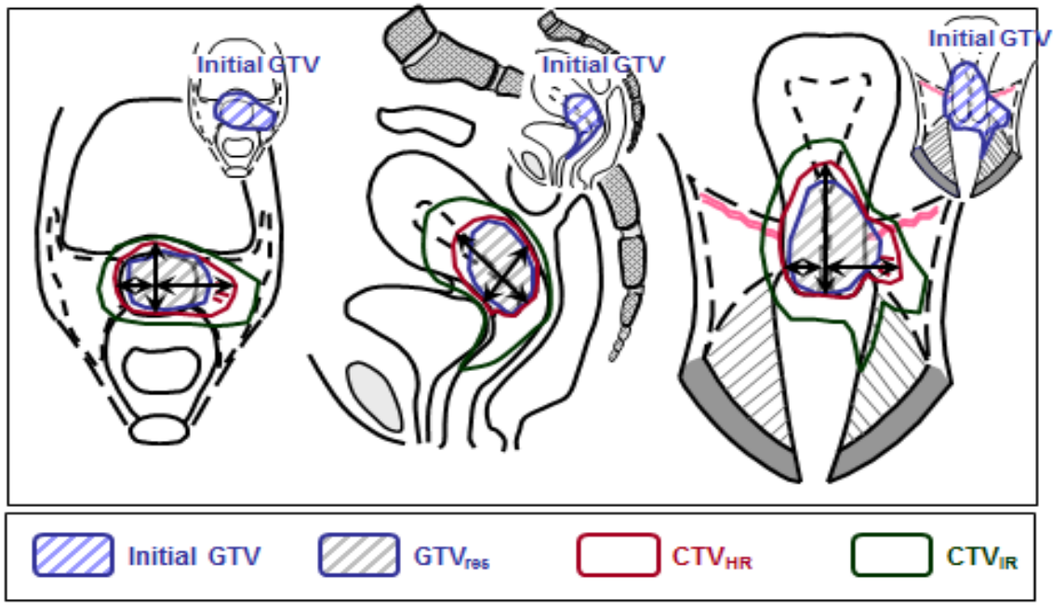
501 Figure 3.3 (Compare figure 9.6 for EBRT) "Schematic diagram for cervical cancer, stage IIB bulky disease and good response after
502 chemo-radiotherapy: GTV-T_{init}, GTV-T_{res} and extra-cervical gray zones, adaptive CTV-T HR, CTV-T IR (GTV-T_{init} plus margins around the
503 CTV-T HR) and CTV-T LR for adaptive brachytherapy: coronal, transversal and sagittal view. Maximum width, thickness and height of
504 the adaptive CTV-T HR are indicated (see also example 5 in the Appendix)" (figure 5.10 from ICRU report 88 in press).



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506 Figure 3.4 (compare figure 9.7 for EBRT). "Schematic diagram for cervical cancer, IIIB, extensive disease, poor response after chemo-
507 radiotherapy: large initial and residual GTV-T (GTV-T_{init}, GTV-T_{res}), extensive gray zones, adaptive CTV-T HR, CTV-T IR (GTV-T_{init} plus
508 margins around the CTV-T HR) and CTV-T LR for definitive treatment: coronal and transversal view. Maximum width, thickness and
509 height of the CTV-T HR are indicated (see also examples 6 and 8 in the Appendix)" (figure 5.11 from ICRU report 88 in press).

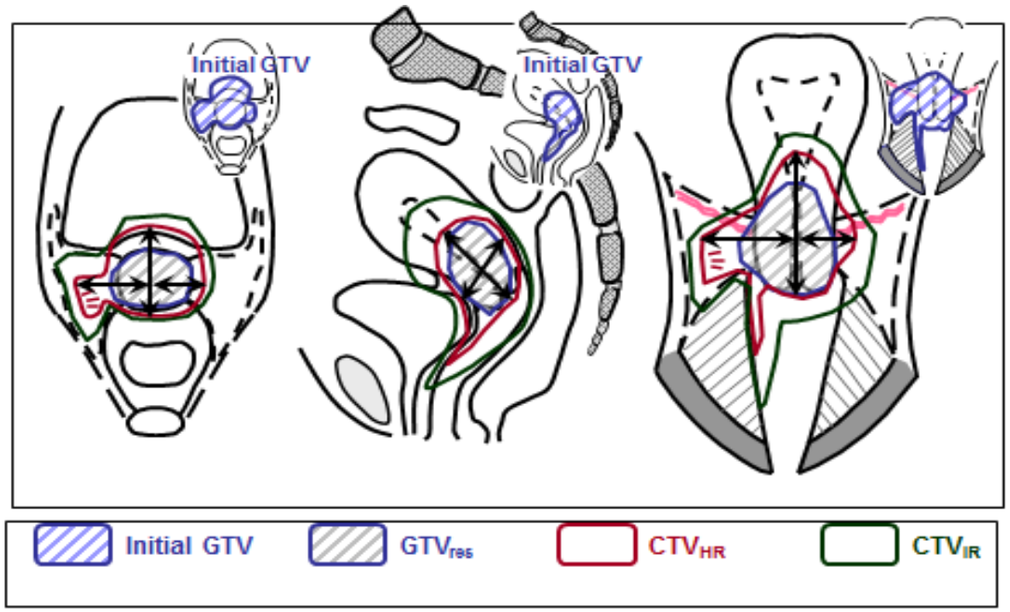


Figure 3.5 (compare figure 9.8 for EBRT). "Schematic diagram for cervical cancer, with bladder infiltration, stage IVA, and good response after chemo-radiotherapy: large initial and residual GTV-T (GTV-T_{init}, GTV-T_{res}), extensive gray zones, residual infiltration in the posterior bladder wall; adaptive CTV-T HR, CTV-T IR (GTV-T_{init} plus margins around the CTV-T HR), CTV-T LR for adaptive brachytherapy: coronal, transversal and sagittal view. Maximum width, thickness and height of the HR CTV-T are indicated." (figure 5.12 from ICRU report 88).

3.3 EVIDENCE FROM THE RETROEMBRACE AND EMBRACE STUDIES

When the prospective EMBRACE study was designed, there was still only limited evidence on dose and effect relations for target or organs at risk (OAR), and it was not yet time to aim for a specific dose prescription for the target or specific dose constraints for organs at risk (OAR). Therefore, brachytherapy dose prescription in the EMBRACE study was based on institutional practice which varied considerably with regard to total dose, fractionation, dose rate, and brachytherapy applicators. This means that a significant variation in dose prescription is present both at the institutional as well as on the patient level in the retroEMBRACE and EMBRACE studies. This heterogeneity in dose administration has provided a unique opportunity to learn about the effect of different dose levels, and a vast amount of new knowledge on dose and effect relationships is currently growing from the EMBRACE and retroEMBRACE studies for GTV_{res}, CTV_{HR}, CTV_{IR}, bladder, rectum, bowel, and vagina. Furthermore, there are a number of mono-institutional studies on dose and effect, in particular on rectum and CTV_{HR} (Georg P. et al. 2012, Koom WS. et al. 2007). The new knowledge from EMBRACE as well as published literature on dose and effect is the prerequisite of designing the EMBRACE II dose prescription protocol with dose planning aims for target and OARs. In the following sections the upcoming dose effect data from retroEMBRACE and EMBRACE is described.

3.3.1 LOCAL CONTROL AND D90 TO CTV_{HR}, GTV AND CTV_{IR}

Relation between target dose (CTV_{HR}, GTV and CTV_{IR}) and incidence of local control was analyzed in a clinical material of 488 pts enrolled in the retroEMBRACE study from 6 institutions performing MRI guided adaptive brachytherapy. A significant dose effect relationship was found for CTV_{HR}, GTV and CTV_{IR} in stage II and stage III disease (figure 3.6). Furthermore, for HR CTV a cox regression dose response analysis showed that both CTV_{HR} volume and dose was related with local control. The data supports a dose constraint of ≥85Gy EQD2 to the CTV_{HR} D90 which is predicted to lead to a 3-year actuarial local control of >96% in tumours ≤30cc and >91% in tumours >30cc. Dose planning aims for CTV_{IR} and GTV_{res} proposed for similar levels of local control are: CTV_{IR} D98≥60Gy and GTV_{res} D98≥95Gy.

Utilization of combined intracavitary/interstitial (IC/IS) applicators is an essential tool for dose escalation in large tumours. In terms of dose, the IC/IS applicators can widen the therapeutic window by 5-10Gy as demonstrated by direct comparison between IC and IC/IS applicators (Fokdal L. et al. 2013). This is further supported by data from the retroEMBRACE and EMBRACE studies which demonstrate that application of IC/IS in a significant proportion of the patients (>20-50%) is essential for reaching a high dose to CTV_{HR} (>85Gy) in the majority of patients. In retroEMBRACE, the CTV_{HR} dose administration was larger by 10Gy in institutions systematically applying combined IC/IS applicators, while doses to OARs were not increased. The increased dose resulted in improved local control in patient cohorts where application of IC/IS was performed in at least 20% of the patients (figure 3.7). Since the target dose escalation did not involve significant increase of dose to OARs, the incidence of morbidity was not different in the patient cohort with frequent application of IC/IS as compared to the cohort where mainly IC was applied, although there was a tendency that vaginal morbidity was slightly increased in the IC/IS cohort.

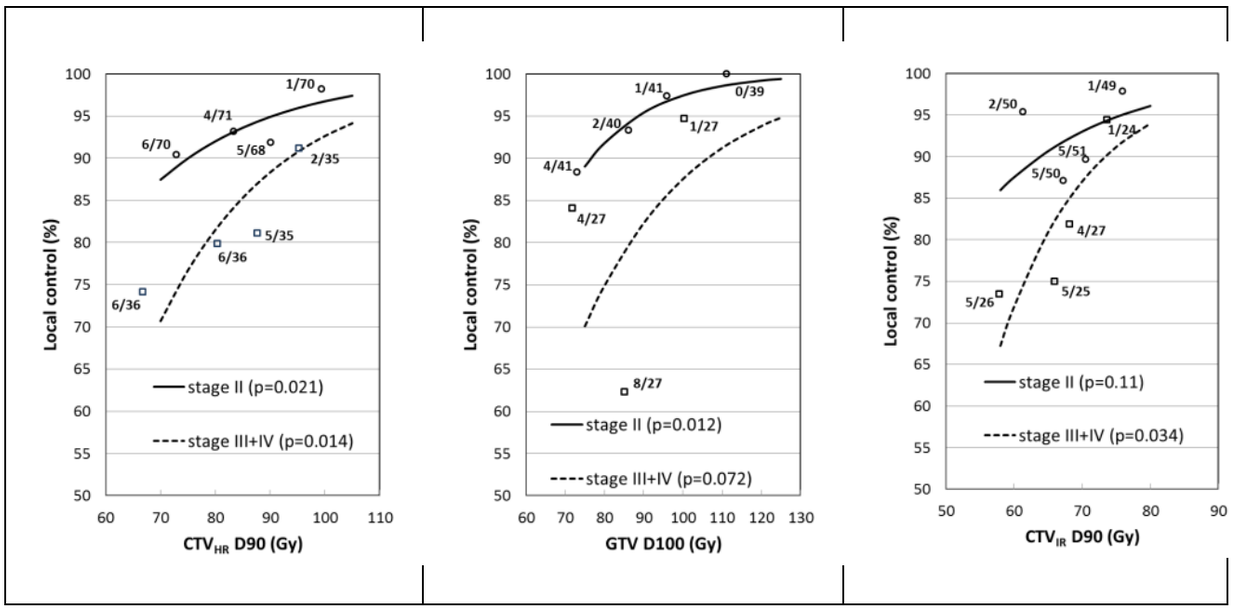
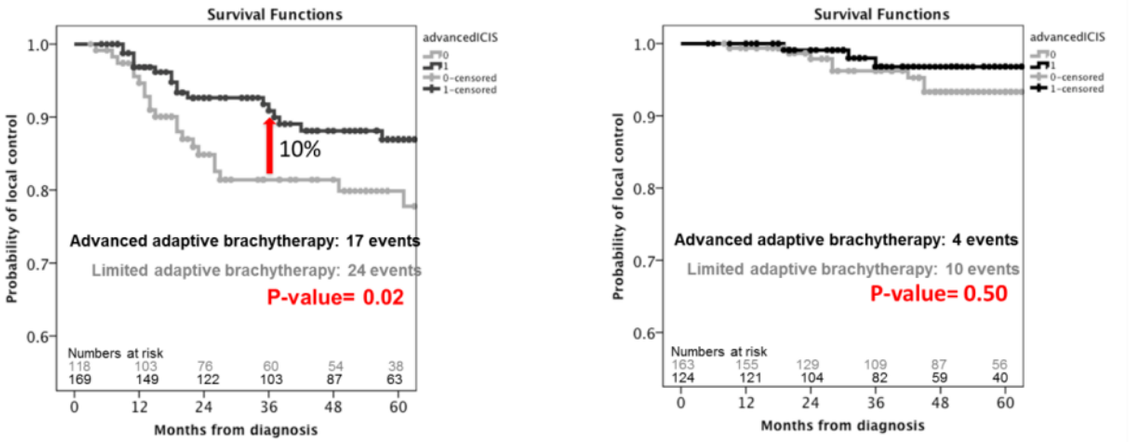


Figure 3.6. Dose response in stage II and stage III for adaptive CTV-T_{HR}, GTV-T_{res} and CTV-T_{IR}. (Tanderup K. et al. in submission 2015)

CTVHR ≥ 30 cm^3 CTVHR < 30 cm^3



gure 3.7. Local control for large (left panel) and small (right panel) CTV_{HR}, as depending on routine application of IC/IS technique. Advanced adaptive brachytherapy implies that >20% of the patients in the cohort were treated with IC/IS. Limited adaptive brachytherapy implies that the majority of patients (<20%) were treated with IC technique. Data from retroEMBRACE (Fokdal L. et al. 2015, RetroEMBRACE work in progress).

3.3.2 OVERALL TREATMENT TIME

The effect of overall treatment (OTT) time was investigated in the same clinical material as in section 3.2.1: 488 pts enrolled in the retroEMBRACE study from 7 institutions. Multivariate Cox Proportional Hazards modelling was performed to include the effects of stage, histology, CTVHR dose, CTVHR volume, and OTT. The effect of OTT shortening by one week was equivalent to escalating CTVHR dose by 5Gy (D90), resulting in increase of local control by 1.0% for CTVHR volume of 20cm3, 1.2% for 30cm3, and 2.5% for 70cm3. The dose constraints and levels of local control introduced in 3.2.1 are valid for a treatment time of 7 weeks, and therefore if treatment time is longer or shorter than 7 weeks, the dose planning aims should in principle be adjusted by 5Gy per week for CTVHR. The data underlines the importance of keeping the OTT as short as possible, in particular for large size CTVHR, where higher dose is needed to reach >90% local control.

3.3.3 URINARY MORBIDITY AND BLADDER D_{2CM3}

A clinical material of 680 pts from EMBRACE was analysed. A total number of 95 events of ≥G2 morbidity occurred (ureter stenosis excluded). The dominating events were frequency, urgency and cystitis. A significant dose relationship was present which indicates that at dose levels beyond 80Gy EQD2 there is a clinically significant increase in ≥G2 morbidity (figure 3.8) (Tanderup K. et al. 2014, EMBRACE work in progress).

The location of the D_{2cm3} has shown to be of significance for development of urinary morbidity, which has been shown by using the ratio between D_{2cm3} and ICRU bladder dose as a surrogate of the D_{2cm3} location (Nkiwane KS. et al. 2015, Mazeron R. et al. 2015).

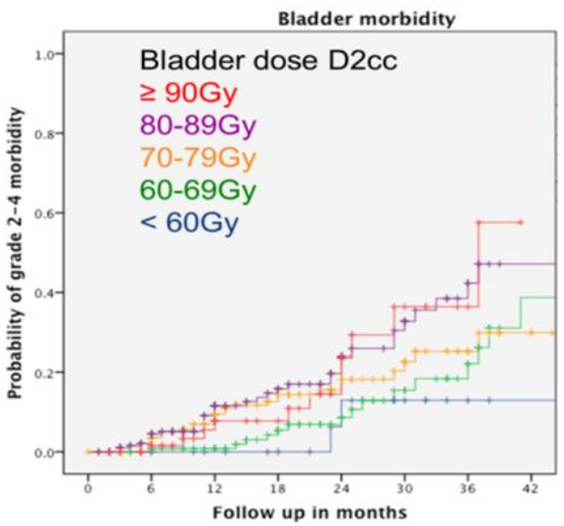


Figure 3.8. Actuarial incidence of G≥2 urinary morbidity (all endpoints except ureter stenosis) grouped according to D_{2cm3} dose levels (Tanderup K. et al. 2014, EMBRACE work in progress).

3.3.4 RECTAL BLEEDING AND RECTUM D_{2CM3}

A clinical material of 701 patients from EMBRACE was analysed. Rectal bleeding (50 events) correlated significantly with dose (figure 3.9). The dose response was shallow below 70Gy, and it is unclear how much clinical impact dose de-escalation below 70Gy could have. However, for doses above 70-75Gy there is a steep increase in risk of rectal bleeding. Analysis of further endpoints such as bowel control is pending.

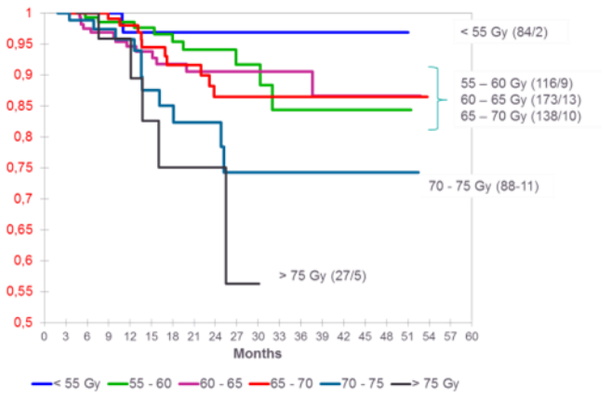


Figure 3.9. Actuarial incidence of rectal bleeding grouped according to D_{2cm3} dose levels (Mazeron R. et al. in submission 2015)

3.3.5 BOWEL MORBIDITY AND SIGMOID/BOWEL D_{2CM3}

In the EMBRACE material (701 pts) it was not possible to identify any significant relation between D_{2cm3} sigmoid and bowel dose and morbidity related to these organs. However, D_{2cm3} assessment in sigmoid and bowel is highly uncertain due to mobility of these organs. EMBRACE does not have any information recorded about the mobility of bowel/sigmoid in between BT fractions, and the EMBRACE data may therefore not be able to reveal any underlying dose response effect. In particular, if adhesions are present, the organ movement will not degrade the dose, and there may be a significant clinical effect of D_{2cm3} in such cases. Based on an assumption that sigmoid and bowel are more radiosensitive organs than rectum, doses of 60-70Gy may have an effect, in case of adherences. Furthermore, in EMBRACE there were only few patients where sigmoid or bowel D_{2cm3} exceeded 75Gy (7% and 10% of the patients, respectively), and any dose effect beyond such dose levels cannot be revealed with EMBRACE data. Therefore, although no dose

response could be assessed in EMBRACE, it may be appropriate to aim for sigmoid and bowel dose planning aim of 70Gy in case there are adherences.

3.3.6 VAGINAL MORBIDITY AND ICRU RECTO-VAGINAL DOSE

Vaginal morbidity has been analysed in 754 pts in the EMBRACE material. The majority of ≥G2 events were vaginal stenosis (140 out of 181 events) which occurred mainly within the first 18 months. In a patient population of 630 pts a more detailed dose effect analysis was carried out. There was a significant correlation between incidence of vaginal stenosis and the dose to the ICRU recto-vaginal point. At a dose level of 65Gy the incidence of vaginal stenosis was 20% and this increased to 27% at a dose of 75Gy (figure 3.10). Furthermore, there was a significant impact of EBRT dose. With lower dose (≤45Gy), the 2-year actuarial probability was 17% vs. 30% with higher dose.

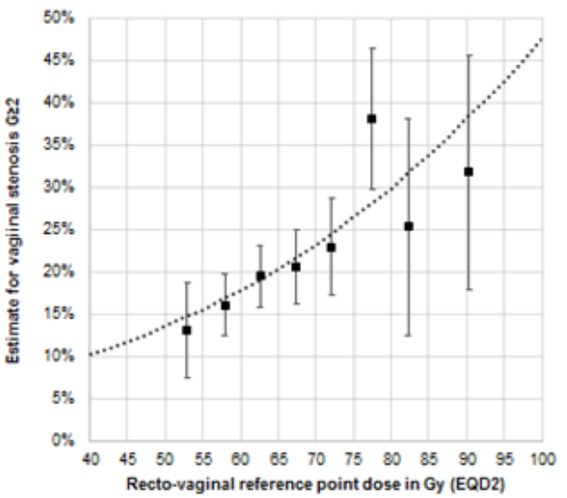


Figure 3.10. Dose effect curve based on Cox regression model of dose to the ICRU recto-vaginal point in total EBRT+BT EQD2 and vaginal shortening/narrowing G≥2. The model represents actuarial probability at 2 years (Kirchheiner K. et al. in submission 2015).

3.3.7 GASTROINTESTINAL/URINARY MORBIDITY AND INTERMEDIATE DOSE LEVELS RELATED TO EBRT

A number of 387 pts with >12 months of follow up were analysed. The influence of intermediate dose levels on development of GI and urinary morbidity (patient reported EORTC QoL) was investigated through parameters related to EBRT: technique (IMRT/CRT) and irradiated volume (43Gy and 57Gy). There was a significant relation between EBRT technique and GI and urinary patient reported symptoms (”quite a bit” and ”very much”). Furthermore, a relation was found between the total body (abdominal) volume which was irradiated to >43Gy and the incidence of diarrhea (figure 3.11). With an increase in volume from 2000cm^3 to 3000cm^3 there was an increase in diarrhea from 12% to 22%. This increase is rather shallow and likely related to the fact that the total irradiated body (abdominal) volume is only a limited surrogate for the volume of bowel irradiated.

Furthermore, preliminary EMBRACE analyses indicate that there is a tendency that IMRT reduces late bowel morbidity compared to 3D conformal EBRT (e.g. diarrhea) (figure 3.12).

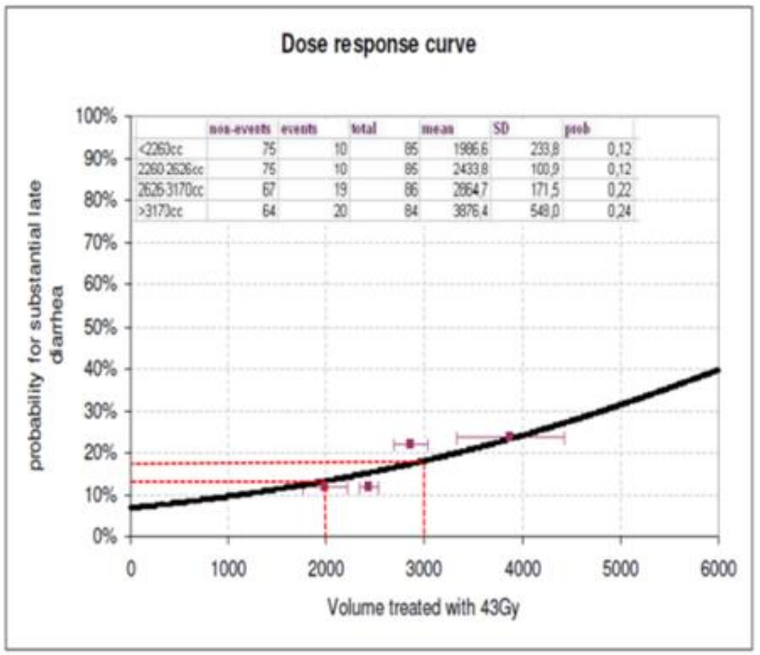


Figure 3.11. Crude incidence of diarrhea (patient reported) according to body (abdominal) volume irradiated to >43 Gy (Tanderup K., Kirchheiner K. 2014, EMBRACE, work in progress).

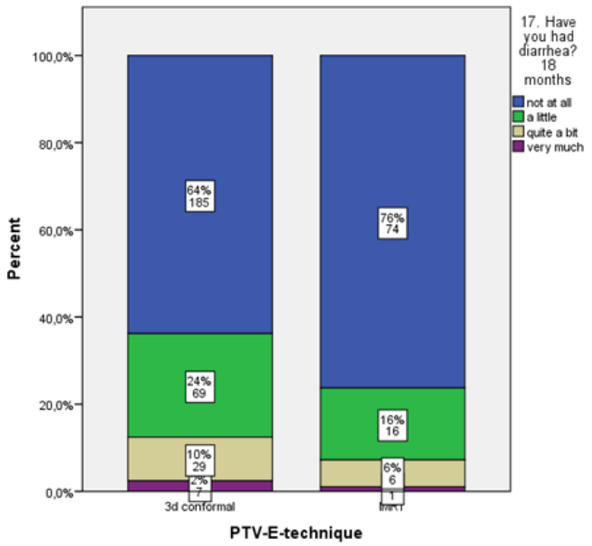


Figure 3.12. Prevalence at 18 months after treatment of patient reported outcome on the question « have you had diarrhea?» comparing IMRT and 3D conformal EBRT (Kirchheiner K. et al. 2014, EMBRACE work in progress).

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607 ### 3.3.8 PATTERNS OF SPREAD AND PROGNOSTIC PARAMETERS FOR NODAL PELVIC AND PARA-AORTIC
608 RECURRENCES

609 In EMBRACE, 47 % of the patients had nodal metastases at time of diagnoses, either verified with surgical approaches or with imaging
610 (CT, MRI or PET-CT). A preliminary analysis of nodal recurrences in 816 patients in EMBRACE showed that nodal disease at time of
611 diagnoses was mainly located in the pelvis (internal/external iliac including obturator and common iliac region) while nodal recurrences
612 after treatment was predominantly seen in para-aortic nodes (see Figure 3.13). Para-aortic failures contributed with 69% of all nodal
613 failures with the strongest predictor being nodal disease at time of diagnosis. In total, 62 para-aortic failures occurred. In 406 N+

patients at diagnosis there were 47 para-aortic failures (11.5%) and 15 (3.7%) para-aortic failures were seen in the N- group of 410 patients. 78% of para-aortic failures in EMBRACE were in patients who did not receive para-aortic irradiation.

Recently published data for node positive cervix cancer patients show promising results after extended field IMRT, not to the cost of treatment related morbidity. The PAN control reported is 95 % in case of PAO negative and 89% in case of PAO positive patients at time of diagnosis (Vargo JA. et al. 2014). Based on these results it is likely that increasing the rate of elective PAN irradiation in patients with nodal disease at time of diagnosis will help increasing tumor control in the para-aortic region. Therefore, PAN irradiation will be further investigated in EMBRACE II with special focus on in the group of patients with high risk features for the development of PAN and distant disease which seem to be mainly location of nodes (common iliac), number of nodes (≥3) and also to some degree nodal size (Nomden C., Fortin I. et al. EMBRACE work in progress).

In an analysis of 304 lymph node negative patients from the EMBRACE cohort, a low risk group for nodal recurrence could be identified with the following features: Stage IB1, IA, IIA1; Tumour diameter ≤4cm, no uterine involvement and squamous cell cancer. In this low risk group 1/71=1.4% nodal failures (pelvic and para-aortic) were identified.

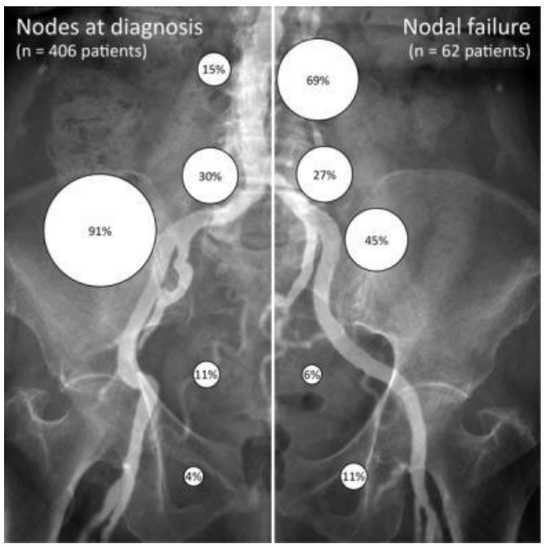


Figure 3.13. Patterns of spread for lymph node disease at time of diagnosis (left panel) and at time of first nodal failure (right panel) (Nomden C. et al. EMBRACE work in progress).

Nodal SUV_{max} seems to be predictive of nodal control and disease recurrence (Kidd EA. et al. 2010) in pelvic lymph nodes. They measured the SUV_{max} of the most FDG avid lymph node in 83 node positive patients. No nodal boost was delivered. The average nodal SUV_{max} was 6.9 (range 2.1-33.0), the average tumour SUV_{max} was 14.0 (2.1-38.4). They found a weak correlation between nodal size and SUV_{max} and between nodal and primary tumour SUV_{max}. Patients with a nodal SUV_{max} > 4.3 had a lower OS, DFS and pelvic control. They also had a higher risk of nodal persistent disease suggesting that these nodes might have benefitted from a more aggressive treatment.

Onal et al. investigated 93 patients with PET-positive pelvic or para-aortic lymph nodes. SUV_{max} was measured for the most FDG avid node. A sequential boost was delivered for all enlarged lymph nodes. The mean SUV_{max} for pelvic nodes, para-aortic nodes and primary tumour was 8.4 (+/- 4.3), 6.7 (+/- 2.8) and 19.7 (+/- 8.0) respectively. A strong correlation was found between nodal size and nodal SUV_{max} and between nodal and primary tumour SUV_{max}. Patients with pelvic nodal SUV_{max} > 7.5 had significantly larger nodes and higher SUV_{max} for both primary tumour and para-aortic nodes. Ten patients had nodal recurrence. 9/10 recurred within the high SUV_{max} nodal region. Patients with higher SUV_{max} had lower DFS and OS (Onal C. et al. 2015).

Finally a recent study by Ramlov et al. investigated 139 patients. Of these 112 had a diagnostic PET or PET/CT performed. Seventy-five patients had totally 209 nodes treated with chemo-radiotherapy and a nodal boost. Total nodal dose, nodal volume and nodal SUV_{max} were determined. SUV_{max} was determined for all PET-positive nodes and not just the most FDG avid node. Six out of 209 boosted nodes recurred. No impact of nodal volume or nodal dose was found for the risk of nodal recurrence. The median SUV_{max} for all nodes was 5.5

(range 2-21) and 11 (range 4-16) for the six recurrent nodes. Nodal SUV_{max} was significantly higher for the recurrent nodes (p= 0.02). The relation between nodal dose/nodal volume and nodal dose/nodal SUV_{max} are presented in figure 3.14 (Ramlov A. et al. 2015).

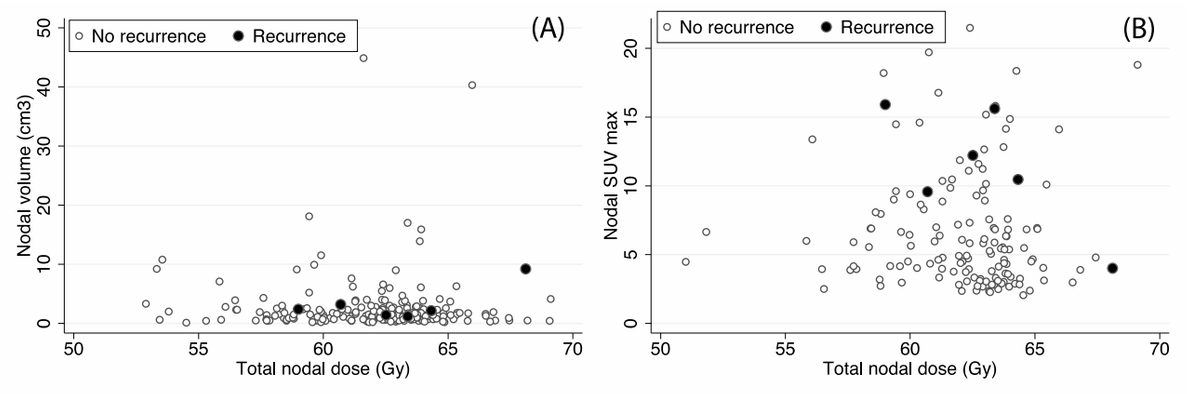


Figure 3.14. Nodal recurrences as depending on dose and volume (left panel) and SUV and dose (right panel) (Ramlov A. et al. 2015).

3.3.9 ADMINISTRATION OF CHEMOTHERAPY

The advantage of chemoradiation over radiotherapy alone has been well documented with several randomized studies over the last decades. Overall survival and event free survival benefit were confirmed in meta-analysis as well. Several platinum based chemotherapy and non-platinum schedule or regimen were studied, but there is insufficient evidence suggesting that a specific regimen/schedule is superior.

However the total number of cycles received during the treatment seems to play an important role in the systemic control in high risk patients (Schmid MR. et al. 2014). An early analysis from EMBRACE study performed on 753 patients shows significantly more systemic relapses in the N+ and advanced stage patients who received 4 chemotherapy cycles and less in comparison with the patients who received 5 chemotherapy cycles or more (Figure 3.14). At 24 months, N+ and advanced FIGO stage patients show a systemic control of 63% vs 88% in patients having received 4 cycles and less versus 5 cycles and more, respectively. At 3 and 5 years, the distant metastases free interval was 79% and 77%, respectively in the whole cohort. These results are in line with those of Schmid et al. 2014 in that the administration of 5–6 full dose cycles of chemotherapy can reduce a patient's risk of developing distant metastasis, especially in patients showing more advanced disease characteristics such as N+ and advanced FIGO stage.

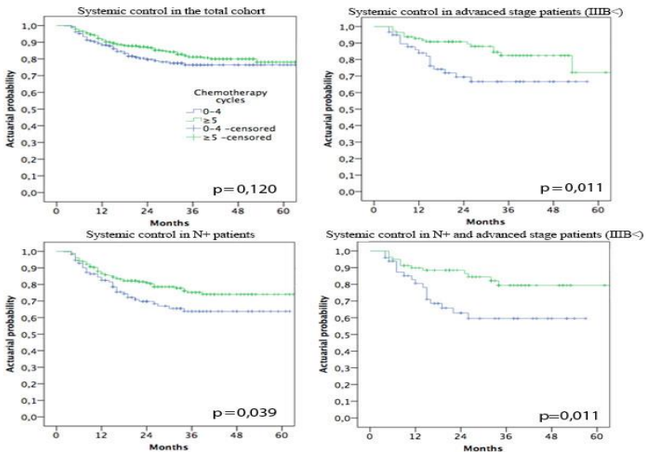


Figure 3.14. Impact of number of chemotherapy cylcles on systemic control. Advanced stage is defined as stage III and IV (Fortin I. et al. Abstract ASTRO 2015, EMBRACE work in progress).

3.4 INTERNAL TARGET MOTION

The use of more conformal inverse planning techniques (IMRT, VMAT, tomotherapy) has raised the importance of the internal target motion during the course of fractionated EBRT. Besides filling status of surrounding bladder and bowel structures, both tumour extension at diagnosis and tumour regression during treatment have impact on internal target motion. Several studies have documented the distances and directions of movement of the cervix and uterus in relation to organ filling on serial CT, MRI, or CBCT imaging, while other studies primarily described the necessary standard CTV to PTV margins for 95% CTV coverage. Importantly the majority of these studies did not use a protocol for bladder or bowel filling.

Main general findings are that the motion is patient specific and that the motion of the uterus (excluding the cervix) is greater than that of the cervix and these can move in independent directions. The greatest motions are observed in the anterior-posterior direction followed by superior-inferior directions. Bladder filling status seems to impact more on the uterine motion and rectal filling more on the motion of the cervix and upper vagina. A systematic review of organ motion in cervix cancer summarises studies on uterine and cervix movements (Jadon R. et al. 2014). For the cervix, the reported mean movement ranges in the anterior-posterior direction between 2-21 mm, with standard deviations ranging between 3.5-10 mm; superior-inferior 2-16 (SD range 3-8 mm); lateral 0-10 mm (SD range 1-7 mm). For the uterine part corresponding figures are anterior-posterior 4-14 mm (SD range 9-12 mm); superior-inferior 2-10 (SD range 7-12 mm); lateral 0-7 mm (SD range 1-8 mm). Observed maximal movements could be up to 4-6 cm again mainly in the anterior-posterior and superior-inferior directions. Different studies report a decrease of mean bladder volume during the course of fractionated radiotherapy, while this was not found for rectal volume. There are few studies that have looked at motion of lymph node related target structures, a study using MRI found mean motions ranging between 5 and 9 mm, while movement of regional vessels was correlated to bladder filling status.

The major shortcoming in the field is that the majority of research on motion has focussed on quantifying the magnitude of the movement in mm or has reported dose coverage. The direct impact of motion on dose has so far only been reported in three studies. Lim et al showed that a 15 mm GTV to PTV margin covered always the GTV to > 98% of prescribed dose (20 patients) (Lim K. et al. 2009). Jensen et al showed that accumulated EBRT D98 to the uterus was >42Gy in 9/10 and 38Gy in 1/10 patients with a 15mm margin from uterus to PTV (Jensen NBK. et al. 2015). Evaluating accumulated EBRT and BT uterus D98, it was always >45Gy. These two studies indicate that even if the CTV is outside the PTV in a significant number of fractions, the impact on accumulated dose is limited due to shallow dose gradients. Furthermore, Assenholt et al. showed that application of a PTV margin of 5mm on pathological lymph nodes boosted with SIB technique resulted always in D98 > 95% accumulated dose (40 lymph nodes) (Assenholt M. et al. Abstract BigART 2015).

4 INTERVENTIONS AND AIMS

4.1 INTERVENTIONS

Based on the evidence for dose effects from the EMBRACE and retroEMBRACE studies there is a clear evidence based rationale to implement an overall dose prescription protocol based on a set of dose planning aims and dose constraints for the target related to the primary tumour (CTV-T) and the 2cm^3 and reference points for OARs (see chapter 10.8). The fulfillment of these planning aims is hypothesized to result in improved local control and decreased morbidity.

The ability to reach these planning aims and dose constraints relies on a change of practice for both EBRT and BT dose administration as compared to current practice in the EMBRACE study. The change of practice involves a number of interventions in terms of systematic utilization of advanced image guided BT and EBRT: advanced BT involves increased use of IC/IS and vaginal dose de-escalation, and advanced EBRT involves application of IMRT and IGRT.

Furthermore, the current pattern of spread for nodal recurrences as found in EMBRACE will be addressed by treating patients at high risk of nodal and systemic recurrence with para-aortic irradiation and patients with a low risk with small pelvis radiotherapy. Patients with an intermediate risk will receive a large pelvis elective nodal target.

4.1.1 INCREASED USE OF IC/IS TECHNIQUE IN BT

In EMBRACE, half of the patients have been treated in institutions performing mainly IC brachytherapy ("IC centers"), where IC/IS was carried out in ≤20% of the patients. The other half of the patients have been treated in institutions with routine application of IC/IS ("IC + IC/IS centers"). The dose administration in the "IC" and "IC + IC/IS" cohorts differs significantly (table 4.1). In centers performing IC + IC/IS the dose to CTV_{HR} was >85Gy for 83% of the patients, whereas this was obtained in 48% of the patients from IC centres. Furthermore, 24% of the patients received >95Gy to the CTV_{HR} - predominantly in small volume CTV_{HR} and in centres using IC/IS in a high percentage of patients.

In most centers routinely applying IC/IS, the rate of application is normally much higher than 20% (table 4.1), since application of IC/IS can also benefit OAR sparing.

Adaptation	HR CTV vol	Application of IC/IS	HR CTV D90	Bladder D2cm^3	ICRU recto-vag. dose	Rectum D2cm^3
IC*	<30cc	7%	87±9Gy	73±11Gy	68±12Gy	62±8Gy
IC + IC/IS**	<30cc	34%	94±11Gy	75±13Gy	65±10Gy	62±9Gy
p-value			<0.001	<0.001	<0.001	0.807
IC*	>30cc	25%	80±11Gy	81±12Gy	74±16Gy	66±12Gy
IC + IC/IS**	>30cc	75%	88±7Gy	79±10Gy	68±9Gy	65±7Gy
p-value			<0.001	0.101	<0.001	0.087

*Centers applying IC/IS in ≤20% of the patients; **Centers applying IC/IS in >20% of the patients

Table 4.1. Practice of dose administration in EMBRACE (Tanderup K. et al. 2015, EMBRACE work in progress)

In EMBRACE II, the improved therapeutic window (through increased application of IC/IS) will be exploited for tumour dose-escalation and/or OAR dose de-escalation (figure 4.1). In tumours with large residual CTV_{HR} volumes at time of brachytherapy, dose-escalation has the potential to improve local control significantly. In limited size CTV_{HR} volumes dose-de-escalation will be performed since dose de-escalation has minor impact on local control while it has potential to reduce morbidity. The strategy of EMBRACE II is to aim for an application of the IC/IS technique in at least 20% of the patients in each institution. The threshold of 20% is relevant for a classical stage distribution of ~20% IB, ~50% IIB, ~20% IIIB and ~10% others. If a given patient population includes significantly higher proportions of limited or extensive disease, the threshold of 20% IC/IS applications must be adapted.

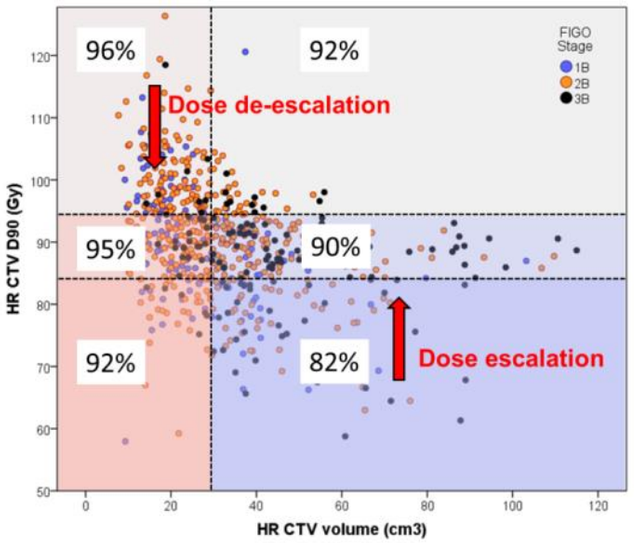


Figure 4.1 Principles for dose de-escalation and dose escalation in EMBRACE II. The figure shows the current distribution of CTV_{HR} dose and volume in the EMBRACE study (each point represents one patient). A number of 6 dose and volume groups are defined according to cut-points of 85Gy and 95Gy for CTV_{HR} dose and of $30cm^3$ for CTV_{HR} volume. For each dose-volume group the expected actuarial local control at 3 years is indicated (according to dose effect data from the retroEMBRACE study (Tanderup K. et al. 2014, RetroEMBRACE work in progress).

4.1.2 REDUCTION OF VAGINAL SOURCE LOADING

A multicenter investigation in 50 EMBRACE patients from 3 institutions (Mohamed SM. et al, in submission 2015) shows that reduced loading in ring/ovoids and increased loading in tandem (and needles when available) can be applied without compromising CTV_{HR} and GTV_{res} dose. Decrease of relative vaginal loading from a mean of 50% to 33% had potential to reduce ICRU recto-vaginal dose by a mean of 4±4Gy, and furthermore, bladder and rectum doses could be reduced by 2-3Gy with the same re-arrangement of loading. Similar evidence is available from a study on simulation of different intracavitary standard loading patterns in EMBRACE patients, where it was shown that limited size tumours could often be covered by tandem loading alone (Nkiwane KS. et al. 2013).

4.1.3 SYSTEMATIC UTILISATION OF IMRT

Many institutions deliver 3D conformal radiotherapy (3D CRT) based on a four-field box technique although IMRT has been available for a number of years. The practice in EMBRACE has been utilisation of IMRT and 3D CRT in 27% and 73% of the patients, respectively. However, EMBRACE morbidity data as well as data published by Mundt et al (Mundt AJ. et al. 2003) indicate that IMRT significantly reduces the incidence of bowel morbidity, and therefore IMRT is considered as instrumental for reducing the incidence of bowel morbidity and with a potential also to be beneficial for urinary morbidity.

4.1.4 UTILISATION OF DAILY IGRT (SET-UP ACCORDING TO BONY STRUCTURES)

PTV margins of 10 mm to the elective lymph node target are currently applied in many institutions. This margin is related to set-up uncertainties with patient positioning performed based on skin marks. However, currently, most institutions have in-room imaging available which makes it possible to perform daily imaging and couch correction according to fusion on bony anatomy. With daily imaging, bony image fusion, and couch correction, a margin reduction from 10mm to 5mm can be performed without compromising target coverage (Laursen LV. et al. 2012). The 5mm margin reduction has potential to decrease the volume irradiated to 43Gy by approximately 500 cm^3, which is expected to decrease bowel morbidity by ~50% (Fig. 3.11).

4.1.5 EBRT TARGET CONCEPT RELATED TO THE PRIMARY TUMOUR (CTV-T) AND INTERNAL MOTION; CONCEPTS FOR OAR CONTOURING

New target concepts are introduced for EBRT related to the primary tumor: initial CTV-T, initial CTV-HR, initial CTV-LR and ITV-LR. The use of this novel contouring approach in conjunction with available MRI will allow to target safely the visible tumor (CTV-T) and the high risk region (CTV-HR intitial) while consenting for dose to a low risk region (CTV-LR initial). Anatomical changes due to bladder and rectal filling variation as well as cervix and uterus position will be considered. An ITV-LR will be outlined using the planning scan and MRI images in patients having a MRI in treating position while a fixed margin will be added to the CTV-LR initial in the patients having only a diagnostic MRI.

Some new concepts will be introduced for OAR contouring. Instead of contouring the abdominal cavity, the bowel loops will be outlined in one volume restricted to the outer contour of bowel loops including the mesenterium. This will allow for a better approximation of the bowel loops volume and optimization of the dose constraints. Rectum and sigmoid structures will be contoured as distinct structures. Vaginal lower border will be not more than 2,5cm from the caudal extend of the tumor (2cm in the ITV-LR initial + 0,5cm PTV).

4.1.6 EBRT DOSE PRESCRIPTION AND REPORTING

There is currently a significant variation with regard to EBRT dose and fractionation in the EMBRACE study with doses ranging from 45Gy to 50Gy and being delivered in 25-30 fractions. Furthermore, there is a wide variety of lymph node boosting strategies. In EMBRACE II, the EBRT dose and fractionation to the elective lymph node CTV and initial CTV-T is fixed at 45Gy in 25 fractions, and lymph node boosting must be performed as a simultaneous integrated boost. The dose de-escalation from 50Gy to 45Gy has potential to reduce morbidity. A system of reporting dose to targets and OARs is introduced in terms of dose volume parameters and a system of point dose reporting for the vagina.

4.1.7 ADAPTATION OF EBRT NODAL ELECTIVE CTV ACCORDING TO RISK OF NODAL AND SYSTEMIC RECURRENCE

EMBRACE and RetroEMBRACE data indicate that para-aortic recurrence is the most frequent location of nodal failures (3.2.7, Fig. 3.13). In order to address this pattern of failure, the EMBRACE study will apply a target concept for nodal CTV which includes the para-aortic region in high risk patients. High risk patients are patients with nodal involvement, who have a considerable risk of para-aortic involvement, recurrence and an inferior survival as compared to node negative patients (EMBRACE and RetroEMBRACE work in progress, Schmid MP. et al. 2013).

Furthermore, the MD Anderson data have shown that the L5/S1 cranial border of the classical pelvic field for cervix cancer is associated with a high number of failures at this field edge (Beadle BM. et al. 2010), which is in accordance with a recent study from Leuven (personal communication).

In addition there is evidence that early disease without risk factors has limited frequency of nodal metastases beyond the iliac bifurcation (1.4% in EMBRACE experience).

Therefore based on the evidence from EMBRACE, RetroEMBRACE and literature findings, three categories will be defined according to the risk of nodal and systemic recurrence: low risk, intermediate risk and high risk. In the low risk group, the nodal elective CTV will be reduced by exclusion of the common iliac region. In the intermediate risk group the target will include the common iliac nodes with inclusion of the aortic bifurcation, internal iliac, external iliac, obturator, and presacral nodal regions (and groins in case of distal vaginal infiltration). In the high risk group the para-aortic region will be included in the target.

The risk groups are defined according to a number of criteria at time of diagnosis which is partly supported by EMBRACE findings and literature support (see chapter 9, table 9.1).

4.1.8 SYSTEMATIC APPLICATION OF SIMULTANEOUS CHEMOTHERAPY

According to international standard and evidence, simultaneous chemotherapy (min. 5x40 mg/m^2 cis Platinum) was prescribed in the EMBRACE protocol for all patients, who qualify for its administration. Certain rules were given for adaption according to international guidelines. Altogether, so far 90-95% of EMBRACE patients received simultaneous chemotherapy, which compares favourably with the 78% that received simultaneous radiochemotherapy in RetroEMBRACE, reflecting that the vast majority of EMBRACE patients received chemotherapy according to the EMBRACE protocol. Most of the EMBRACE cohort is consecutive patients representing the cervix cancer patient population in the respective centers. When analysing the number of patients and the number of chemotherapy cycles received, about 70% received $\geq$ 5 cycles, while 30% received 0-4 cycles. As stated above (3.2.8), administration of chemotherapy has impact on systemic control, which seems to be pronounced in high risk patients (node positive and/or stage III/IV) with a 20% difference in systemic recurrence. Also a center effect has been found in the ability to administer chemotherapy with a variation from 15% and 85% of the patients receiving $\geq$5 cycles of chemotherapy. In order to reach optimal outcome throughout the cervix cancer population and in particular in the high risk group, the EMBRACE II protocol therefore also focusses on the appropriate administration of chemotherapy according to the EMBRACE II protocol and following international guidelines (chapter 11.1).

4.1.9 REDUCTION OF OVERALL TREATMENT TIME

Several studies indicate that maintaining an overall treatment time (OTT) of <=50 days is important for local control. RetroEMBRACE data confirms that OTT remains of importance in the realm of IGABT. As there is significant variation of OTT across patients and institutions in retroEMBRACE, the EMBRACE II study aims to reduce the OTT so that the majority of patients (>80%) will adhere to the <=50 day threshold. The measures to reduce OTT in EMBRACE is to systematically apply 25 fractions of EBRT including lymph node boost, and furthermore to carefully plan the BT schedule, so that brachytherapy is delivered towards the end of EBRT and/or directly after EBRT.

4.2 AIMS OF THE EMBRACE II STUDY

4.2.1 GENERAL AIMS

- To systematically apply IMRT with daily IGRT as well as advanced image guided adaptive BT in a prospective multi-centre setting
- To systematically implement a dose prescription protocol for IGABT
- To implement systematic contouring, prescription and reporting for EBRT CTV and OARs.
- To administer EBRT in different targets which are adapted to the risk of nodal and systemic failure: to improve para-aortic and systemic control in high risk patients and not to decrease lymph node control in low risk and intermediate risk patients
- To systematically administer simultaneous chemotherapy to EBRT to reach prescribed dose in as many patients as possible, in particular in high risk patients
- To benchmark an outstanding high level of local, nodal and systemic control as well as survival with application of advanced EBRT, BT and chemotherapy within limited overall treatment time
- To benchmark a low incidence of intermediate and major morbidity as well as a high level of QoL with application of advanced EBRT, BT and chemotherapy

4.2.2 SPECIFIC AIMS

- To validate that a dose prescription protocol and increased application of IC/IS will result in:
    - Dose escalation to the GTV and CTV_{HR} in tumours with large residual volume at time of brachytherapy and increase local control in these tumours without increasing morbidity
    - Dose de-escalation in vagina, bladder, and rectum with regard to high doses (e.g. >50-60Gy) and improve morbidity without compromising local control
- To validate that vaginal source loading and dose to the vagina can be reduced without compromising GTV, CTV_{HR} and CTV_{IR} dose, and that this can reduce vaginal morbidity without compromising local control
- To validate dose and volume effect relationships which were demonstrated in the EMBRACE/retroEMBRACE study for

  GTVres D98, CTVHR D90 and D98, volumes and local control
  CTVHR D90, CTVHR volume and systemic control
- To validate dose effect relationships for morbidity and QoL which were demonstrated in the EMBRACE/RetroEMBRACE study for high doses in small volumes (2 cm^3) or points related to brachytherapy administration: bladder, rectum, vagina
- To validate that utilisation of IMRT and daily IGRT with reduced margins can reduce the overall body volume irradiated to 45Gy and lead to reduction of GI and urinary morbidity
- To validate that reduction of dose from 50Gy to 45Gy to the elective lymph node CTV does not compromise nodal control and leads to reduction of vaginal morbidity
- To explore the impact of a systematic application of EBRT CTV-T concepts (with regard to the lower PTV border) on vaginal dose and morbidity
- To demonstrate that the application of the initial CTV-T concepts as well as the ITV and PTV margins as prescribed in the protocol does not compromise local control in the primary tumour and uterine body
- To explore dose volume effect relationships related to intermediate EBRT dose levels in bladder, rectum, vagina, bowel and overall body volume
- To demonstrate that it is feasible to administer simultaneous chemotherapy to EBRT to reach 5 cycles of cis Platinum in the majority of patient (in particular in high risk patients) and that this leads to improvement in systemic control
- To evaluate the prognostic significance of SUV in individual lymph nodes for lymph node control
- To explore dose and effect relationship of chemotherapy for nodal and systemic control
- To identify prognostic parameters and define groups of patients at different risk of local, nodal and systemic failure
- To evaluate the impact of continuous web-based and workshop oriented education in contouring and dose planning throughout the study on overall quality and compliance

5 STUDY DESIGN, ENDPOINTS AND HYPOTHESES

5.1 STUDY DESIGN

EMBRACE II is an interventional and prospective multi-centre study which aims at benchmarking an excellent level of local control, nodal control, systemic control and overall survival as well as treatment related morbidity and quality of life in patients with LACC. These aims are targeted through a variety of interventions related to brachytherapy, external beam radiotherapy and chemotherapy. Furthermore, EMBRACE II will prospectively validate the findings on correlations between DVH parameters and outcome as obtained from EMBRACE and RetroEMBRACE for GTV, HR CTV and OARs. The number of patients accrued to the study is determined by the requirement for an appropriate precision (confidence interval) with which disease and morbidity actuarial outcome can be benchmarked at 3 years.

The EMBRACE II interventions are expected to improve the clinical outcome of EMBRACE II as compared to the benchmark of the EMBRACE and RetroEMBRACE studies. The EMBRACE II interventions are hypothesized to lead to specific improvements in radio- and chemotherapy dose administration. Based on the clinical outcome benchmarked in EMBRACE and retroEMBRACE as well as the evidence of dose-effect relationships also established in these studies (see background in chapter 3), the treatment related improvements of EMBRACE II are hypothesized to lead to a specific benchmark in terms of actuarial outcomes for disease, morbidity and survival. While disease and patient characteristics of the cohort may change over time, the assumed benefits are expected to be present in comparable groups which are balanced for example according to prognostic and treatment related factors.

5.2 ESTIMATE OF PATIENT ACCRUAL AND STUDY PERIOD

A number of 16 centers who are currently accruing patients for the EMBRACE study are expected to participate in the EMBRACE II study. According to the accrual rate in 2014, these 16 centers are expected to accrue 200 patients per year for EMBRACE II. Furthermore, new centers have shown interest in EMBRACE II, and it is expected that 10 new centers will be approved for participation and can start accrual in 2016 and 2017, with accrual of 100 additional patients per year. With a study accrual period of 4 years from 2016 to 2019, it is expected to reach a total number of patients of 1000 patients: 150 (2016), 250 (2017), 300 (2018), 300 (2019).

5.3 HYPOTHESES AND ENDPOINTS

Primary endpoints are local control, nodal control, systemic control, overall survival and morbidity and quality of life. Secondary endpoints comprise cancer specific survival, and disease specific survival.

In the following the general and specific hypotheses are listed. The specific hypotheses are defined on two different levels. The first level is related to treatment characteristics in terms of technique as well as dose and volume parameters for targets and OARs. These hypotheses are defined based on the expected change of practice in EMBRACE II as compared to the performance in EMBRACE. The second level of specific hypotheses is related to the clinical effects of the change of practice in terms of local, nodal, systemic control and morbidity as well as survival and quality of life.

These hypotheses have been designed based on the expected clinical impact of the change of practice in EMBRACE II as compared to EMBRACE I. As starting point for the formulation of the benchmarks the mature data of RetroEMBRACE have been taken for the disease related endpoints. For morbidity the EMBRACE I data have been used.

It is well recognized, that the assumed numeric benchmarks may have to be adapted according the observed change of practice in EMBRACE II and the final and mature data of EMBRACE I.

5.3.1 GENERAL HYPOTHESIS ON OVERALL SURVIVAL

The sum of interventions of EMBRACE II as defined for EBRT, BT and chemotherapy will benchmark a high level of overall survival at 3 and at 5 years which is assumed to be 4% superior to RetroEMBRACE. The strongest prognostic predictors for overall survival are at present stage and nodal status, and the hypothesis on overall survival is therefore stated for the overall cohort as well as for two groups according to the risk of disease-related death. The group at lower risk of disease failure is defined as patients with FIGO stage I or II who are also node negative. The group at higher risk is defined as any patients with stage III disease or higher local stage as well as any node positive patients (enlarged nodes, PET positive nodes, nodes proven by histology). In EMBRACE, patients are distributed more or less equally into these two groups: stage III, IV or N+ is 58% and stage I, II and N- is 42%.

Hypothesis for Overall Survival (OS):

- Overall cohort: 81% (3 years) / 71% (5 years) (improvement of 4%)
- Stage I,II and N-: 88% (3 years) / 83% (5 years) (improvement of 1%)
- Stage III,IV or N+: 71% (3 years) / 56% (5 years) (improvement of 7%)

Limitation: the numbers for EMBRACE represent the status of clinical evidence available in 8/2015. For the final definition of the assumed benchmark (EMBRACE II) the final mature EMBRACE I outcome has to be taken into account when available.

5.3.2 SPECIFIC HYPOTHESES ON TECHNIQUE, DOSE AND VOLUMES:

Table 5.1 presents the change of practice in EMBRACE II related to the treatment interventions and as categorized into groups related to administration of EBRT, BT and chemotherapy (column 1). The current level of practice in EMBRACE is listed (column 2), and the effect of the change of practice on technique as well as dose and volume parameters has been quantified into a number of hypotheses (column 3).

Table 5.1 Specific hypotheses on technique, dose and volume.

Change of practice	Current practice in EMBRACE	EMBRACE II hypotheses: technique, dose, and volume
BT dose escalation / de-escalation **in tumours with CTV_{HR} volume ≤30cc**	IC/IS in 21% of pts	IC/IS in >30% of patients*
	CTV_{HR} D90 > 85Gy in 80% of pts	CTV_{HR} D90>85Gy in >90% of pts: mean dose escalation of 8Gy in the group previously treated with <85Gy*
	CTV_{HR} D90 > 95Gy in 38% of pts	Mean dose de-escalation of 5Gy in the group previously treated with >95Gy**
BT dose escalation **in tumours with CTV_{HR} volume >30cc**	IC/IS in 58% of pts	IC/IS in >70% of patients*
	CTV_{HR} D90 >85Gy: 63% of pts.	CTV_{HR} D90>85Gy in >80% of pts: mean dose escalation of 8Gy in the group previously treated with <85Gy*
BT dose de-escalation **in bladder, rectum and vagina**	Mean vaginal loading: 51%	Mean vaginal loading <33%**
		Mean dose de-escalation**:
	Bladder D_{2cm3} <80Gy in 60% of pts	Bladder D_{2cm3}: - 4Gy
	Rectum D_{2cm3} <65Gy in 62% of pts	Rectum D_{2cm3}: - 4Gy

	ICRU recto-vagina dose <65Gy in 52% of pts	ICRU recto-vagina dose: -8Gy Bladder D_{2cm3} < 80Gy in 70% of pts** Rectum D_{2cm3} < 65Gy in 70% of pts** ICRU recto-vagina dose < 65Gy in 70% of pts**
EBRT reduction of OAR irradiation **with IMRT and IGRT**	PTV margins of 10mm are applied for the elective lymph node target in ~70% of institutions 70% of pts are treated with 45Gy and 30% with >45Gy Mean volume irradiated to >43Gy: - IMRT: 2300 cm^3 - 3D CRT: 2700 cm^3	Margin reduction from 10mm to 5mm will result in reduction of PTV volume of 500cm^{3**} 100% of pts are treated with 45Gy Mean volume irradiated to >43Gy is: IMRT/IGRT: <2200cm^{3**}
Adaptation of EBRT nodal elective CTV **according to risk of nodal failure**	26% (102/395) of N+ pts are treated with para-aortic irradiation****	55% of N+ pts are treated with para-aortic irradiation 20% of N- pts are treated with reduced pelvic fields (low risk)****
Overall treatment time **simultaneous integrated lymph node boost**	In ~50% of the patients the OTT is <50 days (RetroEMBRACE)	In 80% of the patients the OTT is ≤50 days*** lymph node boost simultaneous, if indicated
Administration of concurrent chemotherapy	≥5 cycles of concomitant cisplatin is administered in 69% of pts	5 cycles of concomitant cisplatin is administered in >80% of pts*

*Based on current performance of advanced EMBRACE I centres
**Based on pilot data from the EMBRACE research group
***Based on administration of 25fx (with integrated lymph node boost) as well as increased awareness of the timing of brachytherapy
****Based on disease characteristics in the EMBRACE cohort

5.3.3 SPECIFIC HYPOTHESES ON CLINICAL ENDPOINTS

The specific hypotheses on clinical endpoints are listed in table 5.2. This table shows the current status in RetroEMBRACE and EMBRACE studies (clinical evidence as available in 8/2015) as well as the expected outcome in EMBRACE II (actuarial at 3/5 years).

For the definitive numeric benchmarking, the respective final results of EMBRACE I have to be taken into account when available, as well as the observed change in practice in EMBRACE II (5.3.2; table 5.1).

Local control:

Limited volume (CTV_{HR}≤30cm^3):

Local control will be maintained in small volume tumours even with dose de-escalation, due to negligible impact of very high doses in small volume tumours and due to reduced overall treatment time (OTT).

Large volume (CTV_{HR}>30cm^3):

Local control will be improved by 5% in large volume tumours due to dose escalation and reduction of OTT. The hypothesis is based on evidence that:

Improvement of local control is ~0.5% per Gy of dose escalation
AND
Improvement of local control is ~0.5-1% per day of reduced OTT.

Nodal control (incl para-aortic):

Stage I, II and N0:

In the intermediate risk group, nodal control (incl. para-aortic) will be improved by 1% due to improved identification of pathologic lymph nodes (PET imaging and laparoscopy) and systematic application of large pelvis EBRT reducing nodal recurrence at the cranial target border.

In the low risk group (tumour size ≤4cm, stage IA/IB1/IIA1, N0, squamous cell carcinoma, no uterine invasion), the nodal control (98.5%) will not be compromised by reduction of treatment fields.

Stage III, IV or N1:

In the intermediate risk group, nodal control will be improved by 2% due to improved identification of pathologic lymph nodes (PET imaging and laparoscopy), systematic application of large pelvis EBRT, improved administration of concomitant chemotherapy, and improved hypo-fractioned boosting of pathologic lymph nodes.

In the high risk group, nodal control will be improved by 3-4% due to the combined effect of increased administration of para-aortic irradiation, improved administration of concomitant chemotherapy, improved identification of pathologic lymph nodes (PET imaging and laparoscopy), as well as improved hypo-fractioned boosting of pathologic lymph nodes. 78% of para-aortic failures in EMBRACE were in patients who did not receive para-aortic irradiation. The administration of para-aortic irradiation will be approximately doubled (from 25% to 50% of N1 patients) in EMBRACE II, and around 25% of the patients with para-aortic failure in EMBRACE would have received para-aortic irradiation under the EMBRACE II criteria. Based on this, para-aortic nodal control in N+ patients is assumed to improve by 2-3%, mainly due to increased administration of para-aortic irradiation.

Systemic control (excluding para-aortic failures):

Stage I, II and N-:

Systemic control will be improved by 1% due to improved nodal control.

Stage III, IV or N+:

Systemic control will be improved by 5% due to improved local and nodal control as well as improved administration of chemotherapy. Chemotherapy administration of ≥5 cycles is related with 25% less systemic recurrences in this patient group, and 10% additional patients will receive ≥5 cycles in EMBRACE II. Also adjuvant chemotherapy will be used in high risk patients according to center decision.

Cancer specific survival:

Stage I, II and N-:

Cancer specific survival will be improved by 1% according to the accumulated effect of 0%, 1%, and 1% improvement in local, nodal, and systemic control, respectively.

Stage III, IV or N+:

Cancer specific survival will be improved by 7% according to the accumulated effect of 3-5%, 4%, and 5% improvement in local, nodal and systemic control, respectively.

Overall survival:

Stage I, II and N-:

Overall survival will be improved by 1% assuming the same improvement as for cancer specific survival

Stage III, IV or N+:

Overall survival will be improved by 7% assuming the same improvement as for cancer specific survival.

Morbidity:

Urinary morbidity:

G≥2 will be improved by 5% mainly due to BT dose de-escalation which leads to decrease in incidence of G≥2 urinary frequency and incontinence of 1% per Gy of dose de-escalation. Furthermore, the introduction of IMRT is expected to contribute with decreased incidence of G≥2 urinary frequency and incontinence.

G≥3 will be improved by 1%. Although there is currently not any dose-effect relationship established for G≥3, it is assumed that bladder dose de-escalation will have a beneficial effect.

Rectal morbidity:

G≥2 will be improved by 2% mainly due to BT dose de-escalation which leads to decrease in incidence of G≥2 bleeding of 0.5% per Gy of dose de-escalation.

G≥3 will be improved by 0.5%. Although there is currently not any dose-effect relationship established for G≥3, it is assumed that rectum dose de-escalation will have a beneficial effect.

Bowel morbidity:

G≥2 will be improved by 5% mainly due to the introduction of IMRT which has shown a decrease of 5% in patient reported diarrhea (prevalence) as well as tendencies of decreased patient reported problems with bowel control.

G≥3 is assumed to be improved by 1%. Although there is currently not any dose-effect relationship established for G≥3, it is assumed that the overall decrease of irradiated volume will decrease also G≥3 morbidity.

Vaginal stenosis:

G≥2 stenosis will be improved by 7% due to the combined effect of BT dose de-escalation, decreased EBRT dose (prescription of 45Gy pelvic fields to all patients), as well as improved definition of the lower field border. Vaginal stenosis decreases by 0.5-1% per Gy of dose de-escalation, and furthermore the incidence of vaginal stenosis is 13% less in patients irradiated to 45Gy as compared to patients irradiated with 50Gy.

Overview

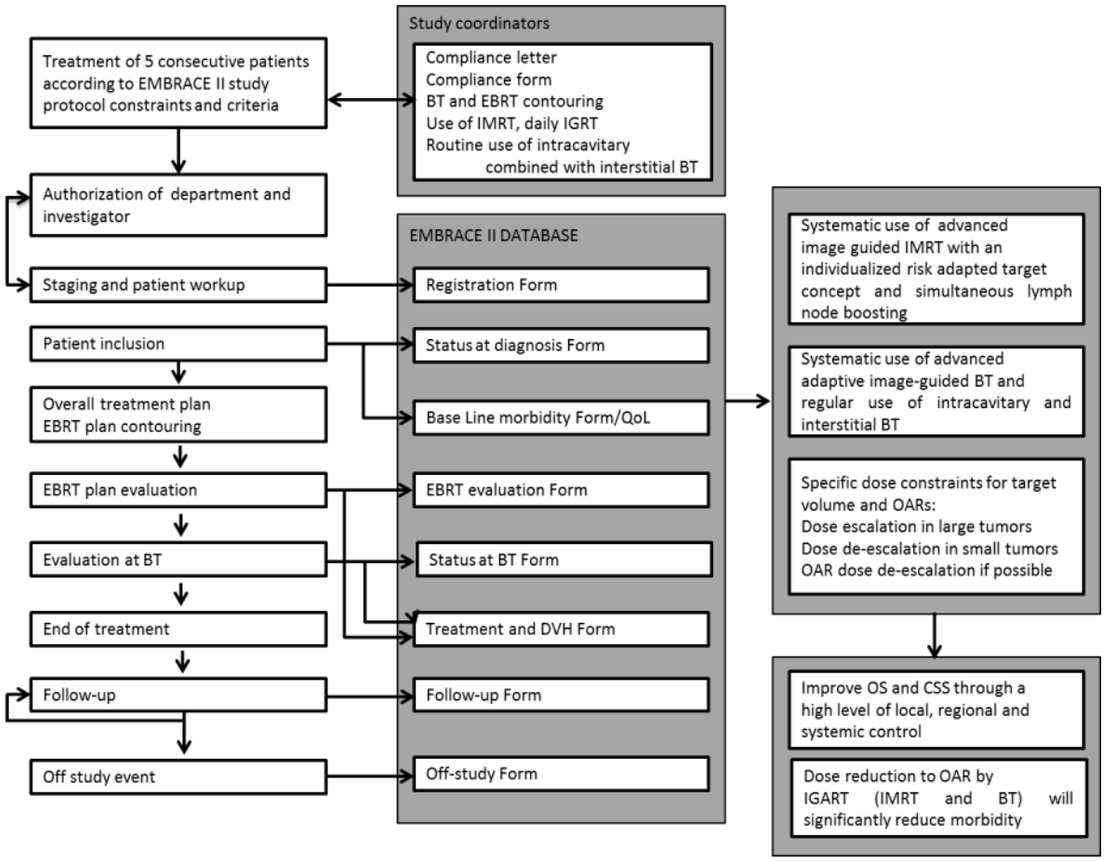
Table 5.2. Hypotheses of the EMBRACE II study in terms of outcome at 3 years (actuarial). Columns 1 and 2 show the clinical outcome in the retroEMBRACE and EMBRACE studies. The improvement of outcome in EMBRACE II is estimated with retroEMBRACE as baseline (evaluated 9/2014) for disease related outcome and with EMBRACE as baseline for morbidity (2014/2015). Limitation: the numbers for

EMBRACE represent the status of clinical evidence available in 8/2015. For the final definition of the assumed benchmark (EMBRACE II) the final mature EMBRACE I outcome (when available) has to be taken into account as baseline for both disease related outcome as well as morbidity.

	retroEMBRACE 3/5y	**EMBRACE 3y**	**EMBRACE II 3y**	**Confidence interval***
Local control				
Overall	91/89%	91%	93%	2%
≤30cm3 HR CTV	96%	96%	96%	2%
>30cm3 HR CTV	87%	88%	91%	3%
Stage IB, IIA	98/98%	95%	98%	2%
Stage IIB	93/91%	90%	94%	2%
Stage III	79/75%	88%	89%	6%
Stage IVA	76/76%	87%	89%	15%
Nodal control (incl para-aortic)				
Overall	88%	84%	90%	2%
N- and Stage I+II	93%	91%	94%	2%
N+ and Stage III+IVA	83%	79%	87%	4%
Pelvic nodal control				
Overall	94%	89%	95%	1%
Pelvic control (local+nodal)				
Overall	87/84%		90%	2%
Systemic control (excluding para-aortic failures)				
Overall	83/79%	83%	86%	3%
N- and Stage I+II	90%	89%	91%	3%
N+ and Stage III+IVA	74%	79%	79%	4%
Cancer specific survival	Consecutive ChT			
Overall	81/74%	-	85/78%	3%
N- and Stage I+II	90/87%	-	91/88%	3%
N+ and Stage III+IVA	69/57%	-	76/64%	4%
Overall survival	Consecutive ChT			
Overall	77/67%	-	81/71%	3%
N- and Stage I+II	87/82%	-	88/83%	3%
N+ and Stage III+IVA	64/49%	-	71/56%	5%
Morbidity				
Bladder CTCAE ≥ G2		26%	21%	3%
Bladder CTCAE ≥ G3		7%	6%	2%
Rectum CTCAE ≥ G2		11%	9%	2%
Rectum CTCAE ≥ G3		2%	2%	1%
Bowel CTCAE ≥ G2		17%	12%	2%
Bowel CTCAE ≥ G3		5%	4%	1%
Vaginal CTCAE ≥ G2		27% (stenosis) 31% (all)	20% (stenosis) 24% (all)	3%
Vaginal CTCAE ≥ G3		4% (all)	3% (all)	1%

*Based on patient accrual of 1000 patients (95% confidence interval).

6 EMBRACE OUTLINE



7 STAGING AND PATIENT WORK-UP

All examinations must be completed before treatment and no investigation should be more than 4 weeks old at the time of treatment initiation. For the purpose of including a patient in the Embrace 2 protocol the following examinations have to be performed:

- Patient history and current status including among others information on hormonal status, co-morbidity, previous major surgery, smoking status (ch. 12, 16, CRF)
- General physical examination, including assessment of performance status (WHO)
- Blood tests including haemoglobin and lymphocytes
- Gynaecological examination (supplemented by cystoscopy and rectoscopy if organ involvement is suspected) with topographic documentation on a specific cartoon (see appendix)
- Biopsy of the primary tumour
- Laparoscopic lymphadenectomy is recommended but not required
- Pelvic MRI (see in detail Gyn GEC ESTRO Recommendations IV (Dimopoulos JC. et al. 2012)
- Preferable whole body (FDG)PET-CT or at least CT scan of thorax, abdomen and pelvis
- Assessment of SUV_{max} in primary tumour and lymph nodes is recommended but not required
- Staging according to FIGO and TNM
- Baseline Morbidity scoring (ch.12, 16, CRF)
- Baseline quality of life questionnaire (ch. 12,16, CRF)

8 PATIENT SELECTION

8.1 INCLUSION CRITERIA

- Cancer of the uterine cervix considered suitable for curative treatment with definitive radio-(chemo)therapy including MRI guided BT
- Positive biopsy showing squamous-cell carcinoma, adenocarcinoma or adeno-squamous cell carcinoma of the uterine cervix.
- Staging according to FIGO and TNM guidelines
- MRI of pelvis at diagnosis is performed
- MRI, CT or PET-CT of the retroperitoneal space and abdomen at diagnosis is performed
- MRI with the applicator in place at the time of (first) BT will be performed
- Para-aortic metastatic nodes below L1-L2 are allowed
- Patient informed consent

8.2 EXCLUSION CRITERIA

- Other primary malignancies except carcinoma in situ of the cervix and basal cell carcinoma of the skin
- Small cell neuroendocrine cancer, melanoma and other rare cancers in the cervix
- Metastatic disease above and beyond the retroperitoneal para-aortic L1-L2 interspace
- Previous pelvic or abdominal radiotherapy
- Previous total or partial hysterectomy
- Combination of preoperative radiotherapy with surgery
- Patients receiving BT only
- Patients receiving EBRT only
- Patients receiving neo-adjuvant chemotherapy or other forms of antineoplastic treatment apart from weekly concomitant cisplatin (40 mg/2). However, adjuvant chemotherapy in the form of 4 courses of 3 weekly Carboplatin (AUC 5) and Paclitaxel (155 mg/m2) is allowed according to departmental policy.
- Contra indications to MRI
- Contra indications to BT

9 EXTERNAL BEAM RADIOTHERAPY

9.1 INTRODUCTION

External beam radiotherapy (EBRT) is an integral part of the overall treatment strategy with the primary aim of obtaining regional and nodal control. In addition, EBRT provides a basis of homogenous dose on which the steep dose gradient of brachytherapy takes off to achieve the very high dose needed to obtain local control of the primary tumour. At the same time, the dose outside of the EBRT target(s) should evidently be as low as possible. Studies comparing IMRT with 3D conformal EBRT, including results from the EMBRACE I study show that IMRT reduces the incidence of late toxicity (mainly gastro-intestinal). With the growing technical possibilities and availability of imaging, the field of image guided EBRT (IGRT) is rapidly evolving. A further decrease of treatment related toxicity is expected from IGRT approaches. For EMBRACE II, pragmatic choices have been made in order to allow safe state of the art treatment delivery within the current clinical workflows of participating centres.

9.1.1 AIMS OF EXTERNAL BEAM RADIOTHERAPY (COMPARE CH 3-5)

1. To introduce systematically MRI and CT guided IMRT for EBRT in cervix cancer with a tailored target and margin concept and defined dose prescriptions for tumour and nodal targets
2. To control overall treatment time (90% of all patients <50 days for EBRT and BT)
3. To maintain and improve the excellent pelvic control (local and regional)
4. To improve para-aortic control by elective para-aortic irradiation in high risk patients (HR LN) and by elective common iliac nodal irradiation (incl. aortic bifurcation) in intermediate risk patients (IR LN) (Table 9.2, Fig. 9.1).
5. To maintain and improve the excellent nodal control through simultaneous hypofractionated integrated boosting (SIB) and coverage probability (CoP) dose planning for treatment of pathological lymph nodes
6. To reduce EBRT related morbidity through reduction of target volume as well as the treated and irradiated volumes:
    - Excluding the common iliac region from the elective target volume in low risk patients (LR LN) (Table 9.2)
    - Reducing set-up error and allowing for PTV margin reduction for the nodal CTV-E (5 mm) and the ITV-T LR through performing daily 3D IGRT with daily online couch correction based on bony anatomy (Fig. 9.9)
    - Introducing an initial CTV-T_{HR} and an initial CTV-T_{LR} based on the primary tumor extent (initial GTV-T) (Fig. 9.2-9.8)
    - Recommending an internal target volume (ITV-T LR) approach for the primary tumour (CTV-T LR) (Fig. 9.9)
    - Using inverse treatment planning techniques (IMRT, VMAT or Tomotherapy) applying systematically dose volume constraints for EBRT

9.1.2 NODAL TARGETS BASED ON RISK GROUP ALLOCATION FOR NODAL SPREAD

The risk of lymph node spread is dependent on various factors. Among the most important are the local spread (FIGO stage), histology and lymph node spread. The pattern of lymph node recurrence has two predominant areas: within the radiation field in the obturator region (in-field), at the cranial field border (marginal) and in the para-aortic region (outside radiation field) (Verma J. et al. 2014 and EMBRACE/RetroEMBRACE work in progress).

In order to tailor the nodal target according to the assumed risk of microscopic nodal involvement three risk groups are introduced with three different elective nodal target volumes. The aim is to reduce morbidity in the low risk group and to improve nodal and systemic control in the intermediate and high risk group.

To summarize the indications for nodal targets based on risk group allocation for lymphatic spread (table 9.1):

- Small pelvis EBRT in low risk patients (LR LN)
- Large pelvis EBRT in intermediate risk patients (IR LN)
- Large pelvis + para-aortic EBRT in high risk patients (HR LN)

Risk allocation is based on primary tumour characteristics and nodal pathology at time of diagnosis and takes into account the probability of developing lymph node metastases in pelvic and para-aortic areas. Risk groups are defined in table 9.1, and criteria for categorising a lymph node as pathologic are defined in table 9.2. This is a general outline, giving the major pathways for tailoring nodal targets based on risk group allocation. Such general outline leaves some space for specific clinical situations where some outstanding clinical features (not listed in detail here) may be taken into account, such as large lymph node size, for defining e.g. a high risk group.

Table 9.1: Risk groups for defining the elective clinical target volumes for lymph nodes and corresponding nodal targets defining the radiation field extensions.

Risk Group LN	Definition	EBRT lymph node regions
Low Risk (LR LN)	Tumour size ≤4cm AND stage IA/IB1/IIA1 AND N0 AND squamous cell carcinoma AND no uterine invasion	**"Small Pelvis"** internal iliac external iliac obturator presacral
Intermediate Risk (IR LN)	Not low risk No high risk features	**"Large Pelvis"** Nodes included in "Small Pelvis" and common iliac region (including the aortic bifurcation). In addition: • inguinal in case of distal vaginal involvement. • Mesorectal space in case of mesorectal nodes and advanced local disease
High Risk (HR LN)	Based on nodal pathology • ≥ 1 pathologic node at common iliac or above • OR ≥ 3 pathologic nodes	**"Large Pelvis + Para-aortic"** Nodes included in "Large Pelvis" and para-aortic region with the upper border of CTV minimum at the level of renal veins (usually incl. L2), and at least 3 cm cranial of the highest pathological node in case of para-aortic nodes].

Table 9.2: Definition of pathologic lymph nodes based on volumetric imaging

Pathologic lymph node	FDG PET positive
	And/OR: short axis ≥ 1 cm on CT or MRI
	And/OR: short axis between 0.5-1.0 cm on MRI with pathological morphology: irregular border, high signal intensity and/or round shape

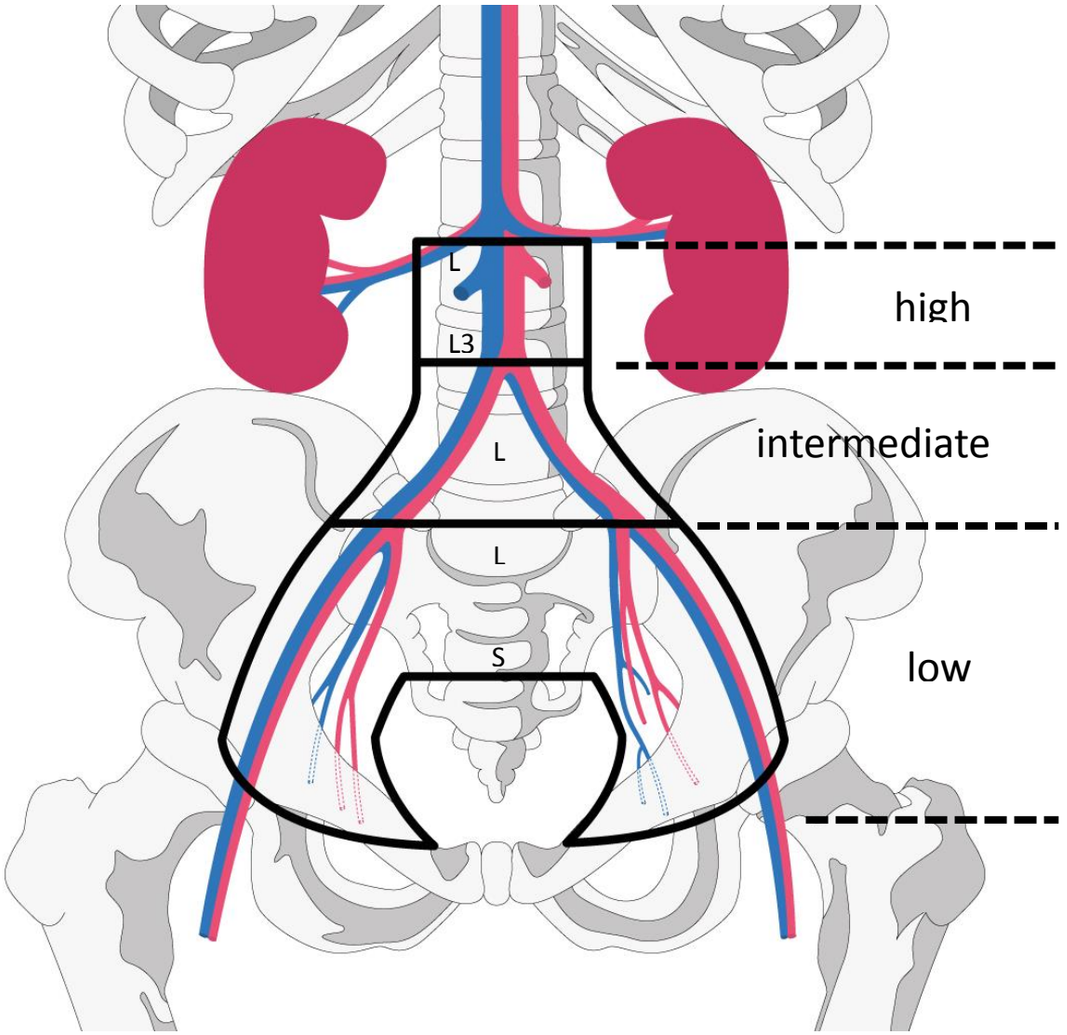


Fig 9.1 Schematic Diagram for lymph node elective CTVs based on risk of lymphatic spread, “Small Pelvis”, “Large Pelvis”, “Large Pelvis + para-aortic” (compare table 9.1)

9.2 PREPARATIONS FOR TREATMENT PLANNING

Gynaecological examination with appropriate documentation on cartoons (see chapter 10), diagnostic T2 weighted MRI and a treatment planning CT in supine position are minimal requirements for target delineation and treatment planning. PET-CT is strongly recommended, but optional. Slice thickness of the treatment planning CT scan should be ≤ 3 mm. The use of intravenous contrast media for the treatment planning CT is optional but use is recommended to ease identification of structures of interest. The choice for immobilization devices is according to the clinical routine of the individual institutes.

It is recommended, but not mandatory, to perform an empty bladder scan on top of the comfortably filled bladder scan. Full and empty bladder scans give information about the range of internal motion of the target volumes, and this can be exploited when defining an individualized ITV as discussed in section 9.3.3. Having multiple (diagnostic and treatment planning) imaging series available with different combinations of bladder and bowel filling, usually from different days contributes further to defining the individualized ITV.

Ideally both the FDG PET-CT and MRI should be performed in treatment position, in order to enable optimal image fusion based on bony anatomy, but this is not mandatory. Thus, pertinent diagnostic-imaging sequences may be used. Further recommendations are to obtain the MRI in three orthogonal planes; to include the aortic bifurcation (cranial) and the inferior border of the symphysis (caudal) as scan borders and to limit the slice thickness to ≤ 5 mm.

Minimization of internal motion at the time of dose planning scans and during treatment is difficult to achieve. The following measures have the goal to prevent taking outlier situations into account when deciding on internal organ motion and to attempt to be as reproducible as possible throughout the period of treatment.

Bladder is intended to be comfortably filled on the treatment planning CT scan and throughout the treatment. Therefore a drinking protocol is mandatory with specifications on 1) timing of voiding and 2) timing and volume of fluid intake. An acceptable drinking protocol would be that the patients are asked to void 1 hour before imaging and each EBRT fraction, then drink 300-500 ml of water/clear fluid and try not to void before treatment delivery.

The rectum and sigmoid should be as empty as possible. The patient is asked to empty the stools before scanning and treatment. If significant gas or filling is discovered while scanning for treatment planning (diameter of gas or filling in rectum > 4 cm maximum extension in any direction), the patient should be asked to empty the rectum or deflation with a catheter or postponing the treatment planning CT to another day could be considered. Special diets with the purpose of reducing internal motion of the gastro-intestinal system are so far ineffective and therefore currently not recommended. The same applies to the use of enemas since there is concern about related gas production.

9.3 TUMOR AND TARGET DEFINITION AND CONTOURING: INITIAL GTV, INITIAL HR CTV-T, INITIAL LR CTV-T, ITV-T; GTV-N, CTV-N, CTV-E; PTV

9.3.1 GENERAL OVERVIEW

The volumes of interest are in principle defined according to ICRU 50/62/83:

GTV: Gross Tumor Volume (at diagnosis).

CTV: Clinical Target Volume = GTV + suspected microscopic tumor extension.

ITV: Internal Target Volume = CTV + internal margins to compensate for internal motions.

PTV: Planning Target Volume = CTV (or ITV) + set-up margin.

Tumour and target contouring for EBRT requires an integration of the spatial information obtained at diagnosis by fused MRI, treatment planning CT, FDG PET-CT if available, and by gynaecological examination.

GTV-T (GTV-N) is defined and contoured based on imaging (MRI (PET-CT)) and clinical characteristics.

CTV is defined and contoured based on the extension of the GTV and the assumed microscopic spread for each specific tumour extension and its biological characteristics taking into account anatomical regions (e.g. vagina), compartments (e.g. parametrium) and borders (e.g. outer rectal wall).

ITV is based on a standard or individualized margin.

PTV is derived from the ITV or the CTV using an isotropic margin.

With regard to the primary tumour target (CTV-T) - when using MRI - the GTV-T, and an initial high and low risk CTV-T can be identified. These definitions correspond to those introduced for the adaptive HR CTV-T for brachytherapy (GEC ESTRO Recommendations, ICRU Report 88):

- The initial HR CTV contains the initial GTV inside and outside the cervix and as a minimum the whole cervix as it presents at diagnosis.
- The initial LR CTV includes the initial HR CTV as starting point. A margin of 20 mm is defined towards the vagina. The whole uterine corpus is included. The anterior border is defined at about 5 mm anterior towards bladder and about 5 mm posterior towards rectum at the level of the cervix (Further details are given in 9.3.1 and in the appendix on EBRT Treatment Planning.)

Identification of such sub-volumes for the CTV-T is important as they allow for tailored treatment with different dose prescription (HR CTV-T, (IR CTV-T), LR CTV-T (see chapter 10), and as they change during treatment.

The initial HR CTV-T and LR CTV-T require different ITV margins according to the location of its borders and their specific motion uncertainties (e.g. laterally fixed parametrial borders, posterior-anterior mobile borders towards rectum and bladder, overall mobile borders uterine corpus). The detailed contouring of the initial HR CTV-T and LR CTV-T in 3D can therefore play an important role in the (individualized) ITV-T concepts. Such contouring enables to reflect the uncertainties due to different motion types at the various CTV borders when defining the ITV-T (see Appendix on EBRT Treatment Planning).

The CTV-T to ITV-T margin for the primary tumour target accounts for uncertainties in size, shape and position of the CTV-T within the patient, which include both inter- and intra-fraction motion.

The total CTV-T to PTV-T margin needs to accommodate random and systematic geometrical errors that are among others caused by: internal organ motion (ITV-T) (e.g. uterine cervix, uterine corpus; rectum, bladder filling status) and geometrical errors in positioning during the course of EBRT for the tumor and lymph node related CTVs (set-up errors). An ITV is most helpful in situations where uncertainties concerning the geometrical CTV location are greater than setup uncertainties, such as may be the case for a primary cervical tumour in a mobile uterus (ITV-T).

The elective nodal CTV of the combined draining nodal regions (CTV-E) is selected according to risk of nodal spread. These nodal regions may be the “Small Pelvis”, “Large Pelvis”, or “Large Pelvis + Para-aortic” (table 9.1). No ITV is defined for the elective nodal target (CTV-E) as internal organ motion seems to play no important role for the CTV-E.

GTVs of pathologic lymph nodes (GTV-N) and their CTVs (CTV-N) are drawn individually. They are included in the CTV-E.

The initial LR ITV-T and the CTV-E form together the ITV 45. The ITV 45 is the basis for the overall PTV which includes the CTV-T and the CTV-E and, if present, also the CTV-N.

As noted above the nomenclature for many volumes of interest follows the ICRU tradition.

In addition some protocol specific nomenclature is used:

- For the subdivision of the primary CTV-T as initial HR CTV-T and initial LR CTV (following in principle the ICRU/GEC ESTRO definitions for the adaptive CTV for brachytherapy (ICRU 88) (for clarification the suffix “initial” has to be used) and
- For the elective nodal target, which is called “CTV-E” along the tradition of EMBRACE I (instead of CTV-N).

The general definition of the different volumes is given in Table 3. The purpose is to facilitate consistent reporting between investigators and the Embrace Study Office along the lines of EMBRACE I. Target definition and contouring are described in more detail in section 9.3.

Table 9.3. Protocol specific nomenclature of volumes of interest.

$GTV\text{-}T_{init}$	Initial Gross Tumour Volume of the primary Tumour
$CTV\text{-}T\ HR_{init}$	Initial High Risk Clinical Target Volume of the primary Tumour
$CTV\text{-}T\ LR_{init}$	Initial Low Risk Clinical Target Volume of the primary Tumour
$ITV\text{-}T\ LR_{init}$	Initial Internal Target Volume of the primary Tumour
GTV-N (#)	Gross Tumour Volume of individual pathologic lymph Nodes; these are numbered as GTV-N1....GTV-N2....GTV-N3...., etc.)
CTV-N (#)	Clinical Target Volume of individual pathologic lymph Nodes; these are numbered according to the corresponding GTV-N
PTV-N (#)	Planning Target Volume of individual pathologic lymph Nodes; these are numbered according to the corresponding GTV-N
CTV-E	Clinical Target Volume of the elective nodal region, including pathological lymph nodes if present
ITV45	ITV-T LR + CTV-E for 45 Gy
PTV45	Planning Target Volume for 45 Gy

To maintain consistent reporting and communication between investigators and the Embrace Study Office the protocol for contouring AND naming of the targets (Table 9.3.) must be followed strictly.

The tumour and target volumes of interest for EBRT are defined in detail in the following paragraphs.

9.3.2 INITIAL GTV AND CTV RELATED TO PRIMARY TUMOUR ($GTV\text{-}T_{INIT}$, $CTV\text{-}T_{INIT}$ (HR, LR))

1. GTV-T:

   Extension of the primary cervix tumour (inside and outside the cervix)

   (defined by T2 weighted MRI, supported by clinical investigation, FDG PET-CT information).

2. CTV-T HR:

   GTV-T and any remaining cervix not infiltrated by tumour.

3. CTV-T LR:

   a. Initial CTV-T HR

   b. The complete parametria bilaterally

   c. The entire uterus

   d. Uninvolved vagina with a 20 mm margin measured from the most inferior position of the initial HR CTV-T, along the vaginal axis (not starting in the fornix)

   e. CTV-T HR plus a margin of about 5 mm anterior and posterior towards bladder and rectum (excluding the non-involved walls)

f. In case of involvement of the pelvic wall, sacro-uterine ligaments, meso-rectum or other involved structures a 20 mm margin around the initial HR CTV-T will be extended into these structures.

g. Any pathological lymph nodes in the parametrium may be included

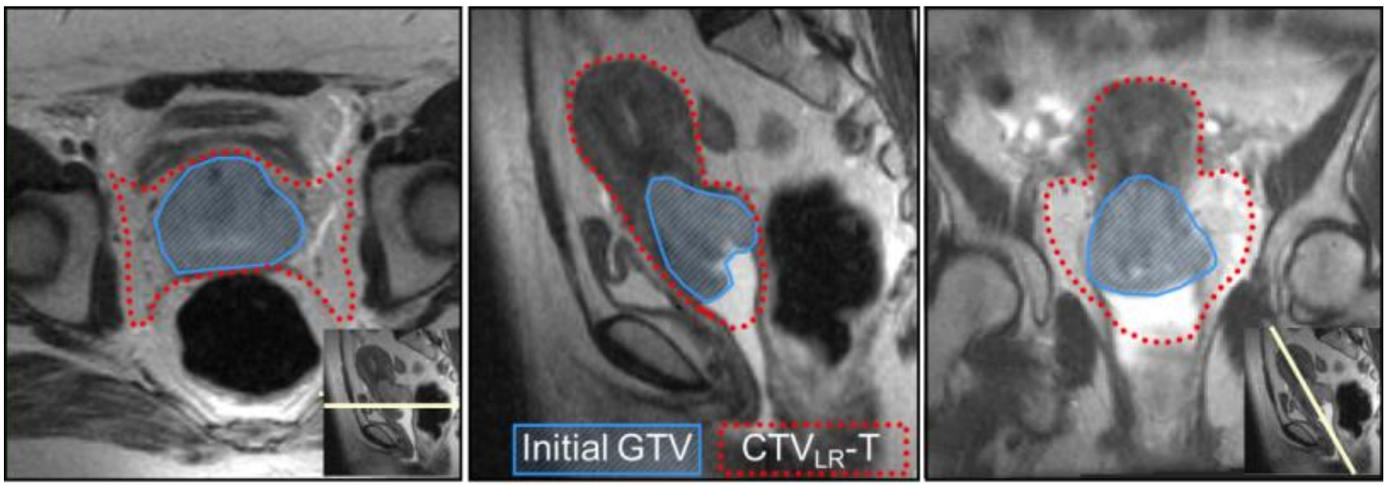


Figure 9.2 MRI at diagnosis (T2 weighted) of stage IIB cervical cancer with the tumour throughout the whole cervix and infiltrating both parametria. The initial GTV-T is indicated, which is in this case identical to the initial HR CTV-T, and the initial LR CTV-T including both parametria, upper vagina and the uterine corpus (from ICRU 88, 2015 in press)..

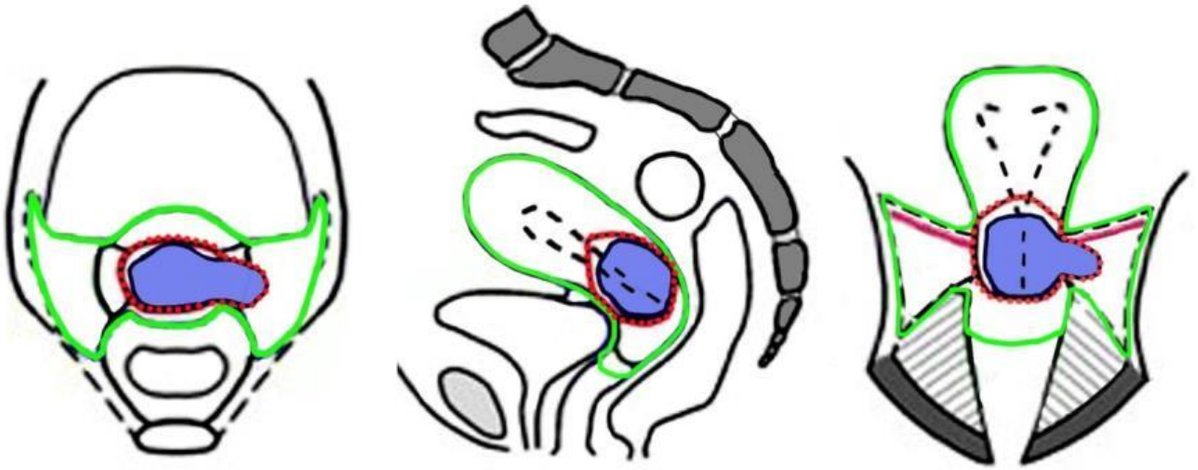


Figure 9.3. Schematic diagram for cervical cancer, stage IIB, invading most of the cervix with unilateral parametrial extension (at diagnosis). The initial GTV-T (blue), the HR CTV-T (red line) and the LR CTV-T are indicated.

In the following, typical examples for initial GTV-T, initial CTV-T HR and initial CTV-T LR for EBRT are shown for various tumor extensions and clinical stages. These figures have been elaborated based on the initial GTV-T demonstration as shown in the figures 10.1-10.5. They are therefore complementary to those figures taken from ICRU report 88 with typical examples for residual GTV-T, adaptive CTV-T HR, CTV-T IR and adaptive CTV-T LR for the brachytherapy boost (chapter 10). See also Figures 2-5 in Appendix on EBRT Treatment Planning (App Fig. 2-5)

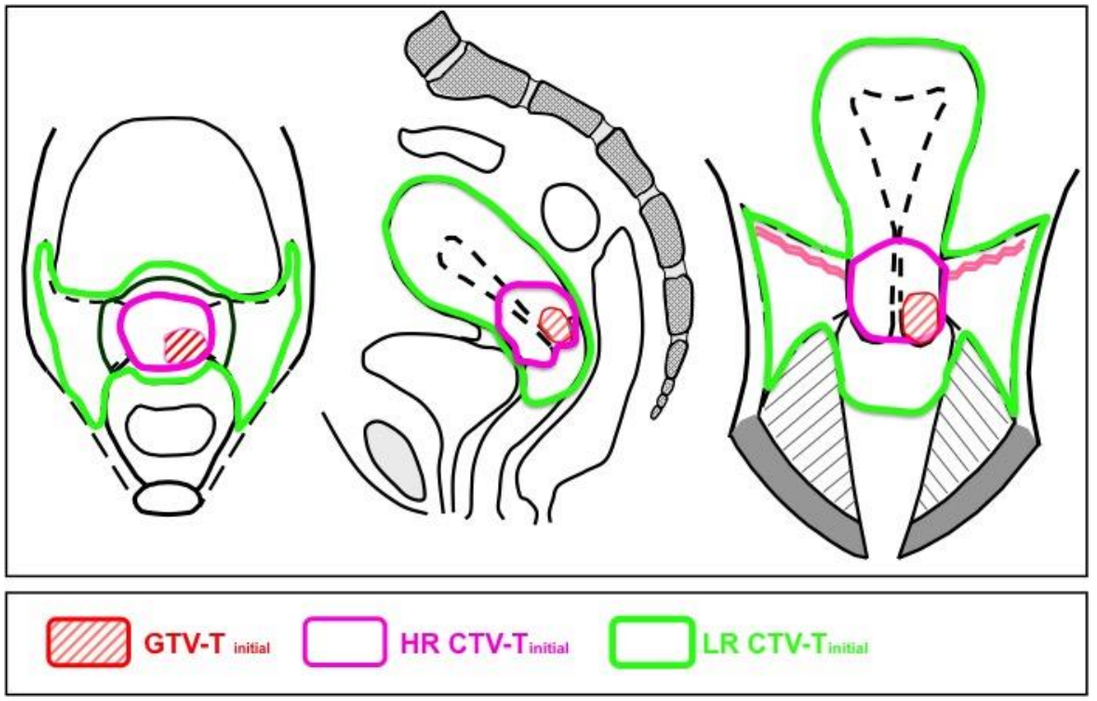


Figure 9.4 (compare figure 3.1 for brachytherapy): Schematic diagram for cervical cancer, limited disease, stage IB1, with initial GTV-T, initial CTV-T HR (cervix) and initial CTV-T LR (margins for whole parametria, whole uterine corpus, upper third of vagina, utero-bladder and cervix-rectum space) for EBRT: coronal, transversal and sagittal view. (modified from Fig. 5.8 from ICRU report 88).

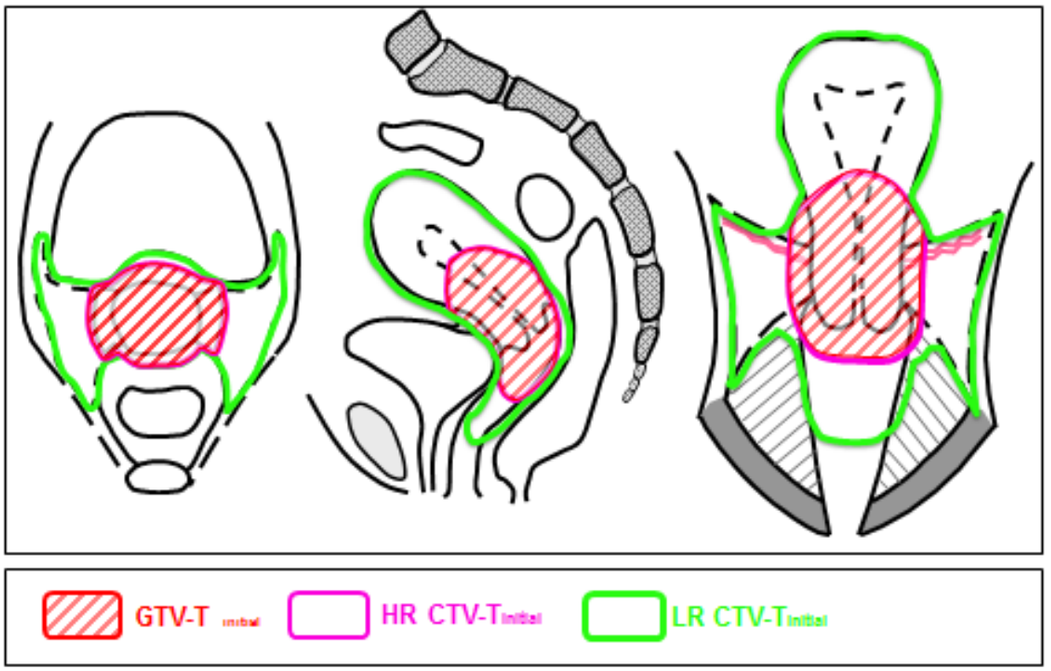


Figure 9.5: (compare figure 3.2 for brachytherapy). Schematic diagram for cervical cancer, stage IB2 (bulky disease) with GTV-T_{init}, CTV-T H R_{init} and CTV-T LR_{init} for EBRT: coronal, transversal and sagittal view. (modified from figure 5.9 from ICRU report 88

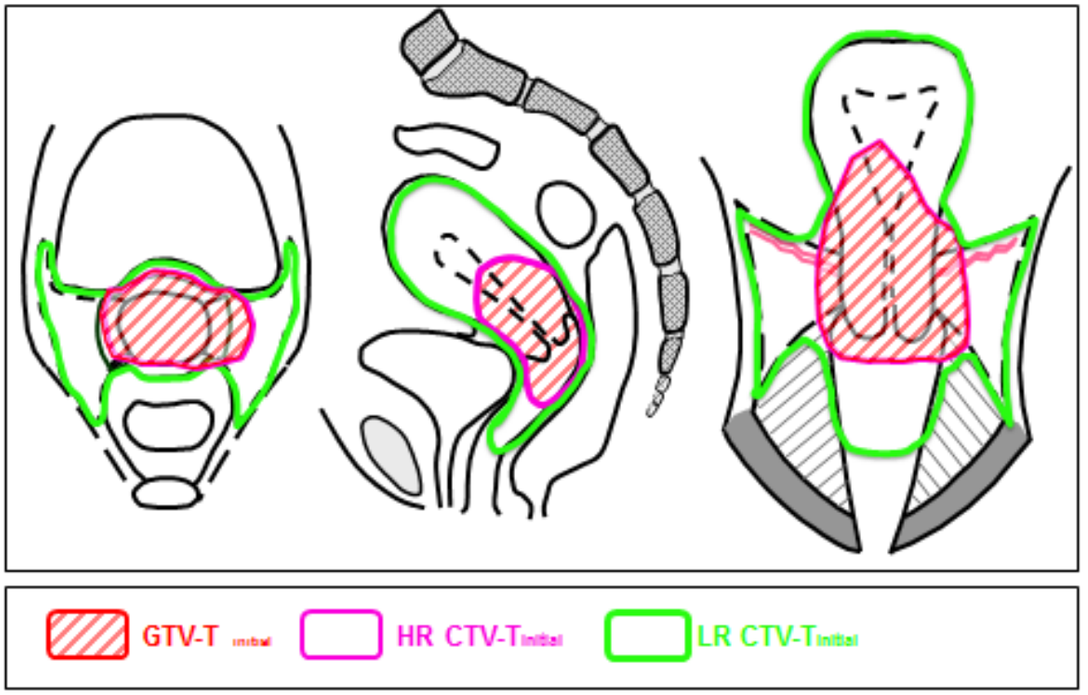


Figure 9.6 (Compare figure 3.3 for brachytherapy) Schematic diagram for cervical cancer, stage IIB bulky disease, large GTV-T_{init},, initial CTV-T HR, and initial CTV-T LR: coronal, transversal and sagittal view. (modified from figure 5.10 from ICRU report 88).

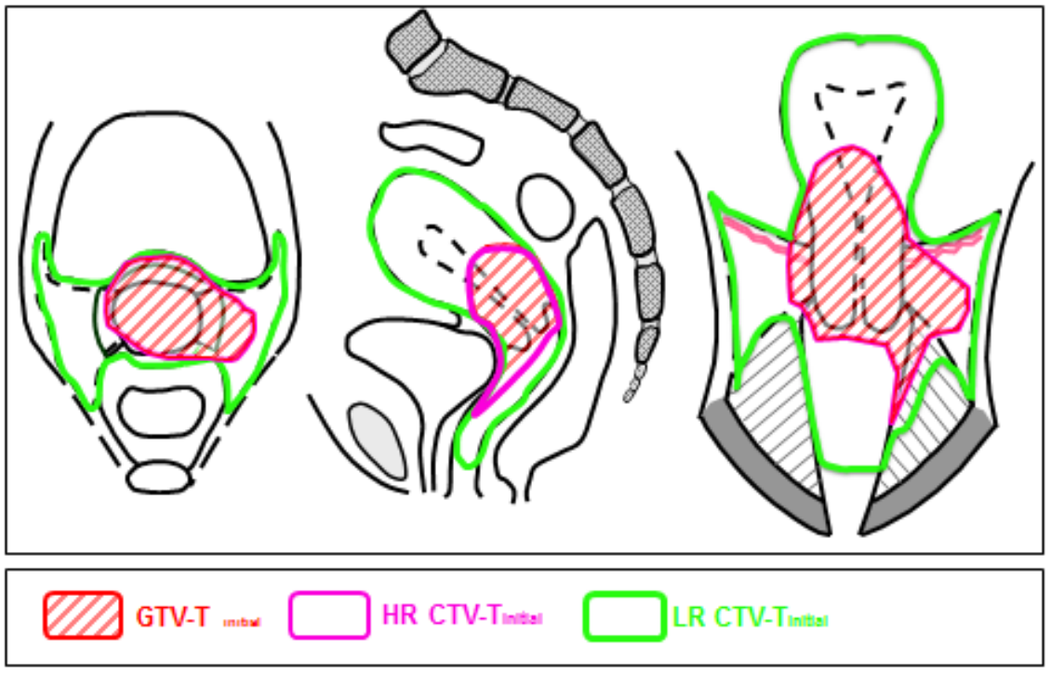


Figure 9.7 (compare figure 3.4 for brachytherapy). Schematic diagram for cervical cancer, IIIB, extensive disease, large initial GTV-T (GTV-T_{init}), initial CTV-T HR, and initial CTV-T LR for definitive treatment: coronal and transversal view. (modified from figure 5.11 from ICRU report 88).

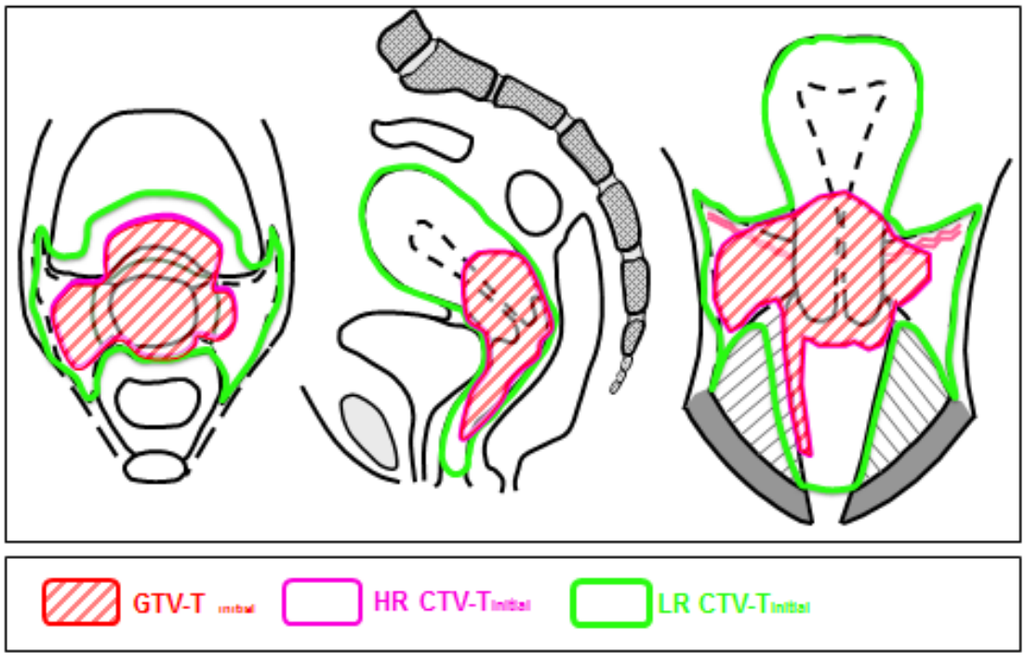


Figure 9.8 (compare figure 3.5 for brachytherapy). Schematic diagram for cervical cancer, with bladder infiltration, stage IVA, large initial GTV-T ($GTV\text{-}T_{init}$) and CTV-T HR, initial CTV-T LR: coronal, transversal and sagittal view. (modified from figure 5.12 from ICRU report 88).

9.3.3 GTV AND CTV FOR PATHOLOGIC LYMPH NODES (GTV-N, CTV-N)

1. GTV-N: Individual GTV-N for each pathological lymph node (defined in Table 1) is contoured (for dose reporting purposes), also if nodal booing is not considered. The outer-contour of the pathological node and visible (macroscopic) extra capsular extension on MRI or CT is included in the GTV-N. GTV-N is contoured on MRI within the field of view. PET-CT should primarily be used for overall guidance and not for precise delineation of the pathological nodes. In case of nodes beyond the field of view of the pelvic MRI, individual contours should be based on PET-CT and planning CT appearance. Each GTV-N should be numbered individually using the exact protocol nomenclature. (App Fig. 9)
2. CTV-N: In principle CTV-N is equal to GTV-N. However, an individualized margin may be considered for each pathologic lymph node around each GTV-N taking into account extra-capsular extension and possible progression during treatment planning interval, avoiding bones and muscles. Furthermore, partial volume effect may lead to different appearance of the upper and lower boundary on CT and MRI. The total CTV-N should encompass the maximum extension as visualized on both CT and MRI. Typically the GTV-N to CTV-N margin amounts to 0-3 mm. The numbering of individual CTV-N should be consistent with GTV-N. (App Fig. 9).

9.3.4 CTV FOR NODAL REGIONS WITH ASSUMED MICROSCOPIC DISEASE (CTV-E)

CTV-E: nodal regions to be included in CTV-E depend on the risk of spread and are specified according to the different risk groups (low, intermediate, high): “Small Pelvis”, “Large Pelvis”, “Large Pelvis + Para-aortic” (Table 9.1, Figure 9.1 and Appendix Fig. 10-15).

a. Nodal regions include the relevant vessels with at least 7 mm perivascular tissue including pertinent clips or lymphocysts (in case of prior nodal resection or lymphadenectomy). For details concerning anatomical boundaries and margins see appendix EBRT treatment planning.
b. Any pathological node within the nodal regions must be fully encompassed.
c. In case lymphocysts shrink extensively during ERBT, re-contouring and re-planning should be considered.
d. In case of excessive uterine/ligamentum latum infiltration, consider to include ovaries into CTV-E.

9.3.5 ITV (ITV-T)

The ITV - required for optimal target coverage - depends on internal target motion and on the level of image guidance during the course of fractionated radiotherapy (IGRT). Major shifts may be expected for CTV-T LR especially in the anterior-posterior direction and have to be accounted for in ITV-T LR with appropriate margins.

No ITV is defined for the elective nodal target (CTV-E).

Different levels of IGRT can be recognized for image guidance and IMRT for cervix cancer EBRT:

1) **Basic IGRT**: standard margins from CTV-T to ITV-T are applied to compensate for internal target motion. Daily online position verification and couch correction based on bony landmarks is required using CBCT, kV or EPID imaging to achieve the aimed decrease in set up errors and corresponding reduction of the PTV margin. CBCT may be used for daily monitoring of uterus movement to decide if re-planning would be an advantage according to the motion patterns observed.

2) **Intermediate IGRT**: the CTV-T to ITV-T margin is individualized based on multiple pre-treatment imaging series that allow the assessment of the individual range of internal target motion. The different images should include different fillings of bladder, which can be achieved by acquiring full and empty bladder scans or by using images obtained on different days. By doing so, the ITV-T can become more representative for the expected range of motion in the individual case. CBCT imaging is used for daily online position verification and couch correction based on bony registration. CBCT may be used for daily monitoring of uterus movement to decide if re-planning would be an advantage according to the motion patterns observed.

3) **Advanced IGRT**: is based on individual library plans in which different plan specific ITV-T margins are applied. At this point in time the library plan approach has been integrated into clinical workflow in some institutions. In this situation daily CBCT is required to select the ITV-T and treatment plan that best covers the CTV-T on that day.

In EMBRACE II, basic IGRT is minimally required and intermediate IGRT is recommended. Intermediate IGRT is recommended since it is expected to result in an ITV-T LR that is better representing the motion in the individual case. Advanced adaptive IGRT is allowed whenever an institution has this advanced approach clinically implemented. Furthermore, an optional sub-protocol for application of daily library plans (adaptive EBRT) will become available in EMBRACE II as an amendment to the protocol.

9.3.6 STRATEGIES TO DERIVE THE ITV-T LR

a) Basic IGRT, standard margin approach (Fig. 9.9.A)

The ITV-T LR includes (see also App. EBRT for Treatment Planning Figure 7):

- CTV-T LR with the following margins:
  - 10 mm anterior-posterior
  - 10 mm superior-inferior
  - 5 mm lateral
- At the distal vagina no additional margin along the vaginal axis in the inferior direction is applied
- The ITV-T LR should not go into the muscle and bony boundaries of the pelvis (in particular, manual adaptation is needed in the lateral parametria)
- In case of tumour involvement of the upper and most mobile uterus an extra 5 mm margin should be applied in all directions from the uterus body

Importantly, a clinical judgment has to be made if the CTV structures as presented on the MRI and treatment planning CT are more or less in the expected average position, based on the rectal and bladder filling state. Having multiple diagnostic image sets fused with the treatment planning CT, facilitates this judgement. If the target volume is not in the average situation, this should be taken into account

in the margins applied in a given patient. For example if the rectum is completely empty it is unlikely that the target volume will be able to move the full 10-15 mm in the posterior-inferior direction. If the bladder is empty (which is, however, unlikely since the aim for the treatment planning CT is a comfortably filled bladder) it is unlikely that the target volume will move the full 10-15 mm in the anterior-inferior direction. It should be kept in mind that several studies found that the average bladder volume decreases during the course of treatment. It is expected that the ITV-T LR contours are modified based on clinical judgement. Reducing the margin in one direction implies normally that the margin is increased to the same degree in the contralateral direction. The minimal required margin in anterior-posterior and superior-inferior directions is 5 mm.

b) Intermediate IGRT, individualized ITV-T approach (Figure 9.9.B):

The key difference for an individualized ITV-T compared to the standard margin approach is that pre-treatment imaging, both diagnostic and for treatment planning, is used to assess the range of motion in an individual patient. A pre-requisite is that these imaging series have different filling status of bladder and rectum. For this purpose a full and empty bladder treatment planning CT can be useful. For patients with a smaller range of motion, a smaller ITV margin can be applied, whereas, in patients with a large range of motion, a margin comparable or larger than that derived from standard motion range may be required.

To generate the ITV-T LR, the different diagnostic and treatment planning image series should be fused to the treatment planning CT with comfortably filled bladder. The ITV-T LR margin is adapted based on the assessed range of motion within the individual patients, keeping in mind the proposed standard motion ranges (figure 9.9).

The margins used under “standard margin approach” should be the starting point and individualisation can be adapted from there. ITV-T LR should not go into the muscle and bony boundaries of the pelvis. Importantly, the ITV-T does not need to include the whole uterus as seen on an image series with an empty bladder, since with the drinking protocol this situation is not expected during the course of fractionated EBRT. It should be kept in mind though that some studies indicate that the average bladder volume decreases during the course of treatment. If daily soft tissue verification (CBCT) is used to monitor the daily uterus position, it is possible to shrink the individualised margins further according to the thresholds defined for re-planning.

9.3.7 GENERATING THE ITV45

The combined ITV-T LR and CTV-E is the target volume which has to be treated with the prescribed dose of 45 Gy by EBRT (see 9.5). It also contains any CTV-N. This combined tumour and lymph node related target volume is named ITV45. This final ITV45 is required for dose reporting.

9.3.8 PTV

A PTV margin of 5 mm is applied for the whole ITV 45 which includes the CTV-E and the ITV-T LR (Fig. 9X and 9Y). This margin is considered appropriate when using daily image guidance and daily couch correction according to bony fusion (see section 9.6).

The PTV45 is consequently the ITV45 with an isotropic margin of 5 mm

For the involved nodes, PTV-N (#) is CTV-N (#) with an isotropic margin of 5 mm. Each individual pathologic node (#) will have an individual PTV-N (#). PTV-Ns are usually encompassed by PTV45. If they are not encompassed, a larger margin of e.g. 10 mm from the CTV may be considered in the specific region.

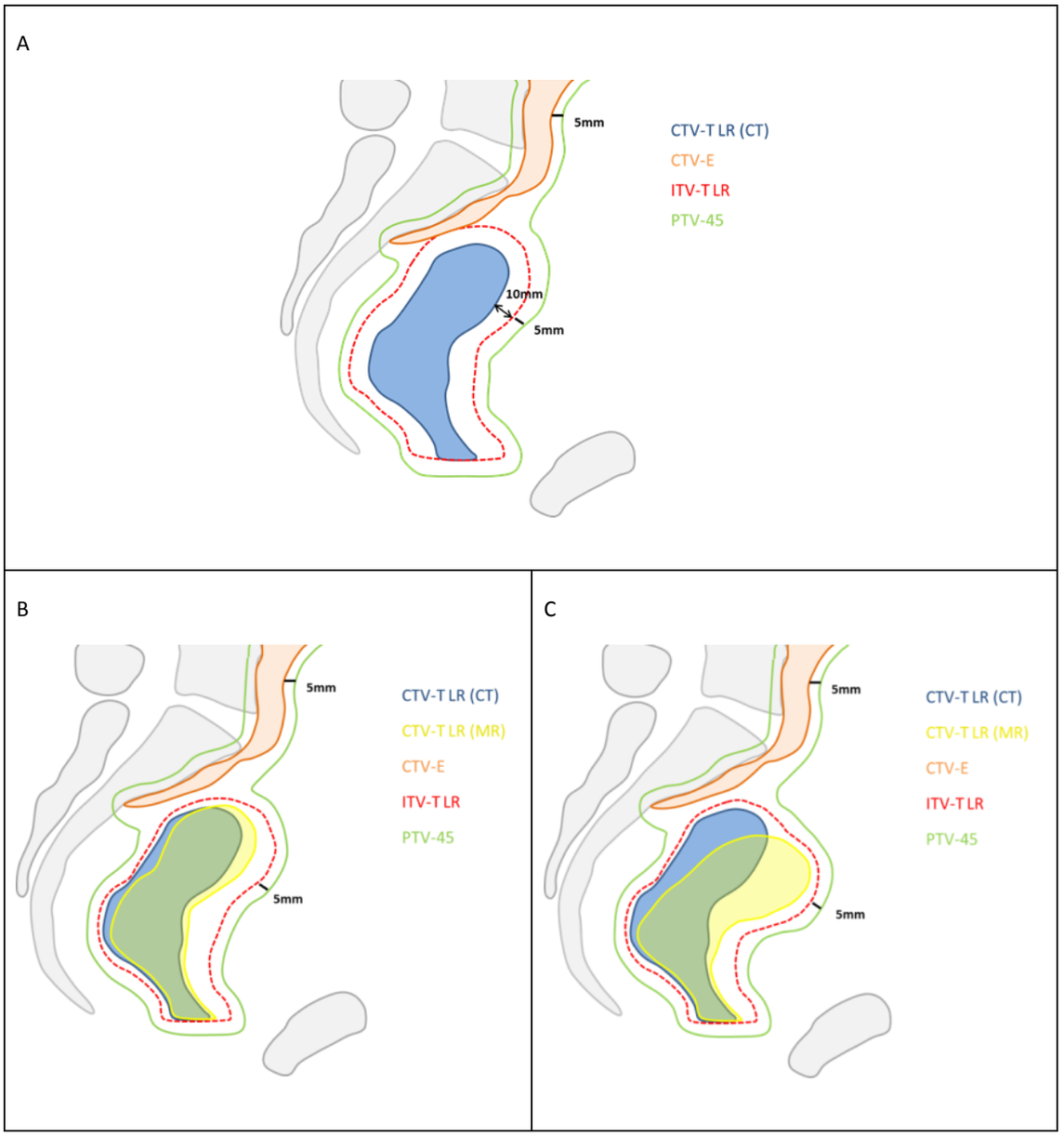


Figure 9.9. Panel A shows the application of the “Standard margin” approach where the ITV is defined according to the anatomy in the CT treatment planning scan. Panel B and C show examples of a “small mover” and “large mover”, respectively, and application of the “Individualised ITV approach”. Further examples of “Standard margin” and “Individualised ITV approach” can be found the appendix 5 “Contouring Atlas for EBRT”.

9.4 CONTOURING OF ORGANS AT RISK, REFERENCE POINTS

The outer contour of the following organs should be delineated separately:

Bladder	Whole organ including the bladder neck
Rectum	From the ano-rectal sphincter to the recto-sigmoid junction
Sigmoid	From the recto-sigmoid junction to the left iliac fossa
Bowel	Outer contour of bowel loops including the mesenterium
Femoral heads	Both femoral head and neck to the level of the trochanter minor

Reference points:

Vagina	Lower and mid-vagina doses (PIBS, PIBS ± 2 cm)

For para-aortic irradiation in addition:

Kidneys	Outer contour excluding renal pelvis
Spinal cord	Outer contour

Optional (if para-aortic RT above L1 is applied):

Duodenum	Whole organ

In case of ovarian transposition

Ovary	Outer contour

9.5 CONTOURING OF TUMOUR, TARGETS AND OARS BASED ON MRI AND CT

Treatment planning is performed on the treatment planning CT with a comfortably filled bladder. The T2 weighted transversal plane MRI is fused to the CT, based on anatomy of the pelvic bones. If MRI is made in the treatment position (flat couch and with bladder filling protocol) the fusion is usually excellent and MRI can be used for contouring all targets and OAR in the whole cranio-caudal length. In these cases additional contouring on planning CT might only be needed for the para-aortic part in case of high risk disease.

If diagnostic MRI scans are used, fusion may be more challenging. Priority should be set at achieving an acceptable match within the pelvis. In these cases it is preferable to use the anatomy as seen on the treatment planning CT for contouring when moving outside the area of acceptable match. It is recommended to start contouring on MRI, exploiting the superior soft tissue resolution when delineating GTV-T and CTV-T HR. As there is usually no bladder filling protocol in diagnostic MRI, the location of OARs and uterus is often not representative, and the next step of contouring normally proceeds on the treatment planning CT to delineate CTV-T LR, ITV-T LR, nodal targets (GTV-N's and CTV-E) and OARs (see figure 9.10). However, if there is an excellent fusion between diagnostic MRI and treatment planning CT, it may be possible to perform GTV-N, CTV-E and OARs on the diagnostic MRI.

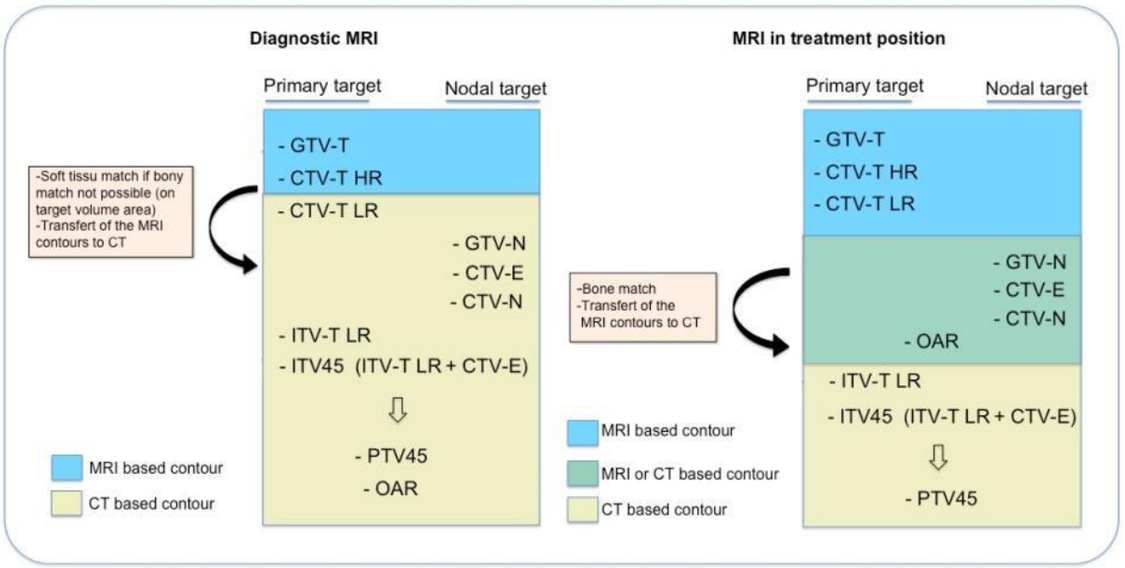


Figure 9.10 Schematic workflow for contouring primary target and nodal target and OARs on diagnostic MRI, MRI in treatment position and CT (see also ch. 26 on EBRT treatment planning, Appendix).

9.6 DOSE AND FRACTIONATION FOR PTV45

The planning aim dose and fractionation schedule for PTV45 is 45 Gy delivered in 25 fractions, 1 fraction per day and 5 fractions per week. All beams and segments involved in a given part of the treatment must be treated at each fraction. Unplanned treatment breaks (>2 consecutive treatment days) should be compensated by two daily EBRT fractions spaced by at least 6 hours. This compensation should only be performed once per week, i.e. the dose accumulation of EBRT in the PTV45 should not exceed 10.8 Gy per week.

Maximal overall treatment time including external beam radiotherapy, brachytherapy and concomitant chemotherapy is 50 days.

The dose to the PTV45 should be homogenous, with at least 95% of the PTV covered by the 95% prescription isodose, and dose maximum less than 107% of the prescribed dose.

Special attention is needed for the OAR irradiation in close proximity to the CTV-T HR (bladder, rectum, sigmoid and bowel) where the high BT dose will be delivered. To ensure even less dose variation in this region, where summation of EBRT and BT dose is critical, a helper contour with a margin of 10 mm might be generated around the CTV-T HR (CTV-T HR +10mm). The dose within this helper contour should be less than 103% of 45Gy to avoid hotspots in OAR walls which are likely to also receive considerable BT dose.

9.7 DOSE AND FRACTIONATION FOR PTV-N (NODAL BOOSTING)

The decision for nodal boosting is left to the individual centre. However, all pathological nodes (with the features described in section 9.3.3.) should be contoured and numbered individually.

Nodal boosting should be performed by use of a simultaneous integrated boost (SIB), with a total number of fractions of 25. Dose prescription to the individual PTV-Ns (PTV-N1, PTV-N2, PTV-N3, etc.) is left to the treating centre. In every case, EBRT dose have to be specified for dose reporting, and, if possible, (expected) contribution from BT to the total EQD2 of the specific node. Biological equivalence calculations are performed by use of the linear-quadratic formulation assuming that the alpha/beta value is 10 Gy for tumour effects.

Dose from BT to each individual node can be calculated based on BT MRI information. However, the expected PTV-N dose contribution from brachytherapy can also be accounted for (Mohamed SM. et al. 2015):

- 3-4 Gy EQD2: Inside true pelvis (external/internal iliac, obturator)
- Negligible: Outside true pelvis (common iliac, para-aortic, inguinal)

Although institutional practise for nodal boosting and dose levels can be followed, the recommendation given within this protocol for the nodal boost is that total EBRT + BT dose should preferably be in the range 55-65 Gy EQD2.

Total dose to PTV-Ns of about 60 Gy EQD2 can be achieved with the following fractionation schedules:

- Inside true pelvis: EBRT with SIB 25x2.2Gy= 55Gy physical dose. This schedule is equivalent to 56 Gy EQD2 EBRT + 3-4 Gy EQD2 from BT which results in a total dose of ~60 Gy EQD2.
- Outside true pelvis: EBRT with SIB 25x2.3Gy =57.5 Gy physical dose. This schedule is equivalent to ~59 Gy EQD2 and BT dose contribution is negligible.

9.8 TECHNIQUE AND PROCEDURES FOR EBRT INCLUDING DAILY IMAGE GUIDANCE

A major aim of the Embrace II study is to optimize EBRT dose distributions in order to minimize the dose to OAR delivered with EBRT. This goal implies the mandatory use of IMRT, VMAT or tomotherapy based on inverse treatment plan optimisation. Photon energy of 18 MV is related with increased neutron dose, and therefore lower energies (e.g. 6 MV or 10 MV) are advantageous in this respect for IMRT/VMAT. However, for higher energies the treatment plan quality is advantagous in terms of decreased low dose volumes for IMRT/VMAT. These two aspects need to be considered when deciding on photon energy.

It is recommended to use coverage probability (CoP) dose planning principles for lymph node boosting. With CoP planning principles it is assumed that the CTV-N is more often occupying the central region of the PTV-N than the edge region. According to this, it is aimed to generate a heterogeneous dose across the PTV-N in such a way that the central dose >100% and the edge dose is cooled down to 90%. In case of large lymph nodes it is possible to escalate the central part of the GTV-N to e.g. D50>102%, while respecting an upper limit of 107%.

Daily 2D (MV or kV) or 3D (CBCT or MVCT) IGRT is mandatory. The daily imaging is used for fusion and position verification on bony anatomy. Couch correction must be performed daily before treatment delivery according to the bony fusion between the on-board imaging and the treatment planning CT. Couch alignment to take soft tissue into account such as e.g. the uterus is NOT allowed as this might take nodes and elective target out of the treated volume. Soft tissue verification (evaluation of the position of uterus) based on CBCT can be performed, but is not mandatory. With soft tissue verification it is possible to evaluate if the daily uterus position is significantly different from expected and this knowledge can be used to decide that a new treatment plan would be beneficial.

In case that 3D soft tissue verification imaging and monitoring shows that significant parts of CTVs are repeatedly outside the 95% isodose volume, the following should be considered:

- Additional tattoos at the level of L2
- Additional planning CT scan for re-planning
- Redefining the ITV, taking the information acquired with CBCT into account.
- Adjustment of the PTV margin (see the section on angulation of the pelvis in relation to the lumbar spine.
- There is allowance for 10% under dosage in the non-involved uterus as accumulated across all EBRT treatment fractions which is equivalent to a total dose of 40Gy. Brachytherapy contributes to uterus dose normally by >5-10Gy, and the aim is to deliver a total of 45Gy EQD2 to the uterus in terms of total EBRT and BT dose (D98).

9.8.1 ANGULATION OF THE PELVIS IN RELATION TO THE LUMBAR SPINE

With para aortic radiation, flexing of the thoraco-lumbar spine in relation to the pelvis can be a concern considering the tight PTV margin. In case of repeated residual misalignment of more than 5mm despite daily correcting to match on bony anatomy the following procedures should be considered: check if immobilization device is used optimally; consider additional tattoos at the level of L2; consider an additional planning CT scan; a last step would be to consider to expand the PTV margin in the para-aortic region where the residual set-up error persists.

9.9 PLANNING AIMS FOR TARGETS AND ORGANS AT RISK

With a prescription dose of 45 Gy to PTV45, and 55-57.5 Gy to PTV-N (#) if applicable, delivered in 25 fractions, the dose volume constraints for organs at risk (OAR) summarized in table 9.4 need to be met. Note that these OAR constraints are based on the PTV definition described in chapter 9.2.3 with a 5 mm ITV to PTV margin.

Table 9.4: Summary of planning aims for OAR and target.

		Hard dose constraints	Soft dose constraints
Targets	PTV45	V95% > 95% Dmax<107%*	
	ITV45	Dmin> 95%	
	PTV-N(#)	D98% > 90% of prescribed LN dose Dmax < 107% of prescribed LN dose	
	CTV-N(#)	D98% > 100% of prescribed LN dose	D50% > 102%
Help contour	CTV-HR +10mm		Dmax < 103%
OARs	Bowel	Dmax < 105% (47.3Gy)*	When no lymph node boost: • V40Gy < 100cm3** • V30Gy < 350cm3** When lymph node boost or para-aortic irradiation: • V40Gy < 250cm3** • V30Gy < 500cm3** Dmax < 57.5Gy
	Sigmoid	Dmax < 105% (47.3Gy)*	Dmax < 57.5Gy
	Bladder	Dmax < 105% (47.3Gy)*	V40Gy < 75%** V30Gy < 85%** Dmax < 57.5Gy
	Rectum	Dmax < 105% (47.3Gy)*	V40Gy < 85%** V30Gy < 95%** Dmax < 57.5Gy
	Spinal cord	Dmax < 48Gy	
	Femoral heads	Dmax < 50Gy	
	Kidney	Dmean < 15Gy	Dmean < 10Gy
	Body	Dmax < 107%*	
	Vagina PIBS-2cm		When vagina not involved: $D_{PIBS-2cm}$<5Gy
Optional	Ovaries	<5-8 Gy	
	Duodenum***	V55<15cm^3	

*In case that lymph nodes are not boosted, ***Verma J. et al. 2014

**Soft constraints which can be used as optimisation constraints as they are not based on clinical evidence. The constraints are not supposed to be fulfilled by all patients, but rather by ~70-80% of the patients.

9.10 REPORTING OF EBRT PARAMETERS

The following parameters are read out from the treatment planning system and entered into the database:

Volume (nomenclature)	Dose and volume parameters
Initial GTV-T (cm^3)	Volume
Initial HR CTV-T (cm^3)	Volume
Initial LR CTV-T (cm^3)	Volume
ITV45 (cm^3, Gy)	Volume, D98
PTV45 (cm^3, Gy)	Volume, D98
GTV-N(#) volume (cm^3)	Volume
CTV-N(#) (Gy)	Volume, D98
PTV-N(#) (Gy)	D98
Bowel (cm^3)	V15Gy
Bowel (cm^3)	V30Gy
Bowel (cm^3)	V40Gy
Bowel (cm^3)	V50Gy
Sigmoid (%)	V30Gy
Sigmoid (%)	V40Gy
Sigmoid (%)	V50Gy
Bladder (%)	V30Gy
Bladder (%)	V40Gy
Bladder (%)	V50Gy
Rectum (%)	V30Gy
Rectum (%)	V40Gy
Rectum (%)	V50Gy
Body (cm^3)*	V43Gy
Body (cm^3)*	V50Gy
PIBS +2cm (Gy)	Point dose
PIBS (Gy)	Point dose
PIBS -2cm (Gy)	Point dose

*Total volume (including PTV and entire body). Depending on planning system a helper structure might be necessary (e.g. Monaco)

10 BRACHYTHERAPY

10.1 INTRODUCTION AND SPECIFIC AIMS FOR BRACHYTHERAPY

Treatment planning and performance of BT is based on the recommendations of the "ICRU 88/GEC ESTRO Report" on "Prescribing, Recording and Reporting Brachytherapy for Cancer of the Cervix" (ICRU report 88, in press 2015) where the concepts and parameters for image guided adaptive brachytherapy are systematically described. A detailed understanding of this report is essential for brachytherapy in EMBRACE II (a brief introduction in target concepts is outlined in chapter 3.2). Reading major parts of this report is therefore necessary for investigators including patients into the EMBRACE II study.

The specific aims for brachytherapy in Embrace II are:

1. To increase the optimal and safe use of cervix cancer brachytherapy by use of a prospective protocol for dose planning and prescription for multiple targets and OAR based on the findings from RetroEMBRACE and EMBRACE
2. To increase the use of combined intracavitary and interstitial (IC/IS) application in order to meet the planning aims and DVH constraints of Embrace II
3. To ensure that the overall treatment time stays below 50 days
4. To maintain and possibly improve a high level of local control in small and well responding tumours
5. To improve local control in large and poor responding tumours through dose escalation by systematic use of combined IC/IS applications
6. To decrease brachytherapy related morbidity through systematic application of brachytherapy related dose volume constraints.
7. To reduce vaginal morbidity through dose-de-escalation in the vagina by reduction of vaginal loading in cases with no vaginal involvement.

10.1.1 OVERALL SCHEDULE FOR EBRT AND BT AND CHEMOTHERAPY

The overall treatment time (OTT), defined from the first external beam fraction to the final external beam or brachytherapy fraction dose is delivered should be < 50 days. Based on analyses of retro-EMBRACE (Tanderup K. et al. in submission 2015) increase of OTT by one week is equivalent to de-escalating CTV_{HR} dose by 5 Gy.

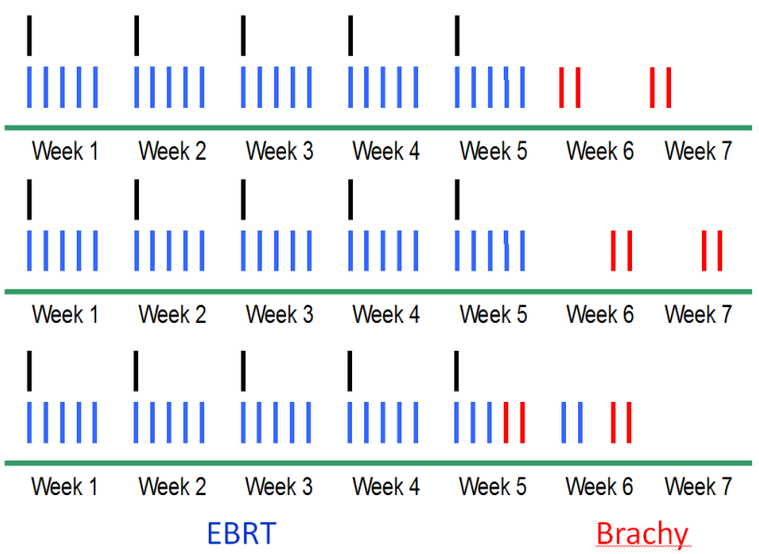


Figure 10.1: Examples of overall schedules administering 25 fractions of EBRT with or without simultaneous integrated lymph node boost (blue bars), 5 courses of concomitant cisplatin (black bars) and 4 fractions of HDR brachytherapy (red bars) within an overall treatment time of 7 weeks (upper panels) or 6 weeks (lower panel). Analogue scheduling applies for PDR brachytherapy.

To obtain maximal tumour regression the treatment should always be initiated with EBRT and concomitant chemotherapy for 4-5 weeks before BT is applied in weeks 6-7 (Figure 10.1, upper panel A). For a small and/or well responding tumour BT may be initiated already during EBRT to shorten the overall treatment to 5-6 weeks (panel B). In any case every effort should be made to keep the overall treatment time < 50 days.

If possible it may be advantageous to initiate EBRT and concomitant chemotherapy in the beginning of a week to avoid loss of 2 days in OTT already during the first weekend. Concomitant chemotherapy given on the first days of the week also theoretically paves the way for sensitizing more fractions of EBRT in that week, rather than giving chemotherapy on a Friday where the sensitizing effect is expected to vanish during the weekend. There is limited data on the optimal timing of EBRT and concomitant chemotherapy on the actual day where it is given. Centres can use their own schedule. However, for some patients it may be optimal to give EBRT in the morning and concomitant chemotherapy later in the day to avoid problems with an overhydrated and nauseated patient during EBRT.

10.1.2 PRE-APPLICATION TREATMENT PLANNING

In order to arrive at an appropriate brachytherapy application for cervix cancer a pre-planning procedure is essential which allows for tailoring the application as much as possible to the vaginal anatomy and the tumour spread as it presents at the time of brachytherapy. This requires in any case a comprehensive clinical gynaecologic examination assessing the vaginal topography and the tumour response as compared to the situation at diagnosis at the cervix, in the parametria and in the vagina. This should be precisely documented on the standard gynaecologic template in three orientations including the speculum view. This examination can be supported by volumetric imaging, preferably MRI, which allows for even more precise documentation of the tumour situation at brachytherapy. Based on this assessment an individual adaptive CTV-T HR is defined with a certain width, thickness and height. Essential is the relation of these dimensions of the CTV to the cervical canal, the later location of the tandem, in particular, if the distances to the borders of the later CTV-T HR are symmetrical or asymmetrical (compare Fig. 10.2-5). Taking these dimensions into account a decision is taken about the method of application, in particular, if it can be only intracavitary or a combination of intracavitary and interstitial application. The most precise pre-treatment planning is with a tandem and vaginal applicators in place, which are only inserted for treatment planning (Petric P. et al. 2009, Fokdal L. et al. 2013).

A basic preplanning procedure must be implemented routinely in gynecologic brachytherapy for a tailored application. For EMBRACE II application adaptation must be a common procedure in daily clinical practice. Systematic use of combined intracavitary and interstitial applicators (based on individual mould, ring, ovoids) is a request for appropriate dose adaptation which is dose escalation in particular for advanced parametrial disease and/or dose sparing in adjacent organs at risk. Continuous further development is necessary based on clinical and imaging information and corresponding applicator design (Dimopoulos JC. et al. 2006, Jürgenliemk-Schulz IM. et al. 2009, Kirisits C. et al. 2006). A systematic pre-application planning strategy, including a pre-procedure CTV-T, is considered important for EMBRACE II to account for the specific clinical situation, the selection and contouring uncertainties in adaptive CTV-T, and the expected geometrical and dosimetrical uncertainties (Fokdal L. et al. 2013, Petric P. et al. 2009, Tanderup K. et al. 2010).

10.2 APPLICATOR INSERTION FOR BRACHYTHERAPY

Bowel preparation should always be used to ensure an empty rectum and sigmoid colon, which is of particular importance when using interstitial needles in addition to intracavitary treatment and also for PDR with prolonged stay in bed. Supportive treatment such as low molecular weight heparin, antibiotics and analgesics are given according to individual patient needs and institutional practice.

Before placement of the BT applicator a clinical assessment of the tumour extension is performed describing tumour dimensions (width, height and thickness) as well as the possible involvement of parametria, vagina, bladder and rectum. The clinical examination is documented by drawings by use of the standard clinical diagram (see appendix 22.1).

A Foley catheter is placed in the bladder and 7 ml of diluted contrast medium (e.g. gadolinium or saline) is injected into the balloon which is suitable to correctly visualize the balloon on MRI.

Each participating department should define standard rules for bladder filling which should be followed both during each imaging procedure (MRI/CT) and the subsequent BT treatments. For HDR this is usually obtained by emptying the bladder and installing a specified amount of saline in the bladder, whereas for PDR an "open catheter policy" during both imaging and treatment is usually applied.

Dilatation of the uterine canal can be guided by ultrasound and the depth of the uterine cavity is measured. An MRI compatible applicator is then chosen depending on the anatomical topography of tumour, uterus, cervix and vagina and placed in close contact with the tumour and cervix. The choice of the applicator type depends on the individual anatomy and the tumour spread at the time of brachytherapy. The choice of applicator type (e.g. ring or ovoid type) is up to the decision of each centre. Additional implantation of MR compatible needles in the parametrium and/or vagina have to be used as appropriate for appropriate target coverage. Vaginal packing must be performed with gauze to push away the rectum and bladder and to fix the applicator against the cervix. The gauze may be filled with contrast medium as diluted gadolinium, US gel or saline water to distinguish the packing from the vagina.

The applicator may be fixed to the patient by elastic bandages or similar. External fixation to the surgical table/board should not be used. Alternatively, an individual mould or other customized procedures may be used for fixation of the applicator according to the practice of the participating institution. Important is a fixed geometry of the applicator in relation to the target volume. In-vivo dosimetry by use of detectors can be used according to institutional practice.

The patient is transferred to the MRI scanner to obtain appropriate images with the patient in the supine treatment position. With sufficient vaginal packing, there is according to available evidence so far no indication of relevant movement of the applicator relative to the CTV or to adjacent OAR.

10.3 IMAGING FOR BRACHYTHERAPY

The primary imaging modality for brachytherapy treatment planning is MRI for each individual applicator insertion. Additional imaging may be performed, if possible, also for each fraction in case of fractionated HDR treatments or as a constancy check during a PDR course if planned in an individual centre.

The first BT fraction has to be planned based on MRI with applicator in situ. Depending on the situation, MRI can be replaced by CT for succeeding insertions/fractions. Each applicator insertion must be followed by at least one 3D volumetric image (preferably MRI) and dose planning, while subsequent fractions using the same implant might be applied with the same treatment plan. Only in case of exceptional circumstances and if the contouring for reporting is based on an MRI performed at a time point close to the first implant also the first fraction might be planned without MRI with applicator in situ. In these exceptional cases at least one of the subsequent fractions has to be MRI based then.

To ensure a reliable reconstruction of the applicator the slice thickness of MRI should be ≤ 5 mm with no interslice gap. Sequences taken parallel to the applicator, i.e. paratransversal, paracoronal and parasagittal (18) are superior to straight transversal, coronal and sagittal images with regard to both target contouring and applicator reconstruction. Marker wires of plastic with saline or solutions of $CuSO_4$ can be used to easy the identification of the source channel and determine any rotation of the applicators (Dimopoulos JC. et al. 2012).

Orthogonal X-rays is not required but may be used in the anterior-posterior and lateral projection with radio-opaque guide wires in the applicator to ensure that the spatial 2D relation between applicator and target and OAR is satisfying. Dose points must be defined directly in the 3D imaging set used for contouring and treatment planning and should not be defined in 2D on the radiographs (see below).

10.4 APPLICATOR RECONSTRUCTION AND DOSE POINTS FOR OARS

Uncertainties of 4% (k=1) due to applicator reconstruction are assumed when reporting dose parameters for cervix brachytherapy (Kirisits C. et al. 2014). This uncertainty level can only be reached by an appropriate step-by-step quality assurance program in each center (Hellebust TP. et al. 2010):

Step 1: The first step is to define the source path (which is subsequent dwell positions of the actual source inside the applicator) in relation to the applicator. This is usually defined or at least checked during commissioning of applicators and afterloaders. The source path can be related to the outer dimensions of an applicator or to marker wires or other indicators placed inside the applicator. A usual way is to perform auto-radiographs to visualize the dwell positions. Such commissioning procedure should result in drawings of the essential dimensions or even applicator templates which can be integrated into treatment planning systems.

Step 2: The accuracy of applicator reconstruction is depending on the resolution of the 3D image set. Appropriate imaging has to be performed, either by reducing the slice thickness, by combining different image orientations (e.g. oblique orientations in transverse, sagittal and coronal) or by using dedicated 3D sequences (e.g. isotropic voxel size). Each department must ensure that the applicator reconstruction can be performed with an uncertainty of < 2 mm. This includes the overall deviation of the planned dwell position to the finally realized dwell position on an anatomical situation as visualized on the planning MRI (or CT). This includes deviations due to source path definition (commissioning), equipment performance (constancy checks) and the reconstruction process in the treatment planning system.

Step 3: For CT reconstructions library plans or direct reconstruction based on CT, markers may be the optimal solution. For MRI reconstructions library plans are the optimal method. Fusion of CT to MRI is most often not helpful for applicator reconstruction; as such fusion techniques have to be based on the already reconstructed applicator in both image modalities. In certain situations the needle reconstruction on MRI is difficult. CT can then be used in addition to MRI, either to identify the correct needle tips, or even by registering MRI with CT via the intracavitary applicator and then use CT for needle reconstruction. However, this depends on the individual settings and MRI can also be sufficient, even for complex implantation geometries.

The dose points for brachytherapy are defined directly in the volumetric imaging study (MRI or CT). In addition, the point of expected dose in a specific organ may be determined and used for in vivo dosimetry for instance if rectal diodes are used (optional).

The following dose points should be defined directly in the 3D imaging study:

- The ICRU bladder point
- The ICRU recto-vaginal point
- Vaginal point doses at level of sources (lateral at 5 mm)
- Lower and mid-vagina doses (PIBS, PIBS ± 2 cm)

Definition of the point A, the recto-vaginal, the bladder and the PIBS reference points on CT and MRI has to be strictly followed according to the ICRU88/GEC ESTRO report. Point A is strictly related to the applicator. Practically a coordinate system is rotated and centered to have it aligned to the applicator, with its origin in the intrauterine applicator axis and the z=0 plane at the surface of the vaginal applicators. When defining the recto-vaginal and bladder reference points the image orientation is essential. Both points are defined according to the patient coordinate system - on anterior-posterior lines, which are strictly perpendicular to the longitudinal axis of the patient. The location of the PIBS points is estimated best on sagittal image orientations, again taking into account the image orientation to define PIBS on a straight anterior-posterior line perpendicular to the patient axis. From PIBS, PIBS+2 and PIBS-2 are defined via ruler function in the TPS or entering coordinates in a correct adjusted patient coordinate system.

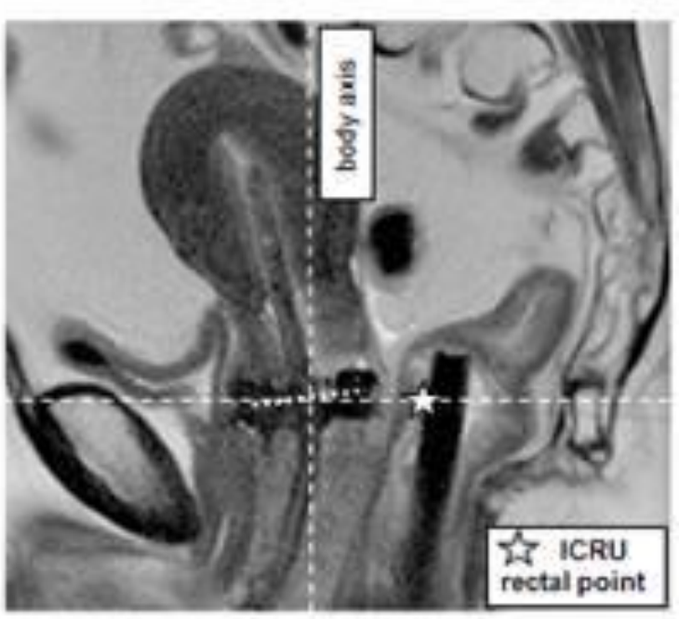


Figure 10.2: The recto-vaginal dose point inserted according to the ICRU/GEC ESTRO report 88 (image from Kirchheiner K. et al. in submission 2015)

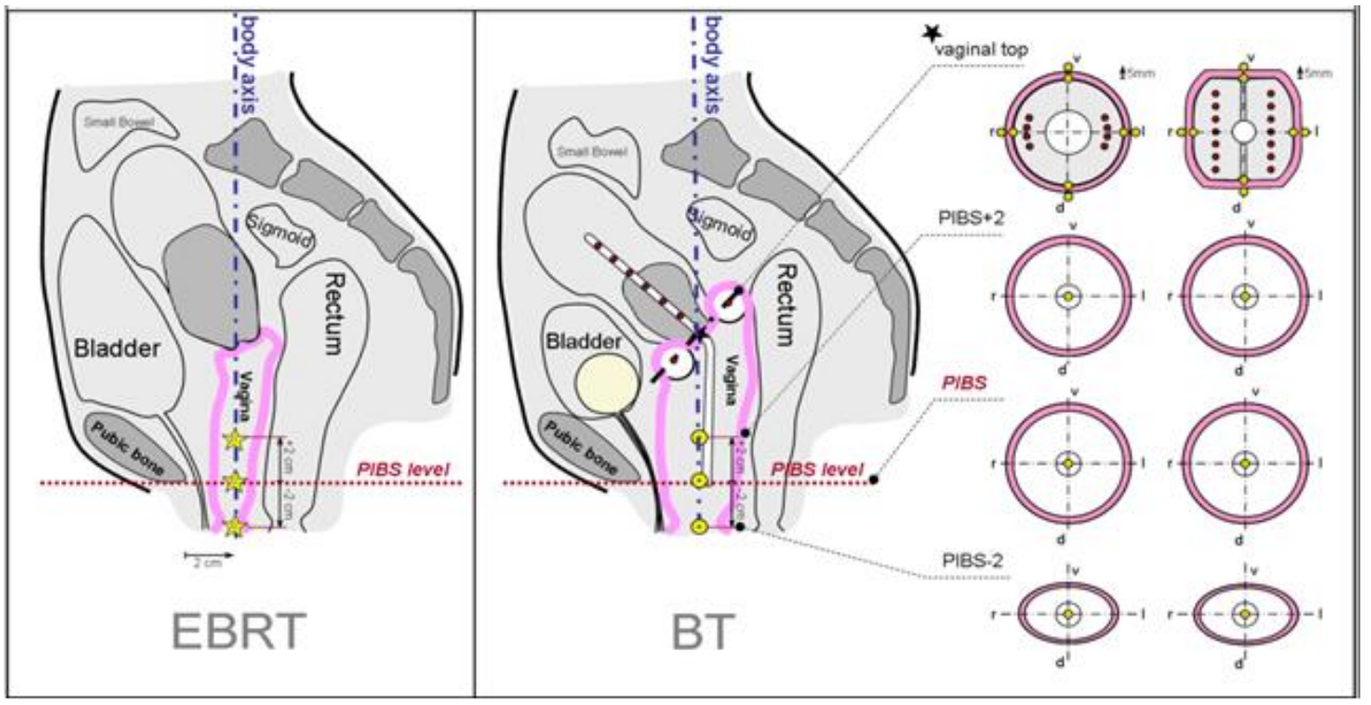


Figure 10.3. Sagittal views showing the vagina at time of EBRT and at brachytherapy with an intracavitary applicator in place. At the level of the vaginal source, dose points lateral to the rings or ovoids can be defined at 0 mm and 5 mm from the applicator surface. Three additional points are defined along the central axis of the vagina in the cranio-caudal direction. The PIBS vaginal-dose point was defined 2 cm posterior from the Posterior-Inferior Border of the pubic symphysis and for BT at the point of this line where it crosses the applicator tandem. From there, two additional points 2 cm up and down along the vaginal axis, are defined with PIBS+2 representing the mid of the vagina and PIBS-2 representing the introitus level (Westerveld H. et al. 2013).

10.5 CONTOURING FOR BRACHYTHERAPY: OARS, GTV_{RES}, ADAPTIVE CTV_{HR}, CTV_{IR}

Contouring for both tumour and OAR is performed for each insertion/implant of BT applicators by contouring on T2 weighted (para)-transversal MRI sequences in a dedicated 3D brachytherapy dose-planning system according to the GEC ESTRO Recommendations and the ICRU/GEC ESTRO report 88 (see for GTV and CTV-T chapter 3.2). The MRI based target delineation can be reused by superimposition in the process of contouring on CT, if for subsequent fractions of brachytherapy only CT can be used with the applicator in place.

To maintain consistent reporting and communication between investigators and the EMBRACE Study Office the protocol for contouring AND naming of targets and OAR must be followed strictly.

10.5.1 CONTOURING OF ORGANS AT RISK

The following organs are contoured (from at least 2 cm below the IR-CTV to 2 cm above the uterus):

- Bladder: Outer bladder wall including the bladder neck
- Rectum: Outer rectal wall from the anal sphincter to the transition into the sigmoid
- Sigmoid: Outer sigmoid wall from the recto-sigmoid flexure to at least 2 cm above the parametria and the uterus
- Bowel loops: Outer contours of loops positioned within 3-4 cm to the uterus and applicator

For cases with significant vaginal involvement it is advised also to contour the urethra separately to be able to assess the dose to this structure. There is no specific DVH constraint known so far for the urethra.

If the anatomical transition from rectum to sigmoid is immediately in vicinity of the applicator it is advised to move the transition up or down to avoid that the $D2cm^3$ for one or the other will be too low.

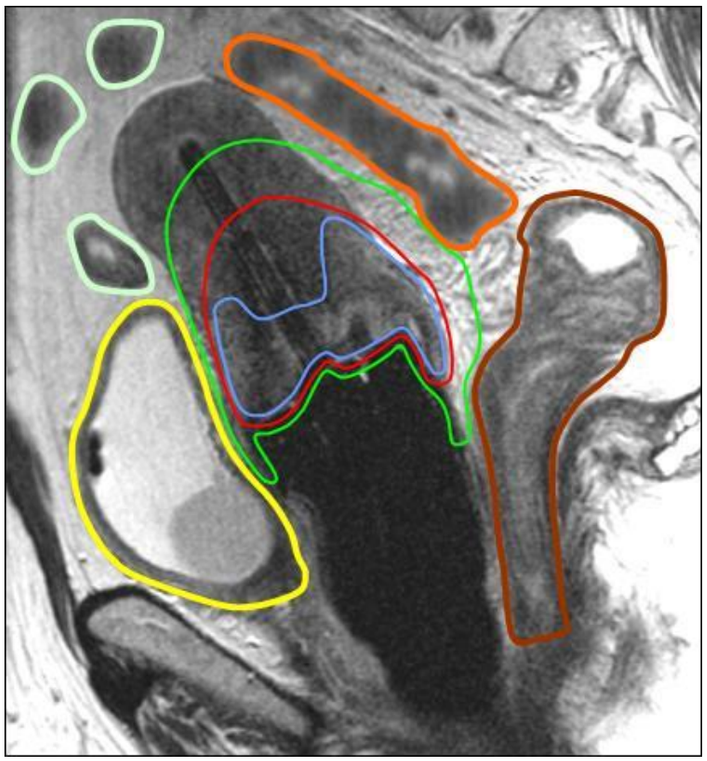


Figure 10.4: The outer contour of bladder (yellow), rectum (brown), sigmoid (orange) and bowel (light green) shown in the sagittal plane (Petric P. in Viswanathan et al. 2011).

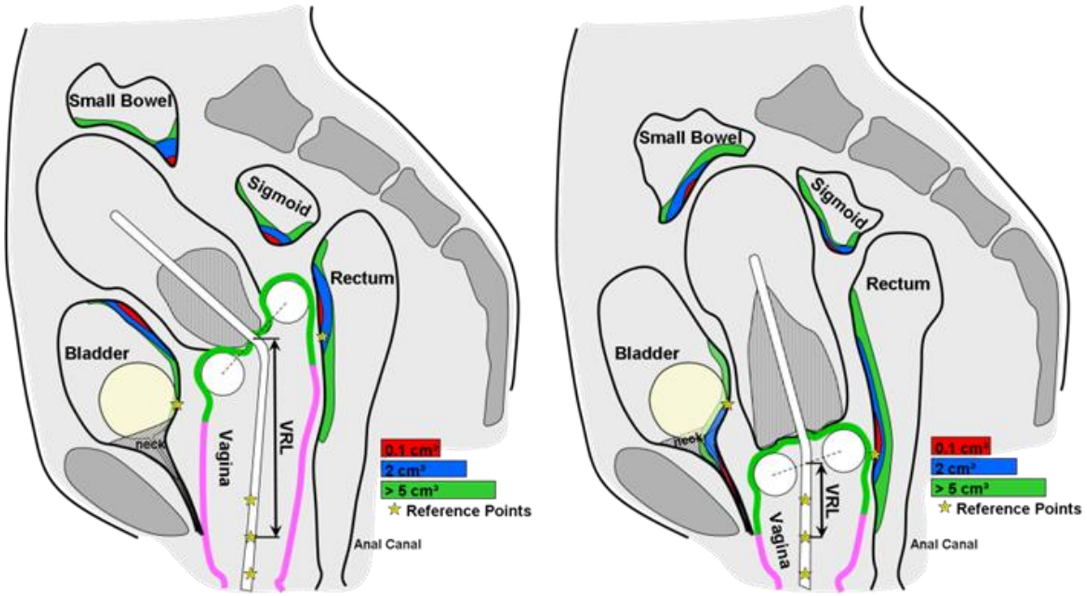


Figure 10.5. "Schematic anatomical diagrams (sagittal view) showing two different positions of the vaginal part of the utero-vaginal applicators, the cervix tumor, the uterus and the reference volumes of OARs in two different patients. The most irradiated-tissue volumes adjacent to the applicator, i.e., the reference volumes 0.1 cm3, 2 cm3, and 5 cm³ are illustrated for the various adjacent organs such as bladder (neck), rectum (anus), sigmoid, and small bowel. The two panels show the different locations of the 0.1 cm3 and 2 cm³ reference volumes in the adjacent OARs (modified from GEC ESTRO Recommendations II, Pötter R. et al. 2006; see also Westerveld H. et al. 2013). Reference points are indicated for the bladder (ICRU Report 38), the rectum and upper vagina (ICRU Report 38), and the mid and lower vagina (PIBS ± 2 cm). Figure: Schematic drawing showing the position of the volumes related to the DVH analysis and with stars the locations of the bladder, recto-vaginal and three PIBS points (PIBS, PIBS+2, PIBS-2). …." (from ICRU Report 88, figure 6.4) The points are in a sagittal image containing the intrauterine applicator except the bladder point, which could be in a parallel plane before or behind this plane, according to the location of the bladder balloon.

10.5.2 CONTOURING OF TARGET VOLUMES

Accurate tumour and target contouring requires that the contouring physician has performed the gynaecological examination that has to be done prior to insertion of the applicator and that information including clinical drawings from gynaecological examination at diagnosis as well as MRI at diagnosis and MRI at time of brachytherapy with the applicator in situ are available at the contouring station (Figure 10.6).

The following targets should be contoured for brachytherapy:

- GTV_{res}: Residual (high signal) Gross Tumour Volume of the primary Tumour
- CTV_{HR}: Adaptive High Risk Clinical Target Volume of the primary Tumour
- $CTV_{IR:}$: Intermediate Risk Clinical Target Volume of the primary Tumour

The targets are primarily contoured on the para-axial sequence, but para-coronal and sagittal sequences should be inspected during the process to ensure target consistency also in these sequences.

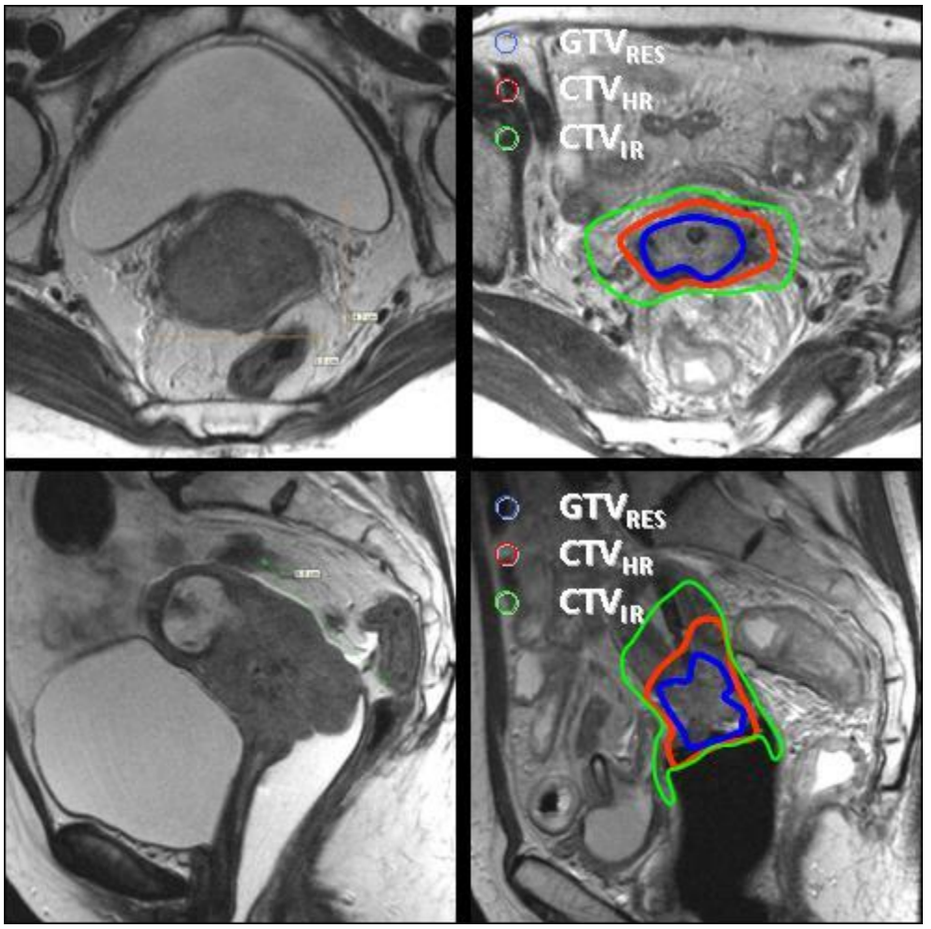


Figure 10.6: MRI at diagnosis (left panels) and at time of brachytherapy with the applicator in situ (right panels). The brachytherapy targets (blue: GTV_{res}, red: CTV_{HR}, green: CTV_{IR}) are contoured in the para-axial slide (upper right panel) and here inspected for consistency in the sagittal sequence (lower right panels). The MRI at diagnosis (left panels) is used to identify grey zones and to ensure that the CTV_{IR} contour fully covers the primary tumour extension. By courtesy of Primoz Petric.

10.6 TREATMENT PLANNING FOR BRACHYTHERAPY

10.6.1 EVIDENCE OBTAINED FROM RETROEMBRACE AND EMBRACE I

The D90 constraints for the CTV_{HR} are based on dose-response curves for retroEMBRACE. In an analysis of 766 cases from EMBRACE in 2014 72% of cases reached a dose of > 85 Gy for this parameter. The same amount of patients reached at least a dose of 67 Gy for the CTV_{HR} D100. As D100 is not used, a conversion to D98 is based on a dataset of 403 cases from EMBRACE in 2014 where also D98 was available. Taking into account the ratios of D98 to D90 and D100 for physical dose, and EQD2 conversion for a PDR schedule of 40 pulses and a HDR schedule of 4 fractions resulted in a dose of ~76 Gy for D98. This was the basis to choose 75 Gy as a constraint for D98 CTV_{HR}. Using the same conversion method for the GTV a D100 constraint of 85 Gy is related to 98 Gy for D98, a D100 constraint of 80 Gy is related to 91 Gy. These values were rounded to 95 Gy and 90 Gy, respectively. The planning aim dose for the CTV_{IR} is based on a review of clinical practice within EMBRACE and by taking into account the historical French experience. The 60 Gy volume should encompass as close as possible the CTV_{IR} which can be described by reaching a near minimum dose D98 of 60 Gy. The planning aim dose for the point A is a safety measure. Conformal adaptation of dose to very small target volumes, probably related to contouring uncertainties, should not result in too small brachytherapy contributions. The planning aim of 65 Gy, which is based on expert review of

the existing practice within EMBRACE, should warn in case of such small brachytherapy dose values. The dose levels proposed as constraints for OAR are based on analysis from EMBRACE. For the sigmoid/bowel no clinical evidence is available so far to define constraints by now. However, suggestions for planning aims and prescribed dose are given, with a clear remark that these constraints are only valid in case subsequent fractions or pulses are always related to the same most exposed volume of this organ. The constraints have been tested within a database of EMBRACE. While the proposed planning aims for rectum and bladder were achieved already in ~60%, the constraints for the recto-vaginal point were achieved in 53% and for sigmoid in 80%. The limits for prescribed dose were reached in >90% of cases, except for the recto-vaginal point (84%).

10.6.2 PLANNING AIMS AND DOSE PRESCRIPTION FOR EMBRACE II

The D90 for the CTV_{HR} should be between 90-95 Gy, while D_{2cm^3} for bladder should be below 80 Gy, D_{2cm^3} for rectum below 65 Gy, for the ICRU vaginal recto-vaginal point dose below 65 Gy, for the D_{2cm^3} for sigmoid/bowel* below 70 Gy and for D98 for the GTV above 95 Gy (planning aim ~ soft constraints). Taking into account the individual patient case and possibilities in application and dose optimization, deviations of these planning aims are allowed. However, for the vast majority of patients, the D90 for the CTV_{HR} should be higher than 85 Gy and the D98 for the GTV higher than 90 Gy, while D_{2cm^3} for bladder should be below 90 Gy, D_{2cm^3} for rectum below 75 Gy, the ICRU vaginal recto-vaginal point dose below 75 Gy and the D_{2cm^3} for sigmoid/bowel* below 75 Gy (limits for prescribed dose ~ hard constraints). Deviations from these constraints are only allowed in special cases with detailed explanation.For OARS there are also two levels with planning aims 5 - 10 Gy lower than the maximum limits for the prescribed dose.

Table 10.1: Planning aims (soft constraints) and limits for prescribed dose (hard constraints) for treatment planning in Embrace II. The EQD2 is calculated using α/β=10 for targets, α/β=3 for OAR and a repair halftime of 1.5h. The EQD2 include 45 Gy/25 fractions delivered by EBRT.

Target	D90 CTV_{HR} $EQD2_{10}$	D98 CTV_{HR} $EQD2_{10}$	D98 GTV_{res} $EQD2_{10}$	D98 CTV_{IR} $EQD2_{10}$	Point A $EQD2_{10}$
Planning Aims	> 90 Gy < 95 Gy	> 75 Gy	>95 Gy	> 60 Gy	> 65 Gy
Limits for Prescribed Dose	> 85 Gy	-	>90 Gy	-	-
OAR	Bladder D_{2cm^3} $EQD2_3$	Rectum D_{2cm^3} $EQD2_3$	Recto-vaginal point $EQD2_3$	Sigmoid D_{2cm^3} $EQD2_3$	Bowel D_{2cm^3} $EQD2_3$
Planning Aims	< 80 Gy	< 65 Gy	< 65 Gy	< 70 Gy*	< 70 Gy*
Limits for Prescribed Dose	< 90 Gy	< 75 Gy	< 75 Gy	< 75 Gy*	< 75 Gy*

** 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*

10.6.3 DOSE OPTIMISATION FOR BRACHYTHERAPY

Dose optimisation is performed by optimising the implant geometry, the dwell time distribution and the fractionation. The use of implant geometries with interstitial needles in addition to an intracavitary applicator is seen essential for unfavourable topography (either larger target volumes or unfavourable relation between target and OARs). It is assumed that at least 20 % of a representative cohort of cervical cancer cases needs such implant techniques to fulfil the planning aims and prescription limits.

10.6.4 INTRACAVITARY TREATMENT PLANS SHOULD BE BASED ON ITERATIVE STEPS

Preferably, a loading resulting in standardized pear shaped isodose distributions normalized to point A should be used as a starting point for optimisation. This is usually achieved by certain loading patterns in the intrauterine and vaginal applicator parts. In a stepwise procedure the loading pattern and the dwell times are optimized until the planning aims are fulfilled. The same procedure should be used in case of combined intracavitary/interstitial application geometries. The loading and dose contribution from the needles is added to the intracavitary dose distribution. This ensures that the dose levels and dose gradients around the implant geometry stay comparable to intracavitary plans and not interstitial plans, where each applicator has a similar weighting. This should ensure to avoid hot spots and cold spots in any areas not directly controlled via dose points or dose-volume relations. The contribution of the TRAK resulting from the interstitial components to the overall TRAK varies on each situation, but is usually between 5-20 % (Trnkova P. et al. 2009).

10.6.5 VAGINAL DOSE DE-ESCALATION

Recent EMBRACE data demonstrates that vaginal stenosis is correlated to the brachytherapy dose delivered in the upper vagina (ICRU recto-vaginal point), and there is significant potential to reduce vaginal morbidity by dose de-escalation. Vaginal dose de-escalation can be performed by decreasing dwell times in ovoid/ring and increasing the loading in tandem/needles. With the use of combined intracavitary-interstitial applicators, it is possible to increase the width of the 85Gy isodose volume by loading the needles, and it is not necessary to heavily load the vaginal sources. Furthermore, limited size tumours often do not need extensive vaginal loading in order to reach a dose of 85Gy EQD2, since they can be reached mainly by loading the tandem (Nkiwane KS. et al. 2013).

Vaginal loading can be monitored by vaginal dose points, vaginal TRAK or by visually evaluating isodose curves. The major priority when performing vaginal dose de-escalation is to decrease the ICRU recto-vaginal point dose according to the dose planning aim of 65Gy, since this is based on clinical evidence.

In a multicenter study by Mohamed et al. it was demonstrated that vaginal dose de-escalation could be performed without compromising target dose. In this study, reduction of the vaginal loading was attempted such that the 140% isodose would be located as close to or within the applicator at the lateral aspect - as judged from visual inspection. The 140% isodose refers to the physical fractional dose which corresponds to 85Gy. E.g. for a fractional schedule of 7Gy in 4 fractions, 140% corresponds to 140%*7Gy = 10Gy. It was possible to reach the 140% vaginal mucosa criteria in around half of the patients. In the same study by Mohamed et al., it was possible to limit the vaginal TRAK to a mean of 30% which should be compared to typical classical loading patterns (Paris and Fletcher) of 50%. In at least 75% of the patients, the vaginal track could be reduced to <40%, and the lateral vaginal dose points (5mm depth) could be reduced to <85Gy EQD2 (total EBRT and BT dose) (Mohamed SM. et al. 2015, in submission).

Table 10.2: Parameters and constraints for vaginal dose control

	Aim	Priority
ICRU recto-vaginal point dose	<65Gy EQD2 (EBRT+BT)	Primary
The ratio of vaginal TRAK and total TRAK	<30-40%	Secondary
Vaginal lateral dose points at 5mm	<85Gy EQD2 (EBRT+BT)	Secondary
Visual inspection of the 140% isodose	Intruding as little as possible into vaginal tissue, and preferentially located within the applicator	Secondary

10.6.6 PTV AND DOSE CONFORMALITY CONSIDERATIONS IN RELATION TO BRACHYTHERAPY

Planning Target Volume (PTV-T) assures that the dose prescribed to the CTV-T is actually applied and has been developed within the frame of external beam radiotherapy (EBRT). The PTV-T margin around the CTV-T takes into account geometric and dosimetric uncertainties and is considered essential in EBRT. In brachytherapy the dosimetric characteristics with sources inside the target volume, the variations and the uncertainties are different from those in EBRT. A PTV-T margin in brachytherapy, selected after implantation of the applicator, may contribute to dose escalation throughout the target. PTV margins should not be used to compensate for uncertainties in 3D image guided intracavitary brachytherapy (Tanderup K. et al. 2010). This applies to intracavitary and interstitial brachytherapy in cervix cancer. Internal target motion is considered minimal when the applicator is fixed by an intra-vaginal tamponade.

However, geometric uncertainties (reconstruction and contouring) may occur, in particular in the longitudinal direction along the tandem. As margins along the longitudinal axis of the tandem have limited impact on the dose throughout the target, longitudinal margins along the axis of the tandem maybe used to compensate for these set up variations. Addition of margins orthogonal to the tandem axis leads to a dose increase throughout the entire target and are therefore not recommended.

When planning the absorbed dose distribution there is no specific aim for target conformality in the cranial direction. Normally a margin of 1cm above the CTV_{HR} is applied for robustness to uncertainties (see section 10.5 on PTV). The aim is to achieve the planning aims as close as possible. However, if those planning aims can be reached, the dose to the parts cranial to CTV (if OAR doses are fullfilled) is not decreased to reach a conformal situation. By this the dose is kept high in a region which is prone to contouring uncertainties and possible systematic uncertainties in the applicator location (shifting of the applicator in caudal direction) as shown in figure 10.7. The longitudinal margin can be secured by visual inspection of isodose lines, and it is not required to draw specifically a PTV.

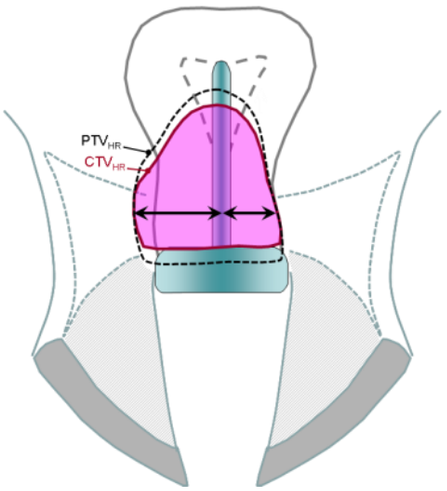


Figure 10.7 ” Longitudinal margins for set up uncertainties in intracavitary image guided adaptive brachytherapy. Margins are added to compensate for uncertainties only in the longitudinal direction, whereas no margins can be added in the orthogonal direction. Therefore a PTVHR may be delineated in the cranio-caudal direction. This may also apply within a planning procedure before the applicator insertion, resulting in a guiding PTV, which may guide the necessary length of the tandem to compensate for set-up uncertainties”. (from ICRU report 88 fig. 5.17). In EMBRACE II a cranial margin above CTV_{HR} of 1cm is advised when this does not compromise OAR exposure.

10.7 DOSE AND VOLUME RECORDING AND REPORTING

Recording and reporting follows the recommendations of ICRU/GEC ESTRO Report 88, where all parameters included in level 1 and level 2 of the reporting standards are included: The physical doses should be reported to the database NOT the EQD2!

Table 10.3. Reporting of dose and volume parameters for BT (from ICRU 88)

GTV_{res}	Volume, D98
CTV_{HR}	Volume, D98, D90, D50
CTV_{IR}	Volume, D98
GTV N*	Near minimum dose (point dose assessment)*
Point A (only when intracavitary)	Point dose
Bladder	D0.1 cm^3, D2 cm^3
Rectum	D0.1 cm^3, D2 cm^3
Sigmoid	D0.1 cm^3, D2 cm^3 and assessment of mobility
Bowel	D2 cm^3 and assessment of mobility
ICRU recto-vaginal point	Point dose
ICRU bladder point	Point dose
Vaginal dose at level of sources	Point dose lateral at 5 mm
Lower and mid-vagina doses	PIBS, PIBS ± 2 cm**
TRAK	

* Lymph nodes which were pathologic at diagnosis (in case of complete regression at time of BT, a representative dose should be estimated for the region where the node was). If the node is not covered by the MRI performed for brachytherapy it is assumed that the dose contribution from brachytherapy to such a node is negligible.

** if PIBS-2cm is outside the MR image object assign a representative dose

11 SYSTEMIC TREATMENT

11.1 AIMS FOR CHEMOTHERAPY

- To improve systemic and nodal control and to improve survival
- To apply systematically simultaneous chemotherapy (minimum 90% of patients who qualify as able to undergo chemotherapy);
- To apply full dose of chemotherapy (5 cycles) in the vast majority of patients (80% of those patients who receive chemotherapy).

11.2 CONCOMITANT CHEMOTHERAPY

Chemotherapy is given according to the studies reported by Key et al. and Rose et al. (Rose PG. et al. 2011, Keys HM. et al. 1999). Cisplatin is to be given intravenously at a dose 40 mg/m^2 once a week for a total of preferably 5-6 cycles according to institutional practice. In EMBRACE I para-aortic and distant control was inferior when less than 5 cycles of cisplatinum monotherapy had been administered. Other chemotherapeutics and schedules might carefully be considered if monotherapy cisplatin cannot be given due to patient related factors, like co-morbidity or early cisplatinum related morbidity and must be reported. Treatment with Cisplatin should be withheld at the discretion of the center. Several guidelines on chemo-radiation protocols exist for cisplatin withhold (Rose PG. et al. 2011, Keys HM. et al. 1999, Pearcey R. et al. 2002). Leucocytes and granulocyte numbers are used as constraints for withhold of cisplatin. Therefore we suggest to use either leucocyte or granulocyte counts as constraints. Guidelines for withhold vary for leucocytes counts around 2.500 or for granulocytes counts between <1,5 to 1.0 X 10_9 cell/L. For platelets guidelines for constraints vary between < 100 to < 50 X 10_9 cell/L platelets. Cisplatin can be resumed in the next cycle once the blood counts exceed these limits. The dose of Cisplatin should be reduced to 30 mg/m^2 if two consecutive cycles of chemotherapy have been given at dose zero. Cisplatin dose should also be reduced to 30 mg/m^2 in case of febrile leucopoenia. Cisplatin should be totally discontinued if blood tests remain unacceptable or febrile leucopoenia recurs despite dose reduction. Cisplatin should also be abandoned in case significant auditory problems (tinnitus, deafness) or neuropathies > grade 2 develops.

Measurement or calculation (Cockroft-Gault) of GFR is performed before treatment and repeated after 3 cycles. Treatment with Cisplatin is abandoned if GFR < 50 ml/min.Haemoglobin should be monitored during treatment. Corrections by transfusion according to institutional guidelines are allowed and have to be reported.

Agent	dose/day	Route	Frequency
Cisplatinum	40mg/m2	i.v. in 3 hours	Weekly for 5-6 cycles

11.3 ADJUVANT CHEMOTHERAPY

According to poor outcome in high risk patients, in particular for systemic recurrence, there is in some centers a practice to apply adjuvant chemotherapy, in particular in the high risk patient group with Carboplatin and Taxol as applied in the OUTBACK trial. Therefore, the EMBRACE II protocol allows for applying this combination in high risk patients based on a center decision.

If decision for adjuvant chemotherapy for the high risk group is made for patients feasible for it, the centre should in general stick to this choice throughout the whole study inclusion period. Stratification for yes or no adjuvant chemotherapy will be performed for treatment outcome analysis.

Adjuvant chemotherapy should in principal be administered according the protocol of the treating centre. In order to achieve a certain level of agreement global recommendations should be followed as given in the protocol of the ongoing clinical OUTBACK trial (https://www.anzgog.org.au/uploads/ANZGOG%20Trial%20-%20Outback.pdf).

Four cycles of adjuvant therapy with carboplatin and paclitaxel should be given at 3 weeks intervals, starting 4 weeks after completion of all radiotherapy (EBRT and BT). Before starting adjuvant chemotherapy the toxicities of the concomitant chemoradiation should be resolved to less than grade 2. Doses should be calculated based on patient's weight at time of start of adjuvant chemotherapy.

Agent	dose/day	Route	Days
Paclitaxel	155 mg/m2	i.v. in 3 hours	1, 22, 43, 64
Carboplatin	AUC 5 (calculated AUC)	i.v. in 3 hours	1, 22, 43, 64

Carboplatin dose is to be calculated according to the Calvert formula:

Dose (mg) = target AUC x (GFR +25)

with AUE being area under curve, GFR calculated according to Cockroft-Gault formula.

Maximum carboplatinum dose (mg) = target AUC (mg/ml x min) x 150 ml/min.

Maximum allowed dose of carboplatin is AUC 5 = 750 mg

Pre-treatment neutrophil count should be ≥ 1/5 x 109/L and pre-treatment platelet count ≥ 100 x 109/L. If counts are below these levels treatment should be postponed for a maximum of 2 weeks. If counts have not resolved after 2 weeks reduced dose levels should be administered or adjuvant chemotherapy should be omitted. Decisions for dose reduction or omission of adjuvant chemotherapy cycles because of hematologic or non-hematologic morbidity is in principle left to the decision of the treating centre but should be preferable follow the recommendations as described in the OUTBACK trial protocol:

(https://www.anzgog.org.au/uploads/ANZGOG%20Trial%20-%20Outback.pdf).

Pre- and post-hydration procedures, the use of anti-emetics and otherwise medication as well as treatment of eventual allergic reactions are left to the decision of the treating centre.

12 OUTCOME ASSESSMENT

Outcome in terms of survival, disease control, morbidity and Quality of Life (QoL) must be assessed prospectively for 5 years by scheduled follow-up according to this table:

Time Point	BL[1]	W4[2]	End[3]	3M	6M	9M	12M	18M	24M	30M	36M	48M	60M
Clinical exam.	●			●	●	●	●	●	●	●	●	●	●
Gyn. exam.	●			●	●	●	●	●	●	●	●	●	●
Diagnostic MRI	●			●			●						
Morbidity scoring	●	●	●	●	●	●	●	●	●	●	●	●	●
QoL	●	●	●	●	●	●	●	●	●	●	●	●	●

[2]Base Line, [2]Week 4 during EBRT, [3]At the end of radiotherapy including BT

The results of the follow-up should be reported to the database as soon as possible (preferably on line) but not later than 4 weeks after the follow-up has taken place. If QoL forms are not returned by the patient 2-3 weeks after a follow-up a new form with request for response should be send. However, no further request should be send if there is no response.

Unplanned follow-up due to suspicious of recurrence and/or development of morbidity should be performed in the same manner as regular follow-ups and reported to the database

Gynaecological examination must include recto-vaginal exploration. General anaesthesia is recommended at 3 month and also if a local recurrence is suspected in order to maximise the possibility for evaluating local tumour control, take biopsies and to reopen vaginal adherences if present.

MRI of the pelvis and retro-peritoneum should routinely be performed at 3 month and at 12 month after end of radiotherapy. It is recommended to perform whole body FDG PET-CT as a routine investigation at the 3 months follow-up as well. MRI, CT and/or PET-CT should be performed according to the clinical needs when a recurrence (local, nodal, systemic) is suspected. Every effort should be made to confirm recurrences by biopsy.

12.1 ONCOLOGICAL OUTCOME AND SALVAGE TREATMENT

The predictive value of the time/volume response of the primary tumour (GTV-T) during radiotherapy will be assessed by comparing the volume of GTV-T contoured on MRI for EBRT and on MRI for each BT implant.

The GTV-T response will be measured according to clinical and imaging criteria for residual disease. The dimensions/volumes are registered in the CRFs.

The investigators categorize in addition according to the following schedule. This is of particular importance for patients with very good response and to assess the patients with complete and uncertain complete remission. This is an area of much uncertainty and the aim of EMBRACE II is to have a more precise assessment of GTV volume response in order to build upon this experience further stratification into risk groups for future trials (both for local and general outcome):

Complete remission:	*CR*	*no residual GTV detectable:*	*no contour*
Uncertain complete remission:	*uCR*	*residual GTV questionable:*	*contour yes or no*
Partial remission:		*residual GTV clearly detectable:*	*contour*
Stable disease:		*no significant change in GTV (+/-10%):*	*contour*
Progressive disease:		*significant GTV increase (>10%)*	*contour*

Table 12.1 Categorization of remission (in addition to measurements)

The first evaluation for local control is at 3 month follow-up. If biopsy is performed and confirms that the primary tumour is still present this will be categorised as persistent local disease. If uncertainty exists at this time point despite MRI and gynaecological examination which are not resolved by biopsies, PET-CT scan or other measures, then the patients should be followed closely at least with gynaecological examination and MRI and/or PET-CT at the subsequent follow-ups until the questions has been resolved. The patient will be categorised as having obtained local control at 3 months, if later follow-up then shows continuous local control. On the other hand if this does not happen and the tumour eventually progresses this will be categorised as persistent disease at 3 months. Salvage hysterectomy should be performed when relevant/possible in case of persistent or recurrent local and central disease.

Pathological nodes are numbered consecutively (N1, N2,…N10) at diagnosis. If persistent or recurrent nodal disease is found on imaging during follow-up bioptical verification should be attempted. The relevant images should then be matched with the pre-treatment scans to see if these nodes match with already known nodes from time of diagnosis (i.e. N1, N2..N10) or if they represent new nodes. New nodes should be evaluated with regard to the PTV45 as inside, marginal or outside. Salvage radiotherapy +/- surgical removal of previously unirradiated nodes should be attempted if there are no signs of systemic recurrences.

Oligometastases in previously unirradiated volume should also be evaluated with regard to the possibility of salvage treatment (surgery, stereotactic body radiotherapy etc.).

The oncological outcome of intended curative salvage treatment (local, regional, systemic) should be reported in the database. Palliative treatments are not reported but the vital status should be updated at least quarterly.

In case patients are lost to follow-up as much information as possible should be gathered and reported, e.g. at least the survival status.

12.2 MORBIDITY

Physician assessed morbidity will be scored prospectively with the Common Terminology Criteria for Adverse Events (both CTCAE v3.0 and CTCAE v4.0, NCI 2003 and 2009) on a priori selected, clinical relevant endpoints regarding gastro-intestinal, genito-urinary, vaginal and several unspecific symptoms (See table above).

Both early morbidity (per definition within the first 90 days after begin of treatment) and late morbidity will be assessed. Early morbidity will be assessed with a short version of the overall morbidity assessment with selected endpoints.

The morbidity endpoints for EMBRACE 2 were selected after a consensus based on yearly interim comprehensive analyses of the EMBRACE 1 material, covering inter alia: longitudinal analyses on manifestation pattern of symptoms, evaluation of the open text

reports of the EMBRACE 1 database, cross-validation with the patient reported symptoms from the quality of life assessment, literature research and joint clinical discussions.

Case report forms are available for download at the EMBRACE 2 website.

Analyses: Morbidity outcomes will be analysed if baseline and at least one follow-up assessment have been recorded. Morbidity will be censored at time of any recurrence (local, nodal, systemic) and baseline morbidity will be taken into account in any analysis in order to differentiate between tumour-related and treatment-related symptoms.

Endpoints will be evaluated both for the overall organ at risk (bowel, rectum, bladder, vagina etc.) and for individual symptoms with prevalence rates, crude and actuarial incidences (Kaplan Meier time to event method). For selected endpoints, a dose effect relation will be investigated based on Cox proportional hazard models; independent risk factors for morbidity will be taken into account by multivariate modelling.

12.3 QUALITY OF LIFE (QOL)

QoL will be assessed prospectively with the internationally established and validated questionnaires of the European Organization for Research and Treatment of Cancer (EORTC; http://groups.eortc.be/qol).

The basic module EORTC QLQ-C30 is of general use for all cancer sites and consists of five functional scales (physical, emotional, social, role and cognitive functioning), a global health status/QoL scale and several symptom scales commonly reported by cancer patients (Aaronson NK. et al. 1993). The cervical cancer module EORTC QLQ-CX24 covers typical disease and treatment related symptoms and items regarding sexuality (Greimel E. et al. 2006). In addition, 6 clinically relevant items of the endometrial module EORTC EN-24 will be added with the permission of the EORTC QoL group (Greimel E. et al. 2011).

All questionnaires are available for download at the EMBRACE 2 website in all translations available. The time points of assessment are scheduled according to the morbidity assessment.

Analyses: In QoL reports, patients with baseline and at least one additional EORTC QLQ follow up will be included. In patients with local and/or nodal and/or systemic evidence of disease in follow-up, the EORTC QLQ data will be censored at the time of recurrence. QoL outcomes will be calculated and linearly transformed according to the scoring manual of the EORTC QoL group; results reported in mean scores (ranging from 0-100) with standard deviation and/or 95% confidence interval (Fayers PM. et al. 2001). Results will be analysed regarding differences in subscales over time in EMBRACE 2 patients and differences between the reference general population and EMBRACE 2 patients.

13 TRANSLATIONAL RESEARCH

13.1 PROGNOSTIC MARKERS

Despite the improved loco-regional control with definitive radio(chemo)therapy in high-risk patients, distant metastasis are still frequent and - in absence of effective systemic therapy options - have a large impact on cancer specific and overall survival. Tumor type (squamous versus adenocarcinoma), FIGO stage, tumor size and (extent) of lymph node involvement are well-established prognostic factors for distant metastasis. When considering the inclusion criteria of current ongoing trials that investigate the value of adjuvant chemotherapy in addition to definitive radio(chemo)therapy, there may be considerable overtreatment. Several promising (epi) genetic molecular markers (e.g. HPV-type, hypoxia markers, tumor infiltrating lymphocytes) have been identified, but none have been compared prospectively in a larger patient cohort nor are they currently applied in clinical practice.

The aim of the translational tumour research project is to establish the value of molecular prognostic markers for local and regional recurrence as well as distant metastasis in relation to well-described clinical and pathological prognostic factors. Better selection of patients at high risk of distant metastasis or recurrence will allow for a highly personalized treatment approach. While comparing tumor samples from the primary tumor with that of primary involved lymph nodes and to those at time of recurrence will help understand which factors contribute to disease progression and therapy resistance. EMBRACE II will include a large cohort of patients treated with a uniform protocol and therefore offers a unique opportunity to make progress in this field.

Paraffin embedded tumor tissue derived from biopsies of the primary tumor and available lymph node metastasis at the time of diagnosis will be collected from all consenting patients.

In addition, paraffin embedded tumor tissue derived from biopsies of local and regional recurrences or distant metastasis, if performed, will be collected. DNA will be extracted and a tissue microarray will be constructed from these paraffin embedded tissue samples, allowing for high throughput analysis. All study samples will be stored in the patient's treating center, coded under study number, until DNA extraction and tissue micro array assembly, which will be done centrally at time of study closure under pseudonymized conditions.

A pilot sub-study is envisioned for collaborating centers with facilities to perform and store snap frozen tumour tissue samples, and collect blood and serum samples (liquid biopsies). The aim of the sub-study is to apply more advanced techniques in a limited number of patients as a discovery set for novel markers of tumour sensitivity and response. Based on available evidence at the time of study closure, a more targeted approach will be undertaken, aiming to validate the most promising markers in the large cohort of patients. For this validation study, preferably more conventional techniques (i.e. hotspot mutation analysis) will be used, facilitating eventual broader clinical implementation.

13.2 PREDICTIVE MARKERS FOR RADIOTHERAPY RELATED MORBIDITY

In EMBRACE II treatment related morbidity, both clinician-assessed and patient reported, as well as health related quality of life, will be assessed prospectively in a large cohort of uniformly treated patients. This offers a unique opportunity for intensive translational research into the identification of biomarkers for the manifestation of (late) treatment-related morbidity. A sub-study is envisioned for collaborating centres with the aim to improve future individualisation of follow-up strategies and eventually treatment protocols. For this, early markers indicative of the individual patient's risk to develop treatment-induced (late) morbidity will be identified and characterised. This will also allow the development of pathomechanism-based interventions for the prevention, mitigation or amelioration of morbidity ("biological morbidity targeting").

Furthermore, indicators of treatment-related morbidities (morbidity biomarkers), assessed pre- or early within the treatment can facilitate the selection of patients with a high individual risk for (severe) treatment complications, with whom less toxic treatment strategies may be discussed with the patient to avoid excessive morbidity and to improve post-treatment HR-QoL. Compared to

outcome predicting biomarkers, much less work has been done in this field, particularly in relation to radiation dose/dose distributions (Bentzen SM. et al. 2010).

Some of the most promising morbidity biomarkers for the associated OAR include:

- Urinary bladder – urine: Urothelial degradation products, inflammatory markers, and immune response markers (Gibson RJ. & Bowen JM. 2011).
- Large bowel - faeces: Inflammatory markers, calprotectin and lactoferrin (Hille H. et al. 2009, Varela E. et al. 2009) and immune response markers (Gibson RJ. & Bowen JM. 2011, Henson CC. & Ang YS. 2012).
- Vagina - vaginal smears: Cell morphology, differentiation markers, inflammatory markers, and immune response markers (Gibson RJ. & Bowen JM. 2011, Shield PW. 1995).
- Various OAR - blood: Growth factors (various OAR), immune cells (immune system and others), immune response markers (epithelia, bone marrow), citrulline (small bowel), other serum proteins (intestine) (Lutgens LC. et al. 2003, Lacombe J. et al. 2011, Chai Y. et al. 2015, Onal C. et al. 2011).

Although many promising morbidity biomarkers have been identified over the years, none has been validated in large datasets, and none has therefore been entered into routine clinical use. Translational (morbidity) research within EMBRACE II will establish and/or optimize the respective analytical procedures, in samples from an initial (small) test population of patients. The most promising candidates for each OAR morbidity endpoint will be defined and the respective analytical procedures will be established in the section for applied and translational radiobiology (ATRAB) in Vienna. Subsequently these candidates will be analyzed in a larger cohort of patients from participating centers. Collection and storage of biological samples will be standardized to avoid center effects.

One essential prerequisite for the morbidity biomarker studies is the precise assessment and documentation of early and particularly late morbidity. This will be standardized within EMBRACE II (see “morbidity and QoL”).

14 PATIENT MATERIAL, BENCHMARKING, VALIDATION, EVALUATION AND STATISTICS

14.1 BENCHMARK OF OUTCOME AND TREATMENT RELATED PARAMETERS

EMBRACE aims at improving outcome of locally advanced cervical cancer through well-defined interventions of advanced EBRT (IMRT/IGRT), IGABT and systematic application of chemotherapy in a limited overall treatment time (section general aims 4.2.1).

EMBRACE II will be benchmarked against the outcome of the retroEMBRACE and EMBRACE cohorts and reports from literature as appropriate. The benchmark will include evaluation of overall survival, cancer specific survival, local control, pelvic control, nodal control (regional, para-aortic), distant control, morbidity (various organs and morbidity endpoints), patient reported outcome and quality of life. The prognostic characteristics of the patient populations may change over time and the evaluation will take into account major prognostic factors through stratification and/or other statistical methods such as propensity score weighting. The general hypothesis on survival (section 5.3.1) and the specific hypotheses on specific clinical endpoints (section 5.3.3). will be tested.

Treatment related factors ("interventions" section 4.1) will be benchmarked and compared with those recorded in the EMBRACE and RetroEMBRACE cohort: target selection, tumor and target volumes, EBRT techniques (IMRT/IGRT) and BT techniques (adaptive intracavitary/interstitial), irradiated volumes, target doses, organ doses, chemotherapy administration, and OTT. Change of practice compared with EMBRACE with regard to technique, dose and volume will be quantified, and the specific hypotheses described in section 5.3.2. will be tested (table 5.1).

The protocol compliance will be evaluated both on the level of the entire EMBRACE II cohort as well as on a centre level. In particular, the performance with regard to the major EMBRACE II interventions will be monitored: BT technique and dose prescription, reduction of vaginal loading, utilization of IMRT/VMAT, utilization of daily IGRT and limited margins, EBRT target concepts related to the primary tumour, EBRT dose prescription and fractionation, selection of elective EBRT target volume, and application of concomitant chemotherapy.

14.2 VALIDATION OF DOSE AND VOLUME EFFECTS

EMBRACE II validates dose and volume effects as found in RetroEMBRACE and EMBRACE I (section specific aims 4.2.2). In EMBRACE I and RetroEMBRACE, dose-effect relationships related to the BT high dose regions have been found for different endpoints (section introduction 3.3). These dose-effect relationships will be validated in the EMBRACE II cohort.

14.3 EXPLORATION AND EVALUATION OF DOSE AND VOLUME EFFECTS

EMBRACE II explores and evaluates dose effect relationships related to intermediate EBRT and BT dose and volume levels in the EMBRACE II cohort comparable to RetroEMBRACE and EMBRACE I for BT high dose regions. Finally, dose and effects of chemotherapy administration will be evaluated.

14.4 IDENTIFICATION OF PROGNOSTIC AND PREDICTIVE PARAMETERS

EMBRACE II will test beside dose and volume various prognostic and predictive parameters for disease outcome, morbidity and quality of life and compare with EMBRACE and literature reports as appropriate.

14.5 STATISTICS

Data will be reported with mean and standard deviation / 95% confidence interval or median and interquartile range, depending on the distribution. Proportions will be evaluated as number of patients with and without the characteristic and as a percentage.

Time-to-event data will be analyzed using the actuarial Kaplan Meier method; time will be calculated with the date of diagnosis as the starting date and the date of the defined event. Data from patients who had not reached the endpoint at the time of the last follow-up will be treated as censored observations.

Local control will be defined as absence of disease in the cervix, uterus, upper vagina and parametria on clinical examination, imaging, and biopsy. Pelvic control will be defined as absence of local and nodal disease within the pelvis. Nodal control will be defined as absence of nodal disease within the pelvis and within the para-aortic nodes. Systemic control will be defined as absence of any organ recurrence and extra-pelvic and extra-aortic nodal recurrence.

Overall survival will be defined as death from any cause and cancer specific survival as death from cervical cancer (disease progression or treatment-related morbidity).

Morbidity outcomes will be analyzed for organs and specific endpoints within one organ if baseline and at least one follow-up assessment have been recorded. Morbidity will be censored at time of any recurrence (local, nodal, systemic) and baseline morbidity will be taken into account in any analysis in order to differentiate between tumor-related and treatment-related symptoms.

Serious late morbidity will be defined as grade 3 (severe), 4 (life-threatening) or 5 (death) complications present at or after 91 days from completion of treatment. Morbidity analyses will also be performed on grade 1 (mild) and grade 2 (moderate) complications.

Endpoints will be evaluated both for the overall organ at risk (bowel, rectum, bladder, vagina etc.) and for individual symptoms with prevalence rates, crude and actuarial incidences (Kaplan Meier method).

Several a priori chosen, clinically relevant patient-, disease- and treatment characteristics (prognostic and predictive factors) will be evaluated as risk factors for outcome events in uni- and multivariable analyses (Cox proportional hazards model). Hazard Ratios (HR) and 95% confidence intervals (CI) will be estimated.

Cox proportional hazards model estimates will be used to evaluate several dose and volume effect relationships with regard to selected endpoints, such as local control and morbidity. Dose parameters will be normalized to 2Gy per fraction (EQD2) using the linear-quadratic model with α/β ratio of 3Gy.

Advanced modeling studies and studies for comparing various cohorts using advanced statistical methods (e.g. propensity score) are foreseen.

Significance level will be set 2-sided at 5% and methods to correct for the increased probability of Typ 1 errors of multiple testing will be applied. All statistical analyses will be performed using the Statistical Package for the Social Sciences IBM SPSS (Armonk, NY: IBM Corp).

15 ACCREDITATION, DUMMY RUN, DATA MONITORING, QUALITY ASSURANCE AND CONTINUOUS EDUCATION

EMBRACE II accreditation includes an evaluation of the current practice of each centre through a "compliance questionnaire" on brachytherapy, external beam radiotherapy and chemotherapy. Furthermore, participation in a dummy run on contouring, treatment planning, and reporting is required. These procedures will ensure that the centre has the infrastructure and expertise needed to comply with the protocol requirements of EMBRACE II.

It is the responsibility of the study coordinators to evaluate and approve participation. Approval requires a successful dummy run with an individual assessment of the performance of each participating centre. Approval of the institution/investigator must be accomplished prior to any patient enrolment in the protocol.

There is no formal on site monitoring, but patient files and treatment plans must be kept at least until closure of the protocol and final analysis of the results is obtained. Continuous quality assurance during the study is projected. The procedure will include a monitoring of the treatment planning parameters of interest for this study and an overall check of the CRFs.

A continuous education programme focussing on contouring will be set up and will give access to online education throughout the study period. Continuous education may be extended to include morbidity assessment and scoring.

15.1 COMMITMENT LETTER, COMPLIANCE QUESTIONNAIRE AND PROCESS DOCUMENT

Each institution has to submit a Commitment Letter to the study coordinators. The centres are also required to complete a web based compliance form which documents the current practice of the centre demonstrating that the centre in question will be able to meet the requirements of the protocol with regard to number of patients as well as EBRT and brachytherapy treatment techniques.

The compliance criteria are:

- Treatment of >10 patients per year qualifying for enrolment in EMBRACE II
- Both EBRT and BT are performed in the centre
- Routine use of IMRT or VMAT
- Routine use of daily IGRT with bony fusion
- Routine use of MRI guided IGABT with applicator in situ (at least for first fraction)
- Routine use of the combined intracavitary-interstitial technique when needed (~20-50% of patients)

15.2 DUMMY RUN

Based on evaluation of the compliance questionnaire, the study coordinators will decide if the centre is ready to proceed with the Dummy Run. The Dummy Run will ensure that the contouring and treatment planning is consistent with the protocol requirements. The Dummy Run will include a training and registration phase as well as submission of contouring and dose planning for evaluation. Based on this, the study coordinators will evaluate if the centre is ready to participate in EMBRACE II.

15.2.1 TRAINING, REGISTRATION, AND SUBMISSION

- Contouring training for EBRT and BT: self-assessment by each physician who will be contouring for EMBRACE II
- EBRT planning exercise: self-assessment by each institution (physicists/physicians)
- Registration of 5 consecutive patients in a registration database within 6 months: self-registration
- Submission of EBRT and BT contours: one set of contours is submitted per institution for evaluation by study co-ordinators
- Submission of an EBRT dose plan: documentation of one case with dose and volume reporting as well as isodose screenshots is submitted per institution for evaluation by study co-ordinators

Contouring training for BT and EBRT will be available online using the Addenbrooke's Contouring Tool (ACT). Contouring will be performed by each physician according to the EMBRACE II guidelines as outlined in chapters 9 and 10. Instructions, case descriptions, diagnostic information and contouring guidelines will be available online in ACT. Tools for self-assessment of the training contours will be available.

An EBRT planning exercise will be downloadable from the EMBRACE website for training of dose planning. IMRT or VMAT dose planning is performed according to the EMBRACE II guidelines in chapter 9. A reporting sheet will be available for DVH reporting and the results can be compared to an "expert plan".

When contouring and dose planning training has been performed, the centre can proceed with registration of 5 consecutive patients in a registration database (within 6 months). The registration database will be a copy of the EMBRACE II database with on-line reporting of 1) Status at diagnosis, 2) Status at brachytherapy and 3) Treatment and DVH parameters. Furthermore, screen dumps of EBRT and BT contours and dose plans are required, as well as cartoons documenting clinical examination at diagnosis and at BT.

After the registration phase, a final submission of EBRT and BT contouring and dose planning has to be performed through the ACT tool (one submission per institution). Specific instructions will be available on the EMBRACE web site.

15.2.2 EVALUATION BY STUDY COORDINATORS

After all information is fully available, the study coordinators will evaluate:

- The submitted EBRT and BT contours
- The submitted EBRT plan
- The completed 5 registered patients

Centres already participating in EMBRACE and having accrued at least 25 patients during the whole EMBRACE period are not required to enter the registration phase of 5 consecutive patients or to complete brachytherapy contouring training.

15.3 DATA MONITORING

Continuous data monitoring throughout the study will be based on reviewing of data reporting, clinical cartoons and contouring/treatment planning screen dumps. The data monitoring will be performed by the EMBRACE II study office.

A committee for patient safety and data monitoring will be established consisting of representative(s) from radiation oncology, medical physics and statistics as appropriate. This committee will meet regularly in large intervals to check the relevant respective issues in the on-going EMBRACE II study.

15.4 CONTINUOUS EDUCATION

Based on ACT, cases will be available for continuous training along the same principles of the dummy run. Annual contouring workshops will be performed at the annual EMBRACE meetings. MDs who are not attending the annual EMBRACE meeting must perform the annual contouring remotely.

16 PATIENT ENROLLMENT PROCEDURE

Patients' registration will only be accepted from authorized investigators in the Vienna study office. A patient can be registered after verification of eligibility by the EMBRACE 2 study office according to the registration form, which includes details on inclusion and exclusion criteria. In addition, the following information must be provided:

- Patients' centre ID (made up of the centres' acronym and the following patient number)
- Patients' initials
- Patients' birthday
- Date of scheduled treatment start

If the patient is included in the study, a number will be allocated to the patient (patient sequential identification number). This number has to be recorded by the investigator. For future communication between the investigator and the EMBRACE 2 database or the study coordinators, the patients' centre ID should be used. After successful registration of a patient, the investigator informs the centre that the data of this patient can be entered in the database. The registration form will be saved electronically by the study office.

Patients must be registered and accepted before any treatment procedures are initiated.

17 CASE RECORD FORMS, PROCEDURES FOR DATA COLLECTION, EMBRACE II DATABASE

Patient data will be collected by web based CRF system. The CRFs must be completed and reported according to the time table below.

It is the responsibility of the investigator to check that all CRFs are completely, correctly and timely filled out.

The following CRFs will be used:

- Registration Form: To be reported before treatment.
- Status at diagnosis Form: To be reported at start of treatment
- Base Line Morbidity Form: To be reported at start of treatment
- Status at BT Form: To be reported within 4 weeks after treatment completion
- Treatment and DVH Form: To be reported within 4 weeks after treatment completion.
- Follow-up Form: To be completed within 4 weeks after each regular follow-up. Visits not scheduled should also be reported within 4 weeks if they concern an event of interest such as recurrence or morbidity
- Vital status Form: In case of any event, this part should be updated frequently.
- Off study Form: Should be reported within 4 weeks after the off-study occurs.
- Curative salvage treatment Form: should be reported within 4 weeks after salvage treatment completion.

After completion of a CRF, a hard copy should be kept in the investigators own patient study file The patient study file is a patient specific portfolio including a paper copy of the registered CRF data for each patient.

At the EMBRACE 2 website the study protocol, appendices, quality of life questionnaires, patient information folders and any other pertinent information in relation to the study will be available.

The EMBRACE 2 database will be placed at the Aarhus University Hospital, Denmark. The Danish Board of Registry has approved the database (pending). Access to the database can be gained through the EMBRACE 2 website, by providing a valid username and password. Entering of all data will be carried out over the Internet using a standard web-browser.

All data will be encrypted before transmission. A number of validation procedures will be installed in order to ensure a high data quality. There will be sent out reminders of all follow-up visits and examinations, and data from these will also be entered via the Internet.

Each centre will be able to log on to the database via the EMBRACE 2 website at any time in order to see descriptive data and number of included patients for own centre as well as for the entire study population. The database will allow for data extraction in Microsoft Windows Excel and the Statistical Package for the Social Sciences IBM SPSS (Armonk, NY: IBM Corp).

18 ETHICAL CONSIDERATIONS

18.1 PATIENT PROTECTION

This study will be conducted in agreement with the Declaration of Helsinki. The protocol has been written, and the study will be conducted according to the ICH Harmonized Tripartite Guideline for Good Clinical Practice. The protocol will be approved by the local Research Ethics Committee in accordance with national guidelines and legislation in the participating centres.

18.2 SUBJECT IDENTIFICATION

To ensure patient privacy, the name of the patient will not be asked for nor recorded at the Study Office. A sequential identification number will be automatically attributed to each patient registered in the trial. This number will identify the patient and must be included on all case report forms. In order to avoid identification errors, patient's initials (maximum of 4 letters) and date of birth and local chart number (if available) will also be recorded, only on the registration form.

18.3 INFORMED CONSENT

Patient information forms will be produced in all the relevant languages, an English version is included as Appendix 10. All patients will be informed by the radiation oncologist of the aims and registration process of the study, the possible adverse events, the procedures and possible hazards to which they will be exposed. The radiation oncologist will hand out the written patient information form, and before deciding to participate, the patient will be offered enough time for consideration the study.

The consent form will include study participation and subject registration, processing and recording of data, participation to quality of life investigation and collection and storage of a paraffin embedded tumour tissue sample under study code for future research. Patients will be informed as to the strict confidentiality of their patient data, but that their medical records may be reviewed for study purposes by authorized individuals other than their treating physician.

It will be emphasized that the participation is voluntary and that the patient is allowed to refuse further participation in the protocol whenever she wants. This will not prejudice the patient's subsequent care. Documented written informed consent must be obtained for all patients included in the study before they are registered at the Study Office. This must be done in accordance with the national and local regulatory requirements.

For European Union member states, the informed consent procedure must conform to the ICH guidelines on Good Clinical Practice. This implies that "the written informed consent form should be signed and personally dated by the patient or by the patient's legally acceptable representative".

18.4 ADVANTAGES AND DISADVANTAGE FOR THE PATIENTS

The radiation oncologist will inform the patients about the possible risks and side effects connected to the involved treatments. At present the standard treatment for patients with locally advanced cervical cancer is EBRT, concurrent chemotherapy with Cisplatin and brachytherapy. Although these same treatment modalities will be used, EMBRACE II aims are to implement an image guided risk adapted dose and volume prescription protocol according to interventions specified in chapter 4. All or some of these advanced technological interventions will be implemented as standard treatment in participating centres, but there may be deviations in the extent to which the standard treatment differs from the study protocol per participating institution. Nonetheless, it is expected that minor deviations between the study protocol and the standard treatment in a centre will not alter the chance of tumour control and treatment related morbidity for a given individual patient. The written patient information should be adapted if necessary to accommodate the institutional standard treatment policy and needs subsequent approval by the local ethics committee.

Advantages of study participation include external review and quality assurance of the treatment planning and execution, and knowledge that the individual patient data will contribute to the understanding and future improvement of treatment for locally advanced cervical cancer. A possible disadvantage of study participation may be the additional time involved in filling out quality of life questionnaires.

19 PUBLICATION OF DATA

1. The major authors of a manuscript consist of the core research group, which substantially prepared and performed the research in agreement with the coordinators of the EMBRACE 2 study and the EMBRACE 2 research group. It usually covers the first author as major contributing scientist, 1-2 active co-workers and 1-2 supervising seniors, according to input.

2. The coordinators of the EMBRACE 2 study and the EMBRACE 2 research group are appropriately represented (minimum 2 persons: Richard Pötter, Kari Tanderup, Jacob Lindegaard, Christian Kirisits).

3. The principle investigators of the centers, who contributed the majority of patients, are listed as co-authors. The principal investigator (PI) may indicate another person from the institution to replace him or her, if appropriate. This co-authorship should be minimum 5 centers in addition to Vienna and Aarhus (as represented by the EMBRACE 2 coordinators). The total number of co-authors based on patient numbers depends on the individual journals requirements.

   If manuscripts cover certain sub-cohorts of the overall EMBRACE 2 patients recruited, the number of patients for the specific analysis of the manuscript is calculated per center, a ranking of the centers is performed according to these numbers.

4. Some journals allow for inclusion of a 'collaborative group', with associated names, which may even be tagged in PubMed. If possible, such a 'collaborative group' should be included. The number of collaborators should be graduated, according to the overall recruiting rate of the center: the PI and 1-2 persons designated by the PI (one physicist as appropriate).

20 STUDY OFFICE, STUDY COORDINATORS, STUDY STRUCTURE, COMMUNICATION

The overall collection of all data and all follow-up for all EMBRACE II patients (e.g. CRFs) remains located in Vienna and is done by the study office (including follow-up of EMBRACE I). The infrastructure of the study office and the communication with centres follows the experience as gained in EMBRACE. E.g. the weekly EMBRACE meeting in Vienna (about 90 minutes) with review of cases and participation of study office, medical physicists, radiation oncologists, clinical and research fellows is to be continued. Regular review of cases will require as in EMBRACE I about 0.5 academic FTE.

In addition, the responsibilities for guiding the brachytherapy and the EBRT branch of EMBRACE II are shared: Vienna will guide the brachytherapy part and Aarhus the EBRT part.

In addition, there will be one regional centre in Utrecht, which takes the responsibility for guiding all centres in the Netherlands in close cooperation with Vienna and Aarhus.

20.1 STUDY-OFFICE EMBRACE II VIENNA (AT PRESENT: 09/2015):

Ian Dilworth (0.5 FTE), Thomas Liederer (0.5 FTE), Eva Weisz (1.0 FTE), academic position (0.5 FTE)
Department of Radiotherapy, Medical University of Vienna, Vienna, Austria

Telephone: +43 1 40 400 2720; E-mail: @akhwien.at

Aarhus-office: 0.5 FTE academic position

20.2 STUDY COORDINATION:

Principal Investigator:

Richard Pötter, Vienna, Austria: Richard.Poetter@akhwien.at

Overall coordinators:

Richard Pötter, Vienna, Austria: richard.poetter@akhwien.at (overall and BT)
Kari Tanderup, Aarhus, Denmark: karitand@rm.dk (overall and EBRT)
Christian Kirisits, Vienna, Austria: christian.kirisits@akhwien.at (overall and BT)
Jacob Lindegaard, Aarhus, Denmark: jacolind@rm.dk (overall and EBRT)

Regional coordinators in the Netherlands:

Ina Juergenliemk-Schulz, Utrecht (for all participating centres in the Netherlands)
Astrid de Leeuw, Utrecht (for all participating centres in the Netherlands

Continuous Education:

Li Tee Tan, Cambridge University

Senior advisors:

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Statistician:

NN, Vienna
Søren Møller Bentzen, Maryland, Baltimore, USA (sbentzen@som.umaryland.edu)

Communication

All coordinators, the senior advisors and the study secretariat communicate regularly (at least twice per year) on relevant questions of the EMBRACE study and take joint decisions.

Each year an annual meeting is held, where the current activities are reported, discussed and future developments discussed and decided (following the annual EMBRACE meetings, which took place from 2008-2015 in Brussels (2008) and then in Vienna). All participating centres are invited for this meeting, including all centres which participated in EMBRACE I.

This meeting forms the body of the study committee: one member of each participating centre, all coordinators, senior advisors, statistician, study office

The major form of continuous communication is through internet, direct e-mailing and the EMBRACE webpage which has an open access and a password protected access part.

21 EMBRACE RESEARCH GROUP

In order to take advantage of the large prospective collection of data as established in EMBRACE (and RetroEMBRACE, >2000 patients with cervix cancer) a multi-disciplinary EMBRACE Research Group has been established in 12/2012. Structures and Principles and Responsibilities for Research have been set up. Regular physical meetings have been held in addition to research visits through researchers in particular going to Vienna, Aarhus and Utrecht and additional much internet communication.

Each centre participating in EMBRACE can also participate in the EMBRACE Research Group according to possibilities of the person interested and the respective centre. On request, also fellows not working in EMBRACE centres can join this Research Group which has been successful so far in several cases.

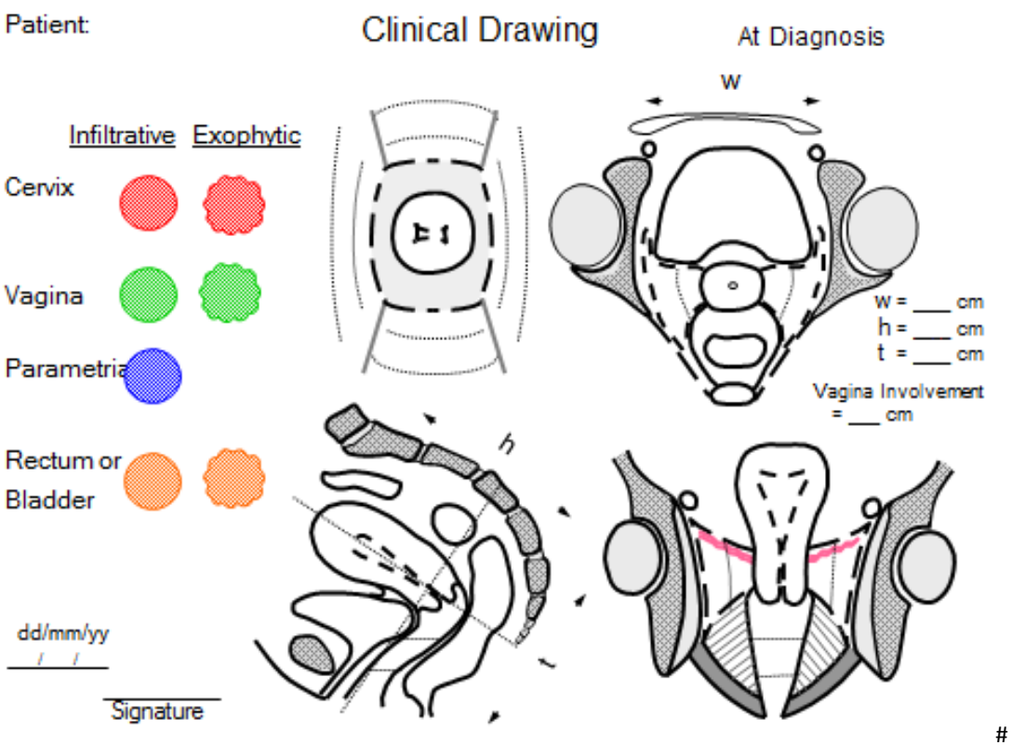
The aim of this EMBRACE research group is to build up a large scientific body of clinical evidence based on the large database of EMBRACE, RetroEMBRACE and the upcoming EMBRACE II study. The topics of research are widespread and related to the whole field of areas investigated in the EMBRACE studies. So far, 13 publications on various aspects of EMBRACE and RetroEMBRACE could be published in leading international journals and 4 more are in the submission process. This ongoing process is planned to be followed and extended in parallel to the implementation of EMBRACE II and will benefit from the maturation of data from EMBRACE I and the upcoming data of EMBRACE II.

The coordination of this EMBRACE research group is the group of coordinators of the EMBRACE I and II studies (n=6) with the principal coordinators Kari Tanderup and Richard Pötter.

So far, there is only limited specific sponsoring for this EMBRACE Research Group (travel and accommodation support for group meetings).

22 APPENDICES

22.1 APPENDIX 1 STANDARD CLINICAL DIAGRAM



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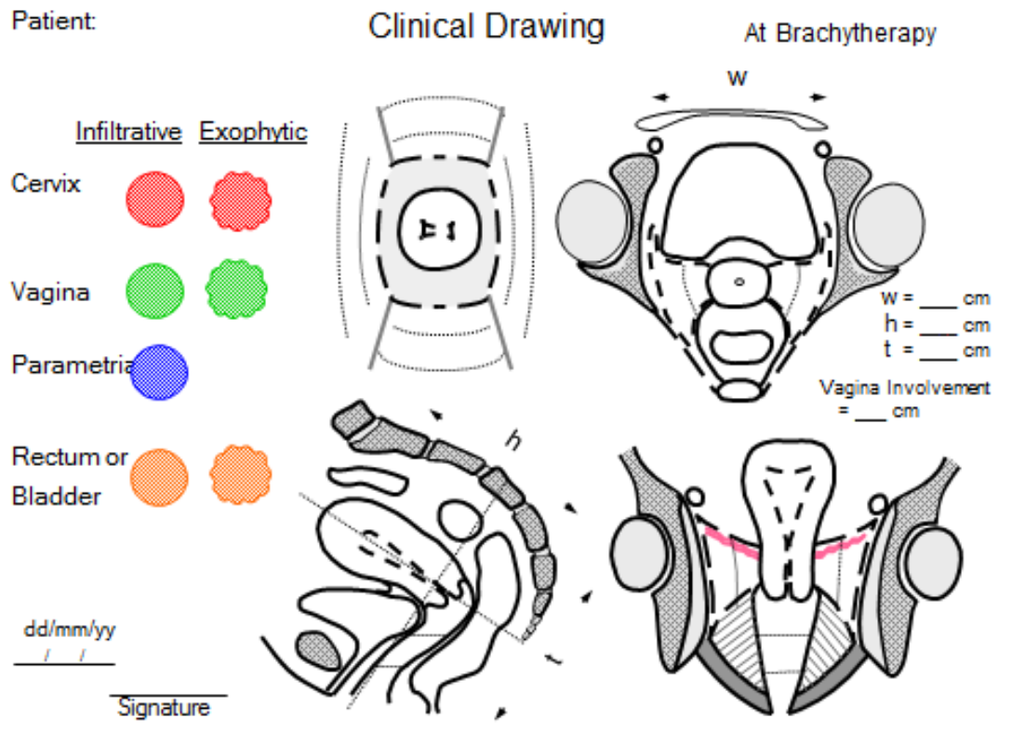

Clinical drawings have traditionally been used to depict the extent of disease based on clinical examination. Tumour that is visible or palpable is drawn manually, usually on paper templates. With the advent of image-guided brachytherapy in cervical cancer, an argument can be made to also incorporate disease findings from imaging examinations into these "clinical drawings".

We aim to develop standarized methods for the creation of these clinical drawings, that would hopefully, eventually, lead to some level of standardization of clinical drawings across different physicians, across different centres, across time, and ultimately, across multiple tumour sites as well.

"At Diagnosis" or "At Brachytherapy" should be marked on each drawing. Treatment received to date, including any external beam radiotherapy (EBRT) delivered to date, should be noted.

Four different views or planes are illustrated: **Specular, Axial, Coronal, and Sagittal.** Dotted lines of the vagina represent a virtual division in thirds. Dotted lines in the parametria represent a border between the proximal and distal half of the parametria. A pink line in the coronal view represents uterine artery.

Tumour dimensions: **height (h), width (w),** and **thickness (t)** should be documented. Height, defined on the sagittal view, is measured along the long axis of the uterus. Thickness, defined on the sagittal view, is measured perpendicular to the height. Width, measured on the axial view, represents the greatest lateral diameter. Vaginal extension of tumour is specified separately.

The date of the evaluation should be recorded. The drawing should be signed.

Manual colour drawing: There are three basic options for the drawing of uniform and reproducible universal clinical drawings. A **first option** utilizes coloured marker pens and a colour legend. Four different, specific colours are used. In addition, tumour can be identified as exophytic in nature by changing the border as outlined in the legend. There are certain advantages to coloured marker approach, such as straightforward and quick implementation, and immediately recognizable distinctions of different anatomical areas of involvement. However, the incorporation of up to four specifically coloured markers into routine clinical practice in clinics and operating rooms may be a challenge to do consistently. Ensuring the consistent availability of the markers in multiple work environments, with multiple caregivers, may not be practical.

Manual line drawing: A **second option** uses a legend that requires only a single pen to convey the same amount of information. Different anatomical areas of involvement are demonstrated using simple line patterns, with a specific pattern for each anatomical site according to the legend. Again, any exophytic tumour can be delineated with a special border. Unlike the colour approach, consistent availability of a pen at any location or with any caregiver should not be an issue. A drawback is that the drawings may appear less readily discernible. However, after a brief learning curve, practioners should be able to draw and read such drawings with ease. This approach seems the most practical and reliable, and could be adopted widely.

Electronic drawing: Finally, a **third option** involves a computer-based method to create the clinical drawings. This method involves electronic versions of the colour or background lines templates, with electronically modifiable tumour cartoons. The cartoons can be modified for the individual patient by way of a Powerpoint© type of application, using relatively simple tools (Figures 3, 4). Clinical drawings can be stored and transmitted electronically. Drawings for physical medical chart record-keeping would have to be printed. Advantages of an electronic approach include the consistency and clarity of the drawings produced. In addition, the electronic format facilitates the storage, access, and distribution of the drawings. Electronic templates could be made available on the internet for clinical use. However, logistical issues such as the availability of a local computer with the appropriate software, the availability of a local (colour) printer for generation of hard copies, and the clinician's familiarity with the software tools needed, may preclude this electronic method's widespread adoption.

Electronical drawing tools will be available for download at the website.

22.2 APPENDIX 2 GYN GEC ESTRO RECOMMENDATIONS I-IV, ICRU 88

Haie-Meder C, Pötter R, Van Limbergen E, Briot E, De Brabandere M, Dimopoulos J, Dumas I, Hellebust TP, Kirisits C, Lang S, Muschitz S, Nevinson J, Nulens A, Petrow P, Wachter-Gerstner N; Gynaecological (GYN) GEC-ESTRO Working Group. 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. 2005 Mar;74(3):235-45. Review.

Abstract

BACKGROUND AND PURPOSE: Brachytherapy (BT) plays a crucial role in the management of invasive cervix cancer from stage I to IV. Intracavitary techniques are based on afterloading devices, with different types of applicators. CT and/or MRI compatible applicators allow a sectional image based approach with a better assessment of gross tumour volume (GTV) and definition and delineation of target volume (CTV) compared to traditional approaches. Accurate and reproducible delineation of GTV, CTV and PTV, as well as of critical organs has a direct impact on BT treatment planning, especially if it is possible to adapt the pear-shape isodose by optimisation using DVH analysis. When introducing a 3D image based approach for GTV and CTV assessment, there is a need for a common language to describe the concepts and to define the terms which are to be used.
METHODS: In 2000, GEC-ESTRO decided to support 3D imaging based 3D treatment planning approach in cervix cancer BT with the creation of a Working Group. The task was to describe basic concepts and terms and to work out a terminology enabling various groups working in this advanced field to use a common language. The recommendations described in this report were proposed based on clinical experience and dosimetric concepts of different institutions (IGR, Leuven, Vienna) and were stepwise validated against the background of different clinical experience.
CONCLUSIONS: As GTV and CTV for BT change significantly during treatment, time frame for assessment of GTV and CTV for BT is specified in this report: at time of diagnosis GTV(D), CTV(D) and at time of BT GTV(B), CTV(B). Furthermore, CTV for BT is defined related to risk for recurrence: high risk CTV and intermediate risk CTV. Beside verbal descriptions detailed examples are given, partly in form of schematic drawings.

Pötter R, Haie-Meder C, Van Limbergen E, Barillot I, De Brabandere M, Dimopoulos J, Dumas I, Erickson B, Lang S, Nulens A, Petrow P, Rownd J, Kirisits C; GEC ESTRO Working Group. 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. 2006 Jan;78(1):67-77.

Abstract

The second part of the GYN GEC ESTRO working group recommendations is focused on 3D dose-volume parameters for brachytherapy of cervical carcinoma. Methods and parameters have been developed and validated from dosimetric, imaging and clinical experience from different institutions (University of Vienna, IGR Paris, University of Leuven). Cumulative dose volume histograms (DVH) are recommended for evaluation of the complex dose heterogeneity. DVH parameters for GTV, HR CTV and IR CTV are the minimum dose delivered to 90 and 100% of the respective volume: D90, D100. The volume, which is enclosed by 150 or 200% of the prescribed dose (V150, V200), is recommended for overall assessment of high dose volumes. V100 is recommended for quality assessment only within a given treatment schedule. For Organs at Risk (OAR) the minimum dose in the most irradiated tissue volume is recommended for reporting: 0.1, 1, and 2 cm3; optional 5 and 10 cm3. Underlying assumptions are: full dose of external beam therapy in the volume of interest, identical location during fractionated brachytherapy, contiguous volumes and contouring of organ walls for >2 cm3. Dose values are reported as absorbed dose and also taking into account different dose rates. The linear-quadratic radiobiological model-equivalent dose (EQD2)-is applied for brachytherapy and is also used for calculating dose from external beam therapy. This formalism allows systematic assessment within one patient, one centre and comparison between different centres with analysis of dose volume relations for GTV, CTV, and OAR. Recommendations for the transition period from traditional to 3D image-based cervix cancer brachytherapy are formulated. Supplementary data (available in the electronic version of this paper) deals with aspects of 3D imaging, radiation physics, radiation biology, dose at reference points and dimensions and volumes for the GTV and CTV (adding to [Haie-Meder C, Pötter 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 2005;74:235-245]). It is expected that the therapeutic ratio including target coverage and sparing of organs at risk can be significantly improved, if radiation dose is prescribed to a 3D image-based CTV taking into account dose volume constraints for OAR. However, prospective use of these recommendations in the clinical context is warranted, to further explore and develop the potential of 3D image-based cervix cancer brachytherapy.

Hellebust TP, Kirisits C, Berger D, Pérez-Calatayud J, De Brabandere M, De Leeuw A, Dumas I, Hudej R, Lowe G, Wills R, Tanderup K; Gynaecological (GYN) GEC-ESTRO Working Group. 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. 2010 Aug;96(2):153-60.

Abstract

Image-guided brachytherapy in cervical cancer is increasingly replacing X-ray based dose planning. In image-guided brachytherapy the geometry of the applicator is extracted from the patient 3D images and introduced into the treatment planning system; a process referred to as applicator reconstruction. Due to the steep brachytherapy dose gradients, reconstruction errors can lead to major dose deviations in target and organs at risk. Appropriate applicator commissioning and reconstruction methods must be implemented in order to minimise uncertainties and to avoid accidental errors. Applicator commissioning verifies the location of source positions in relation to the applicator by using auto-radiography and imaging. Sectional imaging can be utilised in the process, with CT imaging being the optimal modality. The results from the commissioning process can be stored as library applicators. The importance of proper commissioning is underlined by the fact that errors in library files result in systematic errors for clinical treatment plans. While the source channel is well visualised in CT images, applicator reconstruction is more challenging when using MR images. Availability of commercial dummy sources for MRI is limited, and image artifacts may occur with titanium applicators. The choice of MR sequence is essential for optimal visualisation of the applicator. Para-transverse imaging (oriented according to the applicator) with small slice thickness (< or =5 mm) is recommended or alternatively 3D MR sequences with isotropic voxel sizes. Preferably, contouring and reconstruction should be performed in the same image series in order to avoid fusion uncertainties. Clear and correct strategies for the applicator reconstruction will ensure that reconstruction uncertainties have limited impact on the delivered dose. Under well-controlled circumstances the reconstruction uncertainties are in general smaller than other brachytherapy uncertainties such as contouring and organ movement.

Dimopoulos JC, Petrow P, Tanderup K, Petric P, Berger D, Kirisits C, Pedersen EM, van Limbergen E, Haie-Meder C, Pötter R. 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. 2012 Apr;103(1):113-22.

Abstract

The GYN GEC-ESTRO working group issued three parts of recommendations and highlighted the pivotal role of MRI for the successful implementation of 3D image-based cervical cancer brachytherapy (BT). The main advantage of MRI as an imaging modality is its superior soft tissue depiction quality. To exploit the full potential of MRI for the better ability of the radiation oncologist to make the appropriate choice for the BT application technique and to accurately define the target volumes and the organs at risk, certain MR imaging criteria have to be fulfilled. Technical requirements, patient preparation, as well as image acquisition protocols have to be tailored to the needs of 3D image-based BT. The present recommendation is focused on the general principles of MR imaging for 3D image-based BT. Methods and parameters have been developed and progressively validated from clinical experience from different institutions (IGR, Universities of Vienna, Leuven, Aarhus and Ljubljana) and successfully applied during expert meetings, contouring workshops, as well as within clinical and interobserver studies. It is useful to perform pelvic MRI scanning prior to radiotherapy ("Pre-RT-MRI examination") and at the time of BT ("BT MRI examination") with one MR imager. Both low and high-field imagers, as well as both open and close magnet configurations conform to the requirements of 3D image-based cervical cancer BT. Multiplanar (transversal, sagittal, coronal and oblique image orientation) T2-weighted images obtained with pelvic surface coils are considered as the golden standard for visualisation of the tumour and the critical organs. The use of complementary MRI sequences (e.g. contrast-enhanced T1-weighted or 3D isotropic MRI sequences) is optional. Patient preparation has to be adapted to the needs of BT intervention and MR imaging. It is recommended to visualise and interpret the MR images on dedicated DICOM-viewer workstations, which should also assist the contouring procedure. Choice of imaging parameters and BT equipment is made after taking into account aspects of interaction between imaging and applicator reconstruction, as well as those between imaging, geometry and dose calculation. In a prospective clinical context, to implement 3D image-based cervical cancer brachytherapy and to take advantage of its full potential, it is essential to successfully meet the MR imaging criteria described in the present recommendations of the GYN GEC-ESTRO working group

22.3 APPENDIX 3. COMPLIANCE QUESTIONNAIRE

		Aims for EMBRACE II
# patients	Number of cervix cancer patients treated in your institution with radical radiotherapy in the past 12 months (calendar year or year to date) (IMPORTANT: indicate only the number of patients treated with BOTH EBRT and BT in your institution) Answer category: Indicate number	
U	Estimated number of patients to be enrolled in EMBRACE II per year Answer category: Indicate number	*Above 10 pts per year*
Treatment planning scan EBRT	Which imaging do you perform for EBRT treatment planning (with the patient in fixation on flat couch in the treatment position): Answer categories (several possible): CT MRI PET-CT	*CT is required*
BT	What imaging do you perform with the applicator in place? Answer categories (one answer possible): MRI for all applicator insertions MRI for first applicator insertion and CT for subsequent insertions CT for all insertions Other (free text)	*MRI with applicator in place for at least the first applicator insertion. 3D imaging (CT or MRI) must be done for all insertions.*
	Number of cervix cancer patients treated with combined intracavitary-interstitial technique (“Vienna applicator” or “Utrecht applicator” style) in the past 12 months (calendar year or year to date):	*Application of needles in >20% of patients*

	Answer category: Indicate number	
EBRT	What is your bladder filling strategy for external beam radiotherapy (planning and on treatment)? Answer categories (one answer possible): Intent of full bladder Specific drinking protocol with specification of voiding and amount of fluid intake Empty bladder	*Drinking protocol with specification of voiding and amount of fluid intake*
	Number of cervix cancer patients treated with IMRT/VMAT in the past 12 months (calendar year or year to date) Answer category: Indicate number	*Application of IMRT in 90% of patients*
	Overall experience with IMRT: Number of gynae/rectum/bladder patients treated with IMRT during the past 12 months (approximate number) Answer category: 0-20 20-50 >50	
	How often is image guidance performed during external beam radiotherapy? Answer categories (one answer possible): Daily Weekly First 1-5 fractions Other (free text)	*Daily image guidance and bony registration*
	Which kind of image guidance is used during external beam radiotherapy? Answer categories (several possible): CBCT (kV CT) kV orthogonal	*Modalities suitable for bony registration, which can be CBCT, EPID, orthogonal kV, MVCT*

	EPID MVCT Other (free text)	
	How is patient set up performed? Answer categories (one answer possible): Skin marks On line (daily) couch correction based on bony registration Off line couch correction based on bony registration Couch correction based on soft tissue registration Other (free text)	*Online daily couch correction according to bony fusion*
	Which CTV to PTV margin is used for the elective lymph node target (in mm): Lateral: Ant-post: Cranio-caudal:	*PTV margin ≤5mm*
	To which dose do you boost lymph nodes: Answer categories (several answers possible): For each option: a free text box will be available for comments e.g. for criteria for boosting. no boost 50-55Gy 55-60Gy >60Gy	*Lymph node boosting is up to the institution and may be according to size of node. However, a certain prescription is recommended in the protocol.*
Chemotherapy	Which alternative chemotherapy schedules do you apply, in case concomitant chemotherapy cannot be delivered? Answer categories: Free text	
	Adjuvant chemotherapy: in which patients and with which schedule to you apply	

	adjuvant chemotherapy? Answer categories: Free text	
Treatment planning systems	Which treatment planning system (vendor and version) are you using for EBRT Answer categories: Free text	
	Which treatment planning system (vendor and version) are you using for brachytherapy Answer categories: Free text	
Substudies	Are you interested in participating in translational research? Answer categories (several answers possible): Yes, by sending samples to other departments for analysis Yes, by performing analyses in your own laboratory No	
	Are you interested in participating in an EBRT substudy involving daily CBCT guided EBRT with delivery of plan of the day (library plans)? Answer categories: Yes No	

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22.4 APPENDIX 4. CLINICAL CASES FOR CONTOURING

22.4.1 CASES FROM VIENNA, UTRECHT AND AARHUS, CONTOURING TABLES

Will be provided later.

22.5 APPENDIX 5: EBRT CONTOURING ATLAS (COMPLEMENT TO CHAPTER 9)

22.5.1 INTRODUCTION

This appendix document describes the process for radiotherapy treatment planning of cervix cancer and has been developed for the purpose of the EMBRACE II study. A precise target volume definition is crucial for radiotherapy planning and IMRT treatments. It requires detailed knowledge of CT and MRI-based anatomy. In developing the EMBRACE II study, considerable time was spent discussing target definition and OARs. There are differences in views among radiation oncologists regarding their preferred volume of elective nodal irradiation, their PTV margins and organs at risk delineation. To ensure homogenous contours and to provide an efficient workflow when contouring, a step-by-step pictorial guide is provided for the delineation of tumor related target volume, nodal target volume and OARs.

It is well recognized that there is overlap with chapter 9 on EBRT. However, this appendix part is meant as practical guide to contouring which may contain some redundancies.

Please note that we have considered the target volume definition guidelines as used in the ICRU 50/62/83 and also the new concepts of ICRU 88 for brachytherapy.

22.5.2 CLINICAL TARGET VOLUMES RELATED TO THE PRIMARY TUMOR

The following abbreviations are used in the appendix:

GTV: Gross Tumor Volume (at diagnosis).

CTV: Clinical Target Volume = GTV + suspected microscopic tumor extension.

ITV: Internal Target Volume = CTV + internal margins to compensate for internal motions.

PTV: Planning Target Volume = CTV + set-up margin.

Different imaging modalities are used for delineate of different volumes. To facilitate the comprehension of this stepwise contouring atlas, you can use the following schematic workflow (26.1 (App)) explaining which contours should be outlined on the MRI images and CT images respectively.

Considering the difference in clinical practice of imaging in different centers, we propose two different ways of contouring. The choice of the strategies is at the discretion of the center/treating doctor. Each of these approaches needs at least a diagnostic MRI to contour the primary targets (GTV-$T_{initial}$ and CTV-$T_{initial}$ HR).

As explained in the protocol, the planning CT should be done according to a bladder filling protocol allowing the patient to have a comfortably full bladder. In addition to their diagnostic MRI, some patients benefit from high quality MRI images in treatment position in which the range of motion of the cervix and uterus with different fillings of the bladder/bowel can be observed and expectations of most likely motion scenarios during radiotherapy can be defined and in which the image registration between the planning CT and the MRI is reliable. For these cases, we recommend an individualized approach in which the CTV-T $LR_{initial}$ margin is adapted according to the different image sets. As an example: in case of a completely empty rectum at time of treatment planning, it is more likely that the CTV-T $LR_{initial}$ will move in anterior direction and the ITV margin may be increased in anterior direction and reduced in posterior direction (see figure 26.1 (App)).

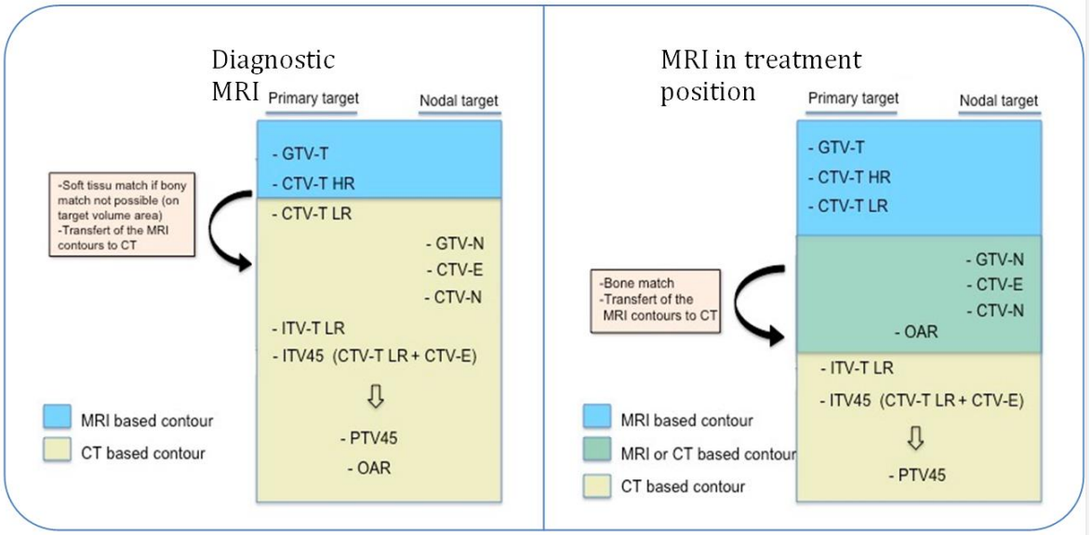


Figure 22.5.1 (App) Schematic workflow for contouring primary target and nodal target and OARs on diagnostic MRI, MRI in treatment position and CT

22.5.3 FIXED MARGIN APPROACH

STEP 1

Considering that every patient has a diagnostic MRI, contour the following structures on the MRI images:

The GTV-T$_{initial}$ (contour in red) is the extension of the cervical tumor defined by T2 weighted MRI supported by clinical investigation and PET-CT (figure 22.5.2).

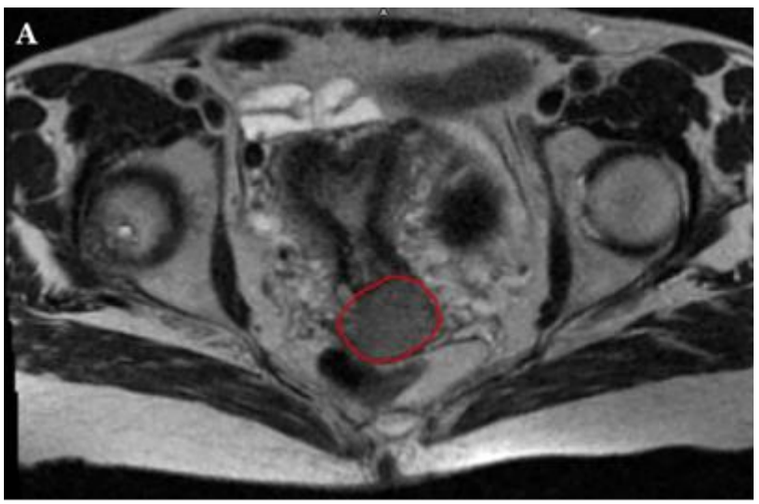


Figure 22.5.2 GTV-T$_{initial}$ on MRI (T2), A : axial view, B : sagittal view

STEP 2

Outline the CTV-T HRinitial (contour in magenta). It's the initial high risk CTV-Tinitial including GTV-Tinitial and any remaining cervix not infiltrated by the tumor (figure 3).

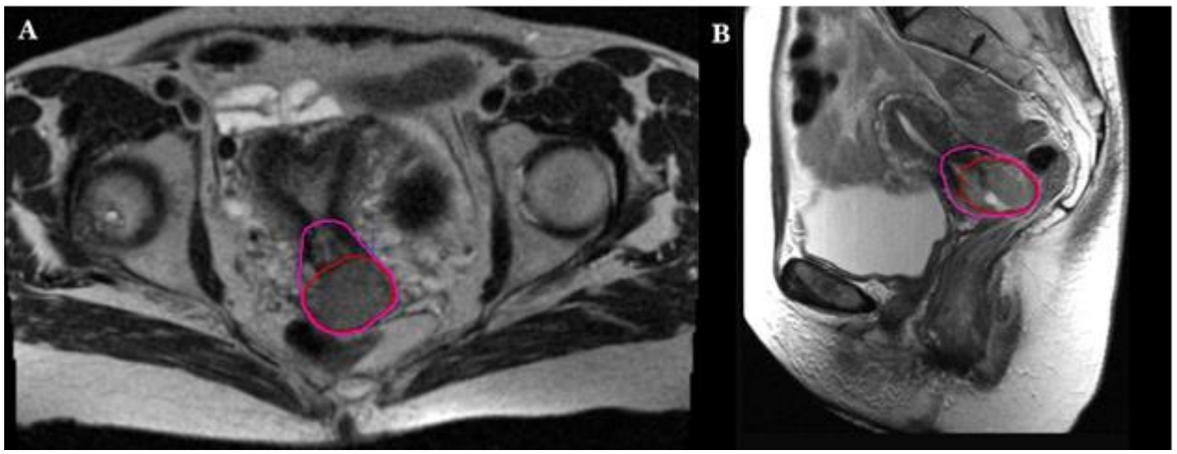


Figure 25.5.3 CTV-T HRinitial (magenta) and GTV-T initial(red) on MRI (T2), A : axial view, sagittal view

STEP 3

Do the registration (fusion) of the MRI images with the planning CT images. The planning CT should have been done according to the bladder filling protocol (see section 9.2). Transfer all previous MRI contours (GTV and CTV's) to the planning CT. If it is impossible to appropriately register the bony structures on the planning CT with the ones on MRI (due to positioning differences for example), try to match locally (the cervix region) on the soft tissue. Once fused, verify your MR-based contour on the planning CT.

On the MRI, identify **the CTV-T LR$_{initial}$** (contour in dark green) which includes:

- Initial CTV-T HR $_{initial}$
- the complete parametria bilaterally
- the whole uterus
- uninvolved vagina with a 20 mm margin measured from the most inferior position of the HR CTV-T$_{initial}$, along the vaginal axis (not starting in the fornix)
- CTV-T HR plus a margin of about 5 mm anterior and posterior towards bladder and rectum (excluding the non-involved walls)
- In case of involvement of the pelvic wall, sacro-uterine ligaments, meso-rectum or other involved structures (e.g. bladder, rectum) a 20 mm margin around the initial HR CTV-T$_{initial}$ will be extended into these structures as appropriate
- In case of excessive uterine/ligamentum latum infiltration consider to include ovaries into CTV-T LR$_{initial}$

The CTV-T LR$_{initial}$ volume is normally delineated as a single contiguous volume but for the purpose of these instructions we have separated the structures to aid description. The MRI information will help you to contour these volumes on the **planning CT**.

Extend the outline of the CTV-T HR$_{initial}$ to include the whole uterus and 20 mm in the vaginal direction. Subsequently, outline both parametria and paravaginal tissue (figure 22.5.4A and 22.5.4B) even if not involved with disease, the borders of the parametria are outlined in the figure 22.5.5 and defined on the table 22.5.1.

In the case of vaginal extension, the CTV-T LR$_{initial}$ lower limit is 2 cm below the caudal extension of the initial HR CTV-T $_{initial}$. If the whole vagina had to be outlined, the CTV-T LR$_{initial}$ should include the vaginal introitus which is located below the level of the pelvic floor (e.g. PIBS minus 2 cm).

STEP 4

Generate the ITV-T LR by adding a 10mm margin around the CTV-T $LR_{initial}$ cranio-caudally and antero-posteriorly and 5 mm laterally (figure 22.5.4C, figure 22.5.4D).

On the ITV-T LR, erase the most caudal contours so that the most caudal delineation of the ITV-T LR correspond to the most caudal outline of the CTV-T $LR_{initial}$ (figure 22.5.4E and 22.5.4F).

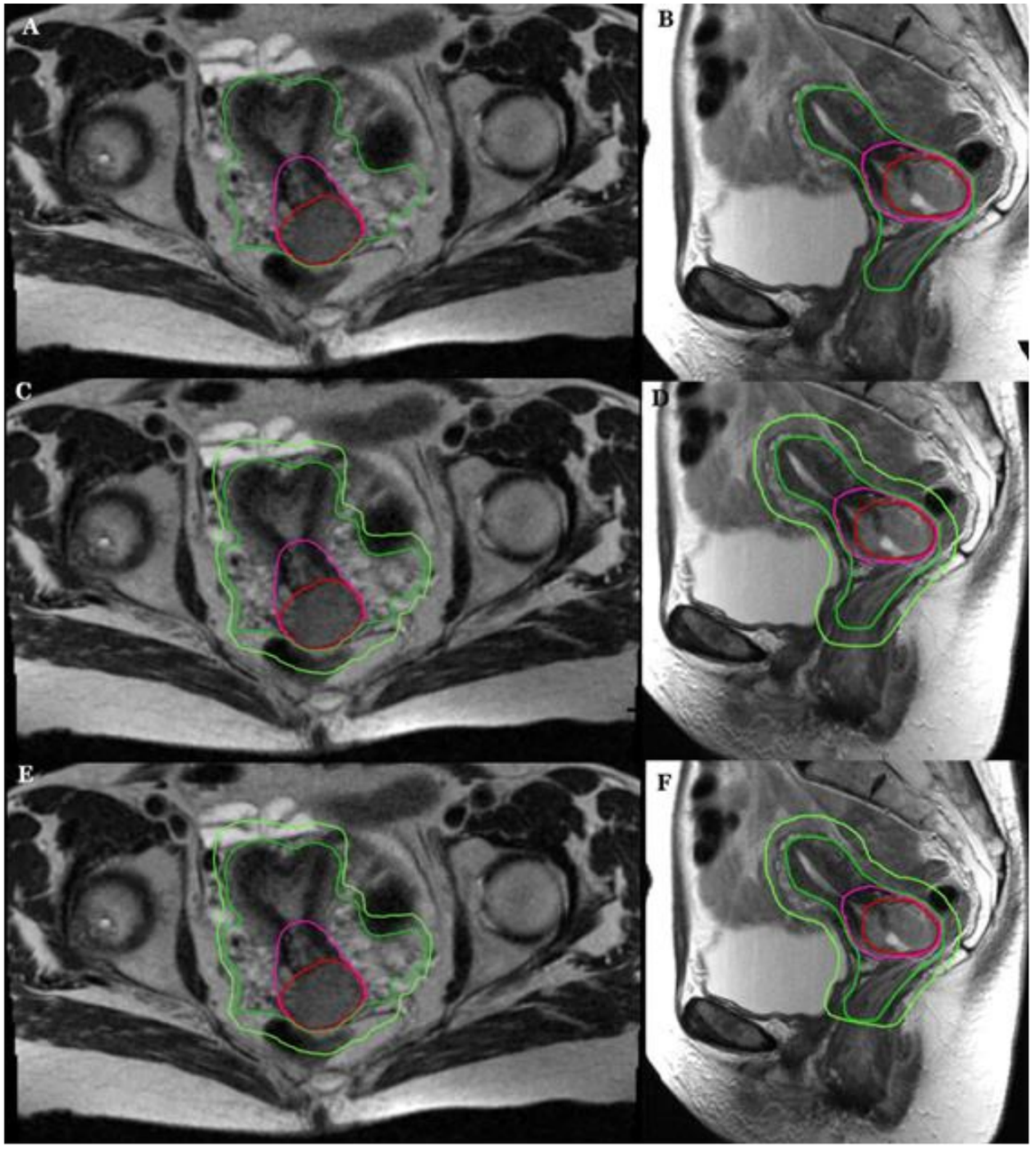
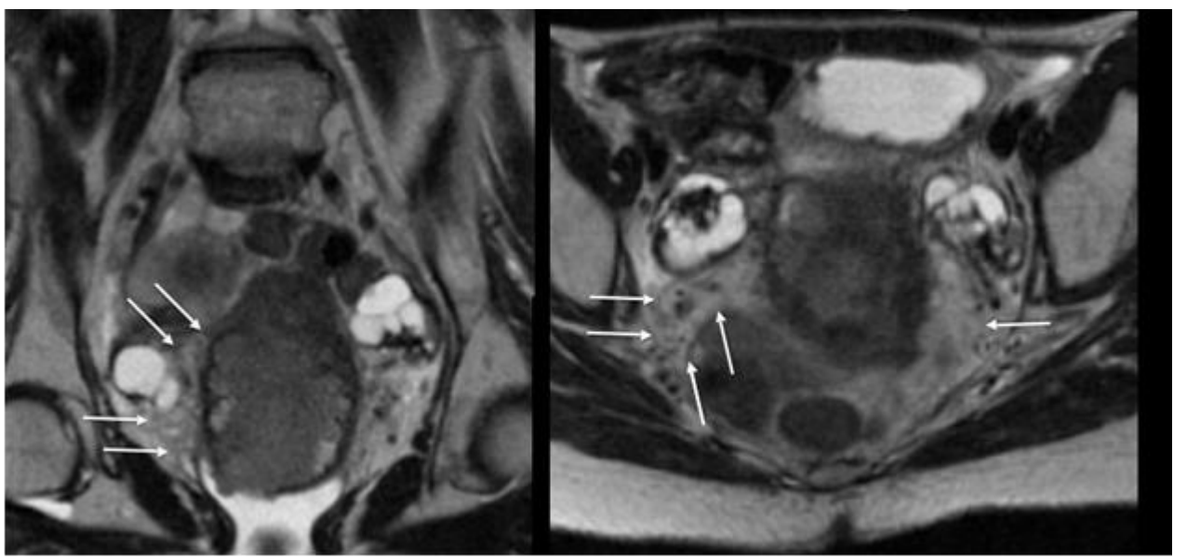


Figure 22.5.4 ITV-T 45 (light green), CTV-T LR (dark green), CTV-T HR initial (magenta), GTV-T initial (red), MRI (T2) A, C, F : axial view, B, D, F : sagittal view

2520

Location	Anatomic structures
Anteriorly	Posterior wall of bladder or posterior border of external iliac vessel
Posteriorly	Uterosacral ligaments and mesorectal fascia (figure 6)
Laterally	Medial edge of internal iliac and obturator vessels
Superiorly	Top of fallopian tube/ broad ligament/uterine arteries. Depending on degree of uterus flexion, this may also form the anterior boundary of parametrial tissue.
Inferiorly	Urogenital diaphragm

2521 Table 22.5.1 Definitions for Parametria delineation



2522

2523 Figure 22.5.5 MRI (T2) A : Coronal, B : Axial, ; a :Superior limit (uterine arteries), b : lateral limit (medial edge iliac vessels region) ,
2524 c :posterior limit (mesorectum)

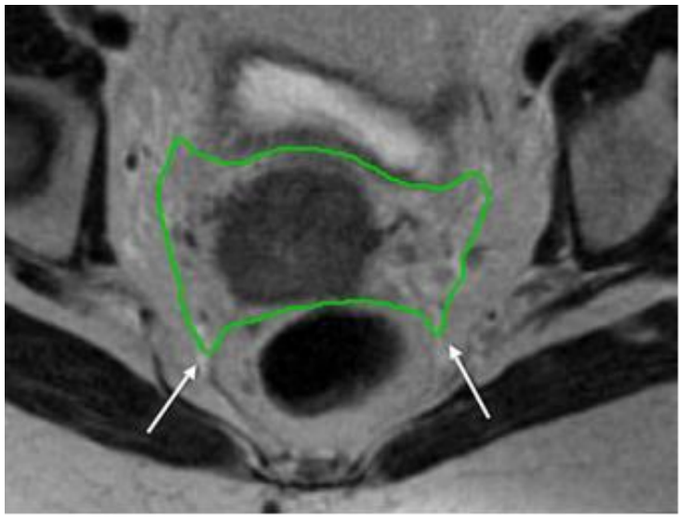


Figure 22.5.6 MRI (T2) axial, initial CTV-T $LR_{initial}$ (dark green) Borders of the parametria

22.5.4 INDIVIDUALIZED APPROACH

Follow the **step 1**, **step 2** as explained above.

STEP 3

On the MRI, identify **the CTV-T $LR_{initial}$** (contour in dark green) as defined for the standard approach.

The CTV-T $LR_{initial}$ volume is normally delineated as a single contiguous volume but for the purpose of these instructions we have separated the structures to aid description. The CTV-T LR is outlined on the **MRI** images.

- Extend the outline of the CTV-T $HR_{initial}$ to include the whole uterus and 20 mm in the vaginal direction. Subsequently, outline both parametria (figure 3A and 3B) even if not involved with disease, the borders of the parametria are outlined in the figure 25.5.5 and defined on the table 25.5.1.
- In the case of vaginal extension, the CTV-T $LR_{initial}$ lower limit is 2cm below the caudal extension of the tumor. If the whole vagina had to be outlined, the CTV-T $LR_{initial}$ should include the level of the introitus located below the level of the pelvic floor.

STEP 4

Do the registration (fusion) of the MRI images with the planning CT images. The planning CT should have been done according to the bladder filling protocol (see section 9.1). Transfer all previous MRI contours (GTV and CTV's) to the planning CT. If it is impossible to appropriately register the bony structures on the planning CT with the ones on MRI (due to positioning differences for example), try to match locally (the cervix region) on the soft tissue. Once fused, verify your MR-based contour on the planning CT.

On the planning CT, generate the ITV-T LR by adding an individualized margin around the CTV-T $LR_{initial}$ for the different directions (figure 25.5.7A and 25.5.7.B). The margins are independent in any direction and are chosen according to the information on the bladder, rectum, uterus, and primary target motion from the different image set available (example figure 25.5.8).

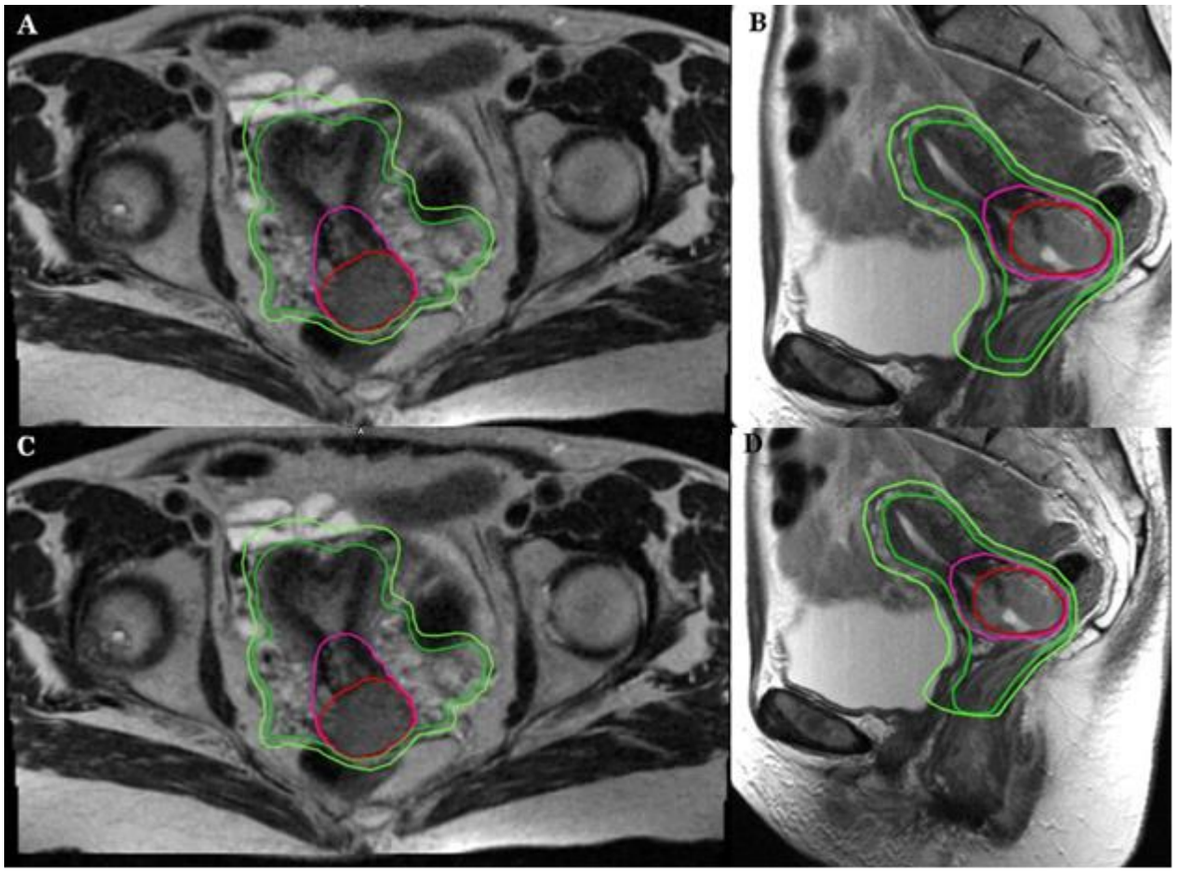


Figure 7 MRI (T2) axial, ITV-T 45 (light green), CTV-T LR $_{initial}$ (dark green), CTV-T HR $_{initial}$ (magenta), GTV-T $_{initial}$ (red), A,C: axial view, B,D: sagittal view

On the ITV-T LR, erase the most caudal contours so that the most caudal delineation of the ITV-T LR corresponds to the most caudal outline of the CTV-T LR initial (figure 25.5.7C and 25.5.7D).

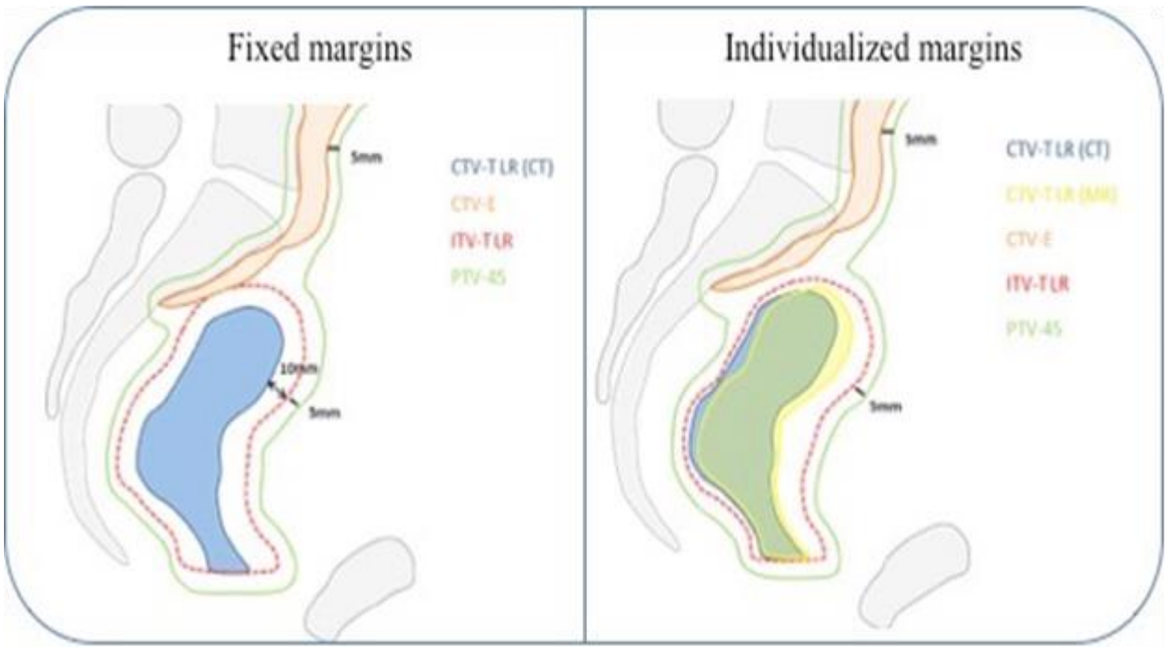


Figure 25.5.8 Margins for the ITV-T LR if using a diagnostic MRI for the fusion (left) or an MRI in treatment position (right)

22.5.5 CLINICAL TARGET VOLUMES FOR NODAL METASTASES AND NODAL REGIONS

*we recommend that the **step 1** and **step 2** are done on the MRI but they could be done on the CT as well.

STEP 5

Outline the **GTV-N** (contour in red) if the nodes are visible on the MRI for each pathological lymph node (figure 9B). They must be contoured and numbered, even if nodal boosting is not contemplated. PET-CT should primarily be used for overall guidance and not for precise delineation of the pathological nodes. Include extracapsular extension if visible. In case of nodes beyond the extension of pelvic MRI individual contours should be based on PET-CT appearance. Nodes are considered pathologic if they are:

- FDG PET positive
- Short axis diameter of ≥ 10 mm on CT or MRI
- Diameter of 5-10 mm on MRI with pathological morphology: irregular border, high signal intensity and/or round shape.

STEP 6

On the MRI/CT contour the **CTV-N** (contour in turquoise) for each pathologic lymph node with 0-3 mm margin around each GTV-N taking possible progression during treatment planning interval and not visible extra-capsular extension into account, avoiding bones and muscles. Furthermore, partial volume effect may lead to different appearance of the upper and lower boundary on CT and MRI. The total CTV-N should ideally encompass the maximum extension of the pathologic node as visualized on both CT and MRI. For pragmatic purpose and because there is only minor movement in nodal region, there is no need to draw a real ITV-N. The volume will allow for adequate inclusion into CTV-E and together with the PTV-N margin also if boosting is intended. Numbering of individual CTV-N should be consistent with GTV-N.

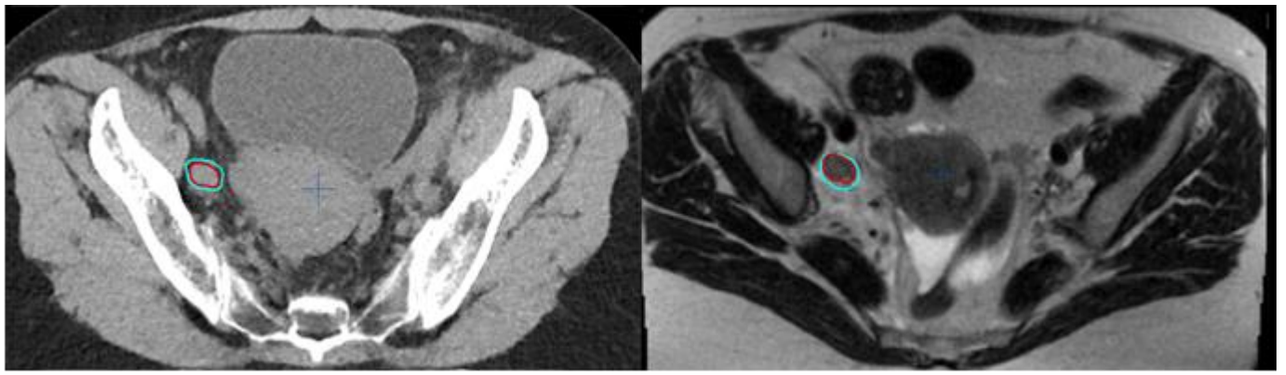


Figure 25.5.9 A : CT scan, axial view B : MRI (T2) axial view, CTV-N1 (turquoise), GTV-N1 (red),

The **CTV-E** (contour in blue) encompasses all individual CTV-N **and** the bilateral lymph node regions for elective nodal irradiation.

Risk patients	Lymphatic nodal region to contour
Low risk	Internal iliac, external iliac, obturator and presacral regions
Intermediate risk	common iliac, internal iliac, external iliac, obturator, and presacral regions, (groins in case of distal vaginal infiltration)
High risk	para-aortic, common iliac, internal iliac, external iliac, obturator, and presacral regions, (groins in case of distal vaginal infiltration)

The extent of the nodal regions within CTV-E is determined according to the risk spread as defined in the introduction of chapter 9:

STEP 7

Transfer all previous MRI contours (GTV-N and CTV-N) to the planning CT if applicable

- Identify the iliac blood vessels (figure 22.5.11A). The most superior axial outline should be at the aortic bifurcation. The most inferior border should be at the level of ischial spine and upper edge of obturator foramen were internal iliac vessels leave or enter the true pelvis) which represents the caudal margin of the external and internal iliac vessels.
- Nodal regions should be contoured on the planning CT or pelvic MRI including the relevant vessels with at least 7 mm of perivascular tissue including pertinent clips or lymphocysts (figure 22.5.11B) (in case of prior nodal resection or lymphadenectomy). See the table 4 at the end of this annex for a more detail lymph nodes anatomical boundaries definition.
- Using the drawing tools, join the outlines around the internal and external iliac vessels parallel/medial to the pelvic sidewall (figure 22.5.11C). This ensures the obturators and infra-iliac nodes to be included. Internal iliac border should be extend to the pelvic sidewall.
- Continue to contour inferiorly to cover the obturator nodes (figure 22.5.10). The most inferior axial slice to include should be at the level of the pelvic floor (usually below the femoral heads). This outline should not include muscle or bone.

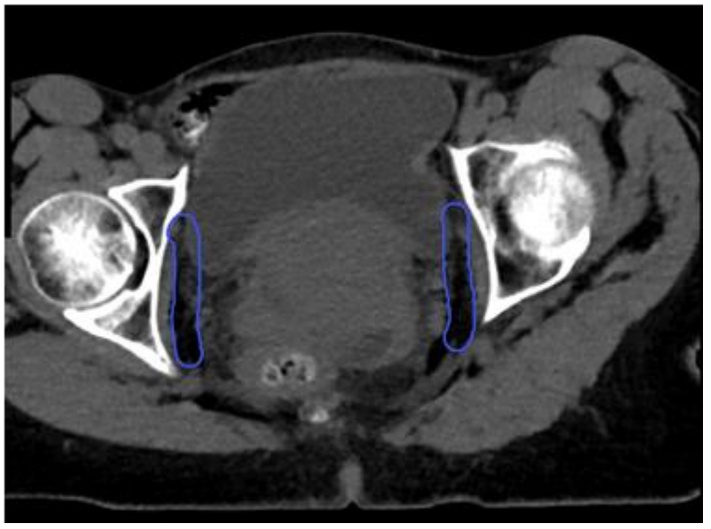


Figure 22.5.10 Contouring obturator nodal region on a CT scan, CTV-E (blue)

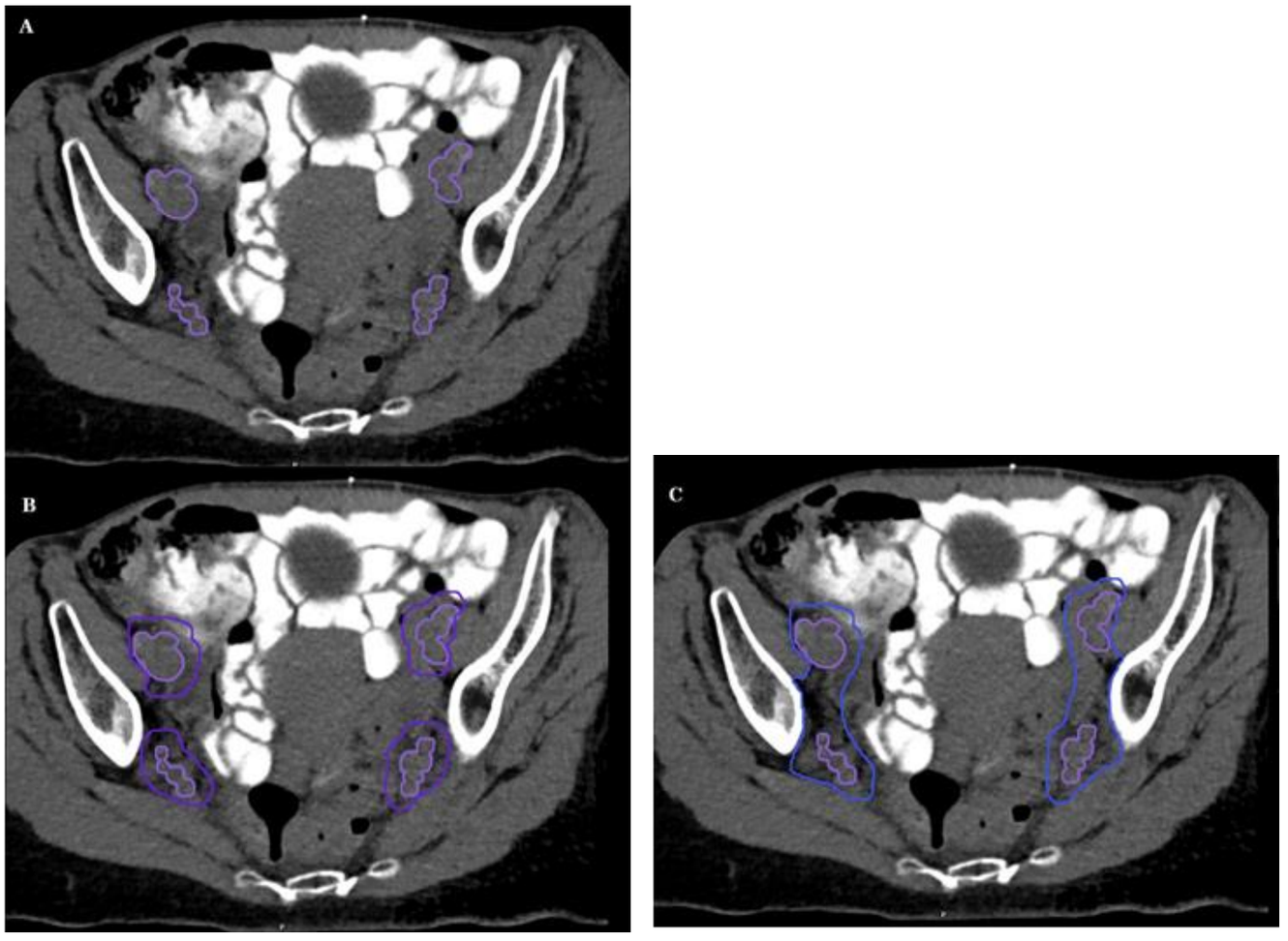


Figure 25.5.11 Contouring steps for internal and external nodal region on a CT scan, A contour of illiac vessels, B :extension of vessel volume, C : CTV-E (blue)

- To cover the presacral region, connect the volumes on each side of the pelvis (figure 22.5.12A) with a 10-mm strip over the anterior sacrum (figure 22.512B) to the lower level of S2. You do not need to extend into the sacral foramina (figure 22.5.13)
- For the common iliac vessels, extend the outline posterolaterally, it must be extended to the psoas muscle and vertebral body.

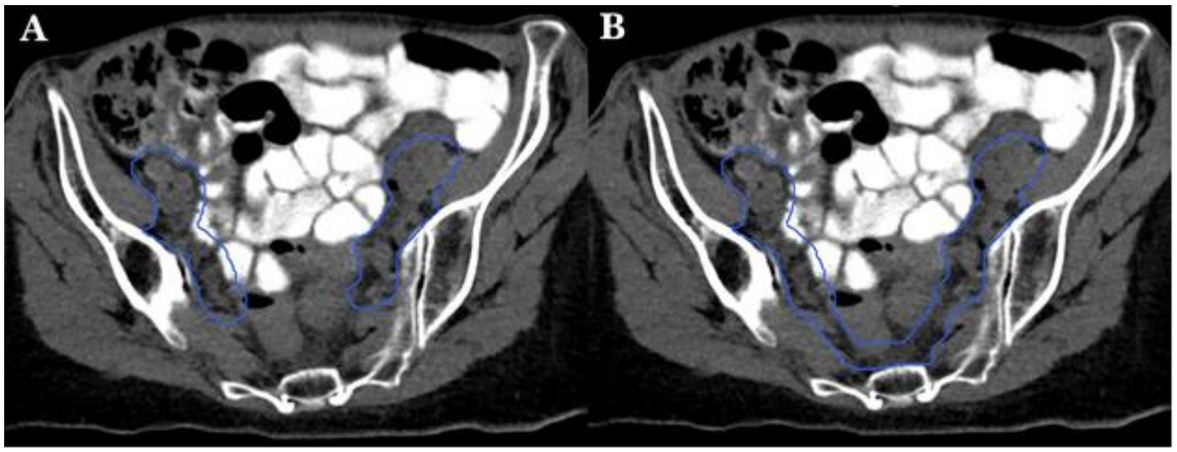


Figure 25.5.12 Contouring steps for sacral nodal region on a CT scan, B : CTV-E (internal, external and presacral nodal region (blue)

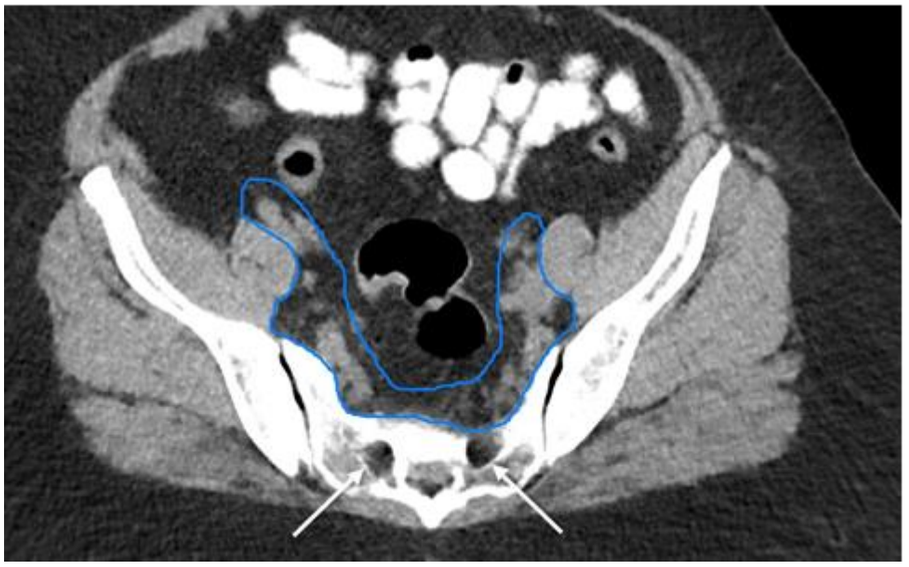


Figure 25.5.13 Contouring sacral nodal region on a CT scan , arrows : sacral foramina

- The level of the cranial pelvic irradiation field border is defined according to the patients risk.

Risk patients	Cranial border of irradiation field
Low risk	One slice below the bifurcation of common iliac artery
Intermediate	One slice below the aortic bifurcation
High risk	Cranial border of L1 with a minimum of 3 cm superior to the upper border of the last positive lymph node(s)

Table 22.5.3 Superior irradiation field border

22.5.6 PARA-AORTIC NODES

STEP 8

Nodal regions should be contoured on the planning CT including the relevant vessels (vena cava and aorta) (figure 22.5.14A) with at least 7 mm of perivascular tissue including pertinent clips or lymphocysts (figure 22.5.14B)

STEP 9

Edit to exclude any muscle or bone. Subsequently, extend the contour posterior-laterally along the vertebral body (figure 22.5.14C) to cover the left para-aortic area or any lymphocysts.

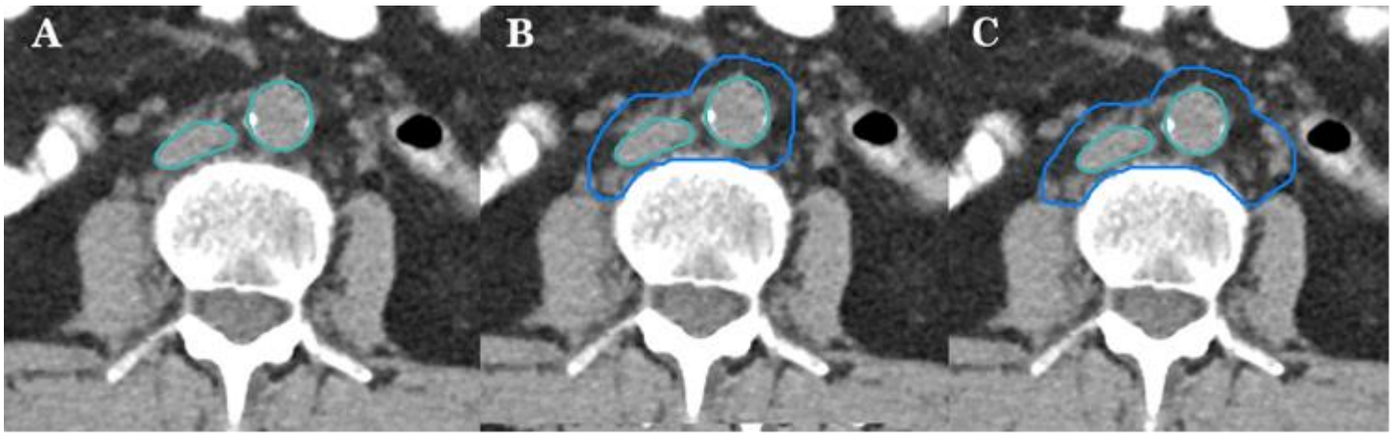


Figure 22.5.14 Contouring paraaortic region on a CT scan, axial view, A : Great vessels, B : 7mm extension, C : CTV-E (blue)

22.5.7 INGUINAL NODES

Inguinal lymph nodes irradiation should be added in case of positive inguinal lymph node or involvement of the lower third of the vagina.

STEP 10

The inguinal/femoral region should be contoured as a compartment with any identified nodes included (especially in the lateral inguinal region). The outline should have a minimum of 7-10 mm margin around vessels. The caudal extent of the inguinal region should be 2

cm caudal to the saphenous/femoral junction. The posterior border is the ventral fascia of the pectineus muscle. The lateral border is the ventral fascia of the ileopsoas and sartorius muscles (figure 22.5.15).

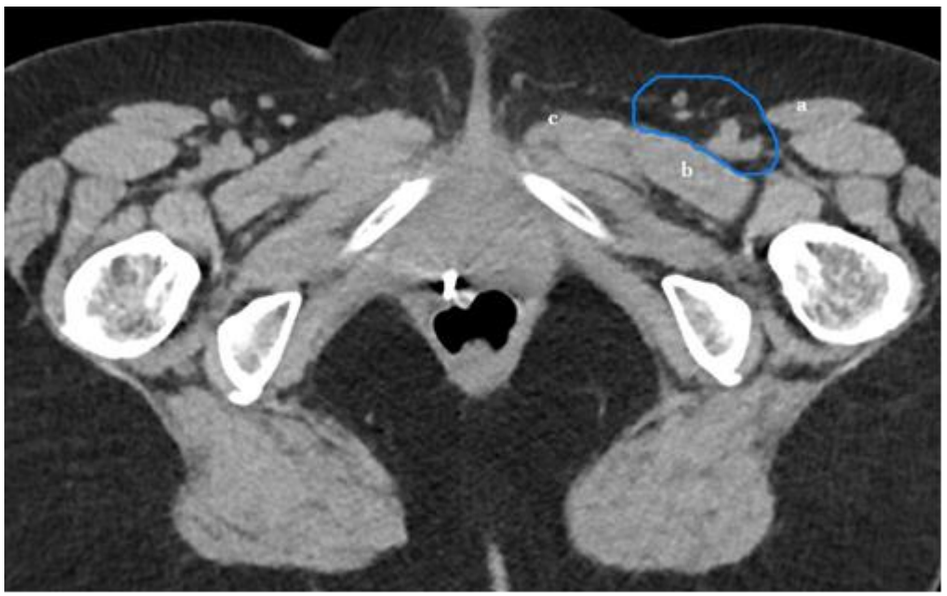


Figure 22.5.15 Left inguinal lymphatic region, CT, a : sartorius, b : pectineus muscle, c : adductor longus, CTV-E (blue)

22.5.8 PLANNING TARGET VOLUMES (PTV)

STEP11

Create one large volume (ITV 45) by fusing the following contours: ITV-T LR, and CTV-E.

STEP12

Add a margin of 5mm to the ITV 45 to create the PTV 45.

Lymphocysts after lymphatic surgery should be included into PTV 45, In case lymphocysts shrink extensively during ERBT, re-contouring and re-planning should be considered (figure 22.5.16).

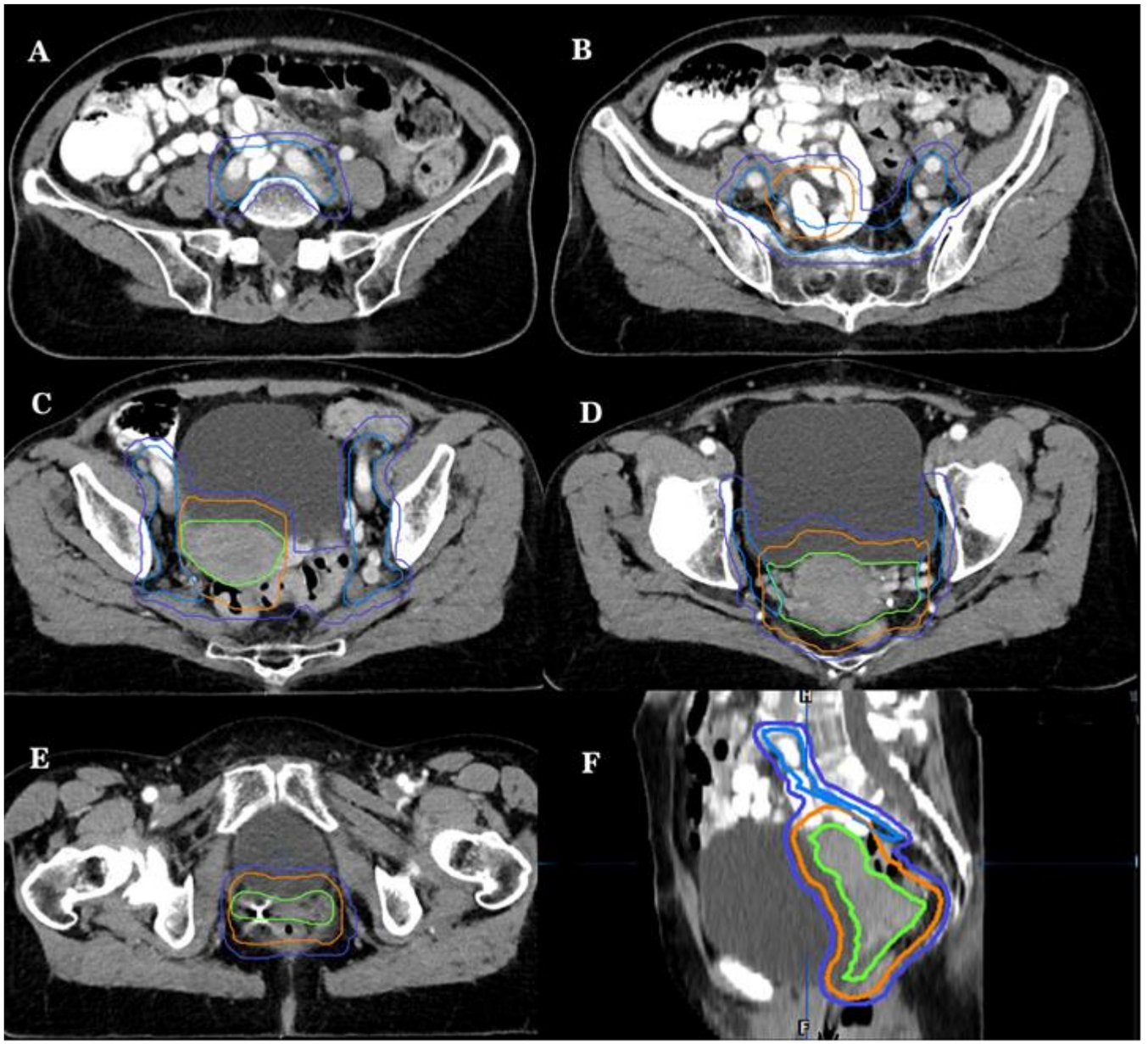


Figure 25.5.16 CT,PTV 45 (purple), ITV-T 45 (orange), CTV-E (blue), CTV-T LR$_{initial}$ (light green) ; A, B, C, D, E : axial view, F : sagittal view

22.5.9 NODAL BOOST

STEP13

Add a 5mm margin to each CTV-N1, CTV-N2, … to create PTV-N1, PTV-N2, …

22.5.10 PRIMARY TARGET CONTOURING SUMMARY WITH DIAGNOSTIC MRI*

On MRI	1- Contour the **GTV-$T_{initial}$.** It's the extension of the primary tumor at the cervix
	2- Outline the **CTV-T $HR_{initial}$.** It's the initial high risk CTV-T including GTV-$T_{initial}$ and any remaining cervix not infiltrated by the tumor

Surimposition/Registration/ fusion between the MRI and the planning CT*

* if impossible to fuse the MRI with the planning CT on the bony structure, try to match locally (the cervix region) on the soft tissue or surimpose the images side by side. Once fused, verify your MR-based contour on the planning CT and do adjustments if necessary

On CT	3- Contour the **CTV-T $LR_{initial}$** in including the following structures: -the CTV-T $HR_{initial}$ -a 20 mm margin centripetal around GTV-$T_{initial}$ in the direction of the vagina -the complete parametria bilaterally -the whole uterus -the sacro-uterine ligaments and the mesorectum if involved -In case of excessive uterine/ligamentum latum infiltration consider to include ovaries into CTV-T $LR_{initial}$ -invaded organs (bladder, rectum, sigmoid, bowel) 4- Contour **GTV-N** and **CTV-N** (margin 0-3mm) and numerate them accordingly 5- Delineate the **CTV- E** in contouring the nodal region corresponding to the patient risk category and including all the CTV-N 6- Generate the **ITV-T LR** by adding a 10mm margin (fixed margin approach) around the CTV-T $LR_{initial}$ cranio-caudally and antero-posteriorly and 5mm laterally
	7- On the **ITV-T LR**, erase the most caudal contours so that the most caudal delineation of the ITV-T LR correspond to the most caudal outline of the CTV-T $LR_{initial}$
	8- Join the ITV-T LR and the CTV-E outline to form the **ITV 45.**
	9- Generate the **PTV 45** in adding a 5mm margin to the ITV 45
	10- Outline the **OAR**

22.5.11 PRIMARY TARGET CONTOURING SUMMARY WITH AN MRI IN TREATING POSITION

On MRI	1- Contour the **GTV-$T_{initial}$**. It's the extension of the primary tumor at the cervix
	2- Outline the **CTV-T $HR_{initial}$**. It's the initial high risk CTV-T including GTV-$T_{initial}$ and any remaining cervix not infiltrated by the tumor
	3- Contour the **CTV-T $LR_{initial}$** in including the following structures: -the CTV-T $HR_{initial}$ -a 20 mm margin centripetal around GTV-$T_{initial}$ in the direction of the vagina -the complete parametria bilaterally -the whole uterus -the sacro-uterine ligaments and the mesorectum if involved -In case of excessive uterine/ligamentum latum infiltration consider to include ovaries into CTV-T $LR_{initial}$ -invaded organs (bladder, rectum, sigmoid, bowel
Surimposition/Registration/ fusion between the MRI and the planning CT*	
On MRI and or CT	4- Contour **GTV-N** and **CTV-N** (margin 0-3mm) and numerate them accordingly 5- Delineate the **CTV- E** in contouring the nodal region corresponding to the patient risk category and including all the CTV-N 6- Outline the **OAR**
On CT	7- Generate the **ITV-T LR** by adding an individualized margin (individualized margin approach) around the CTV-T LR independently in each direction
	8- On the **ITV-T LR**, erase the most caudal contours so that the most caudal delineation of the ITV-T LR correspond to the most caudal outline of the CTV-T $LR_{initial}$
	9- Join the ITV-T LR and the CTV-E outline to form the **ITV 45**
	10- Generate the **PTV 45** in adding a 5mm margin to the ITV 45

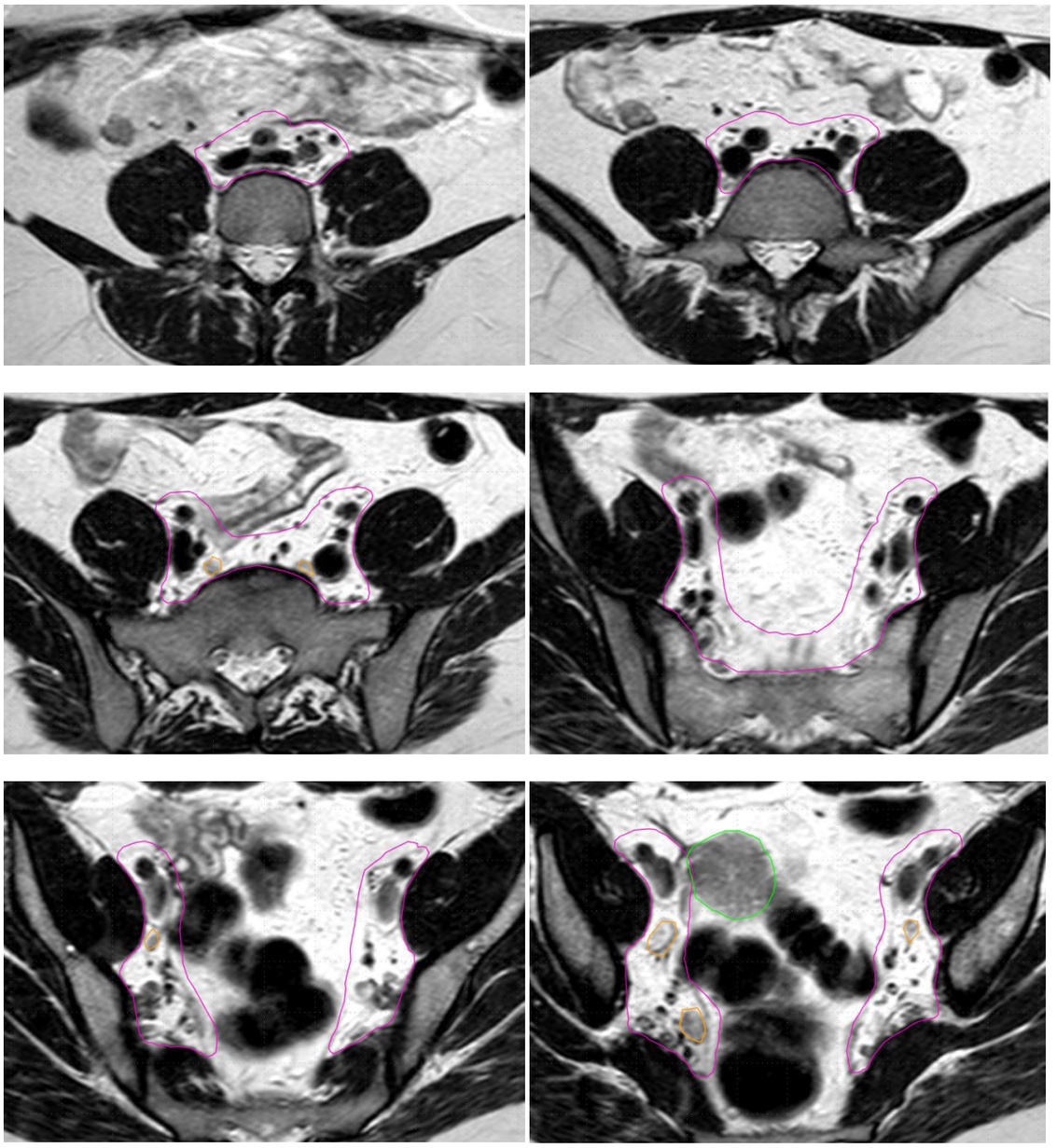


Figure 22.5.1 Atlas example FIGO IB2 cervical cancer with pathological lymph nodes. MRI (T2) in treatment position, axial slices at regular interspaces from left to right and top to bottom, CTV-E (magenta), GTV-N (orange), CTV-T LR (green).

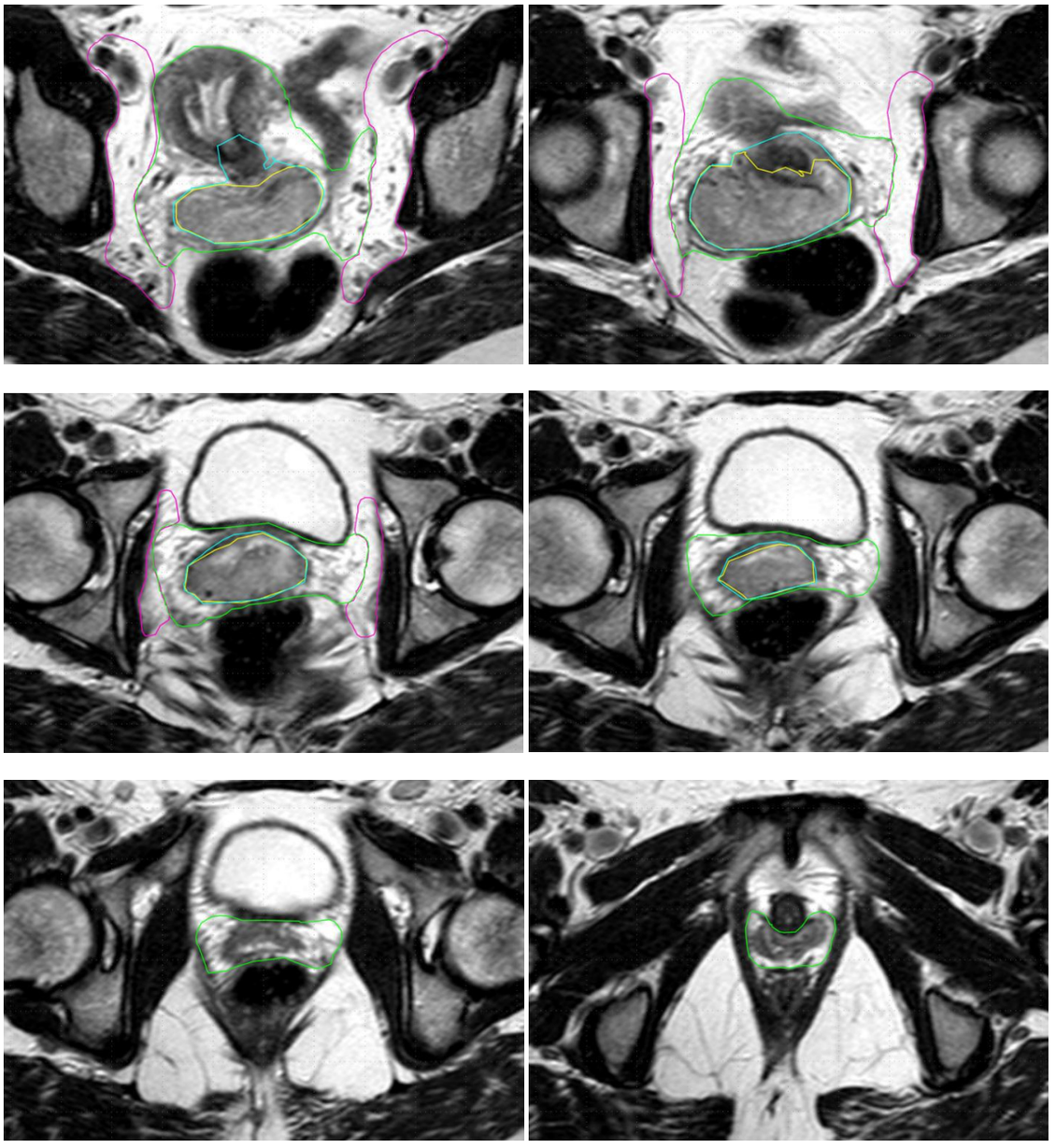


Figure 22.5.2 Continued: MRI (T2) in treatment position, axial slices at regular interspaces from left to right and top to bottom, CTV-E (magenta), GTV-N (orange), CTV-T LR (green), GTV-T initial (yellow), CTV-T HR initial (light blue).

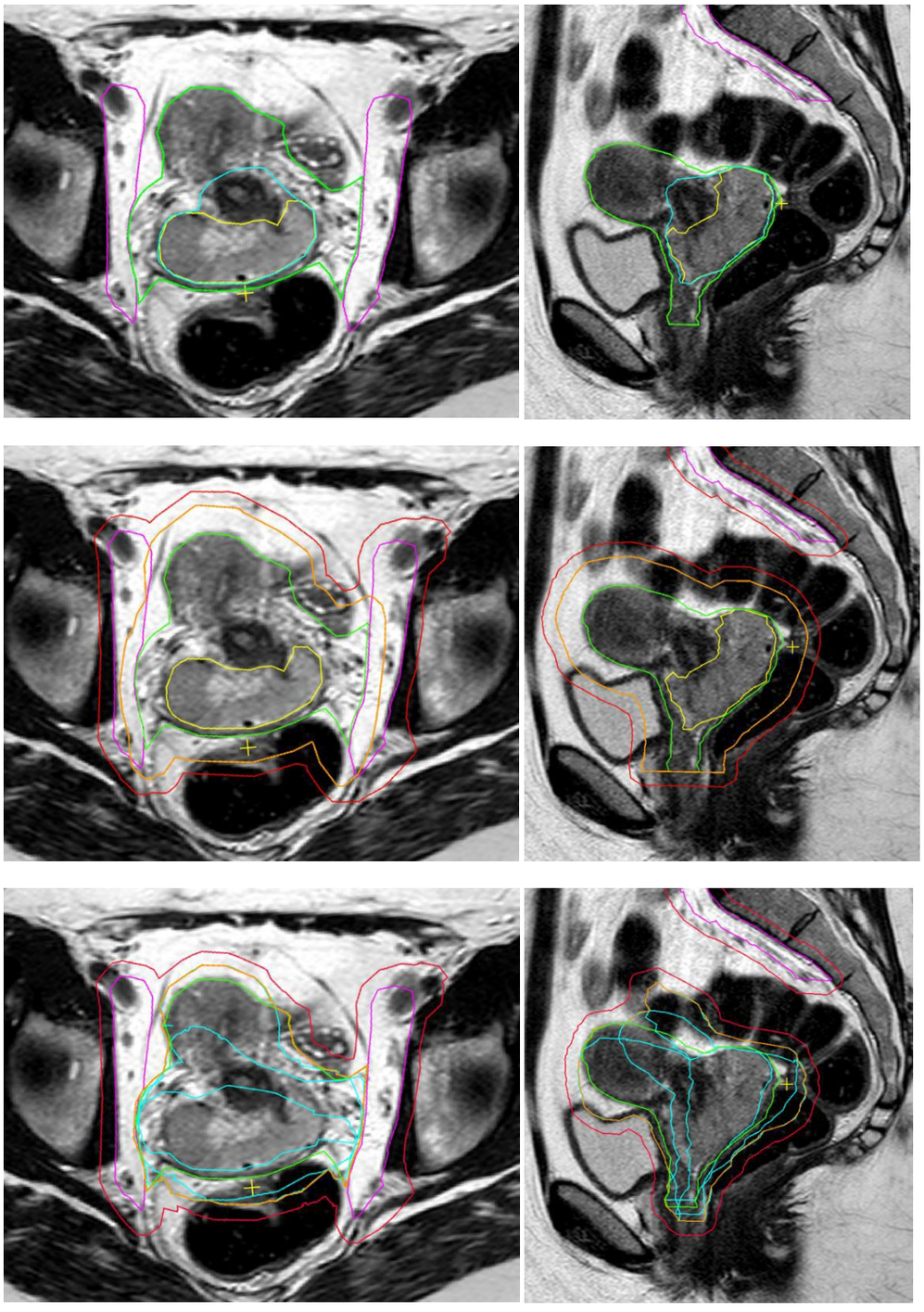


Figure 22.5.3 Continued: MRI (T2) in treatment position; top left axial and top right sagittal CTV-E (magenta), CTV-T LR (green), GTV-T initial (yellow), CTV-T HR initial (light blue); middle left axial and middle right sagittal CTV-E (magenta), CTV-T LR (green), GTV-T initial (yellow), ITV-T LR using standard margins (orange) and PTV45 (red); bottom left axial bottom right sagittal CTV-E (magenta), CTV-T LR in treatment position (green) and three additional positions from different fused MRI and PET-CT scans (light blue), GTV-T initial (yellow), ITV-T LR using individual margins (orange) and PTV45 (red).

22.5.12 CONTOURING OF ORGANS AT RISK

The outer contour of the following organs should be delineated separately:

Bladder: Outline the whole organ including the bladder wall and the bladder neck (figure 17).

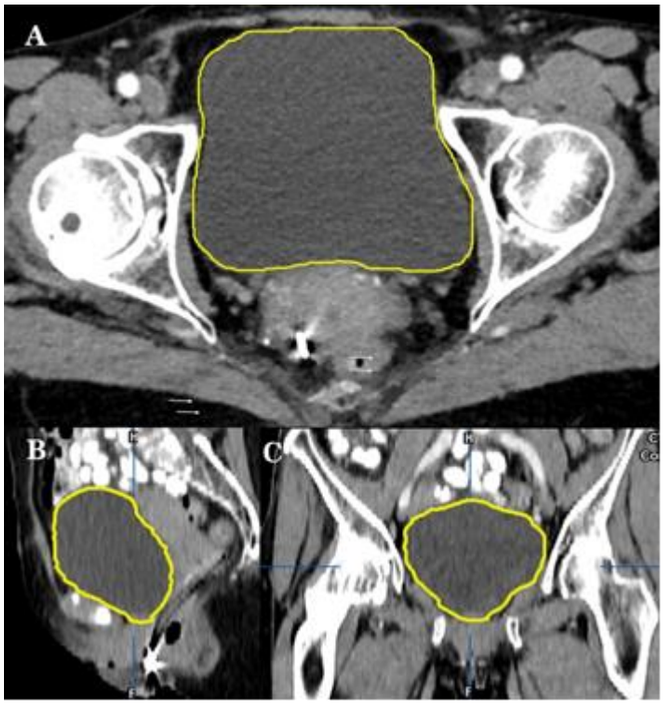


Figure 22.5.17 CT, Bladder contour (yellow) A :axial view, B : Sagital view, C : Coronal view

Femoral heads: Both femoral head and neck to the level of the trochanter minor. (figure 22.5.18)

Rectum: Outline the rectum from the ano-rectal sphincter (level of PIPS) to the recto-sigmoid junction (retroperitoneal deflection), including the rectal wall (figure 22.5.19).

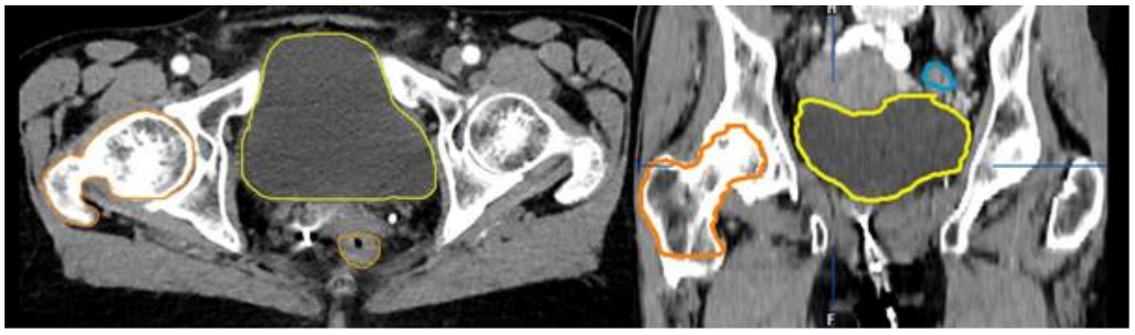


Figure 22.5.18 Right femoral head contour (orange), A : axial view, B : coronal view

Sigmoid: From the recto-sigmoid junction to the left iliac fossa (figure 22.5.18).

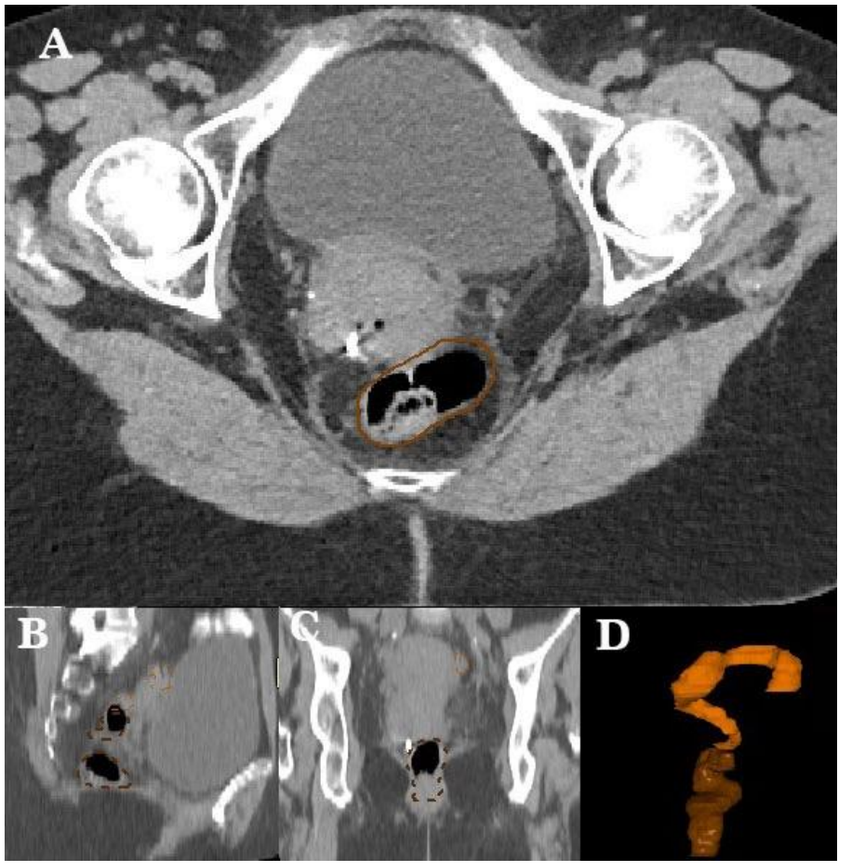


Figure 22.5.19 CT, rectum contour (brown) and sigmoid contour (orange), A :axial view, B : Sagital view, C : Coronal view, D : 3-D reconstitution

Bowel: Outer contour of bowel loops including the mesenterium. Do not include abdominal cavity without bowel or sigmoid (figure 22.5.20).

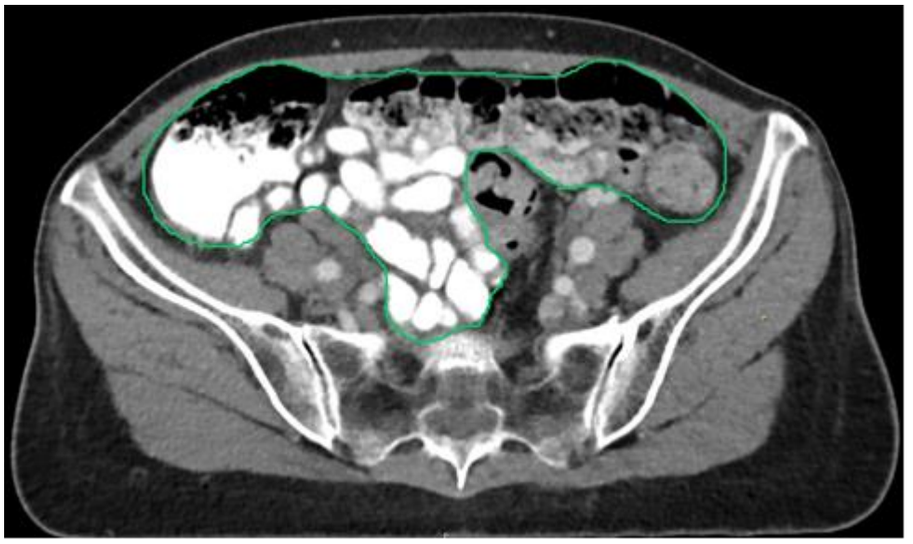


Figure 22.5.20 CT. bowel contour (green)

22.5.13 FOR PARA-AORTIC IRRADIATION IN ADDITION

Kidneys: outer contour excluding pyelum (figure 22.5.21)

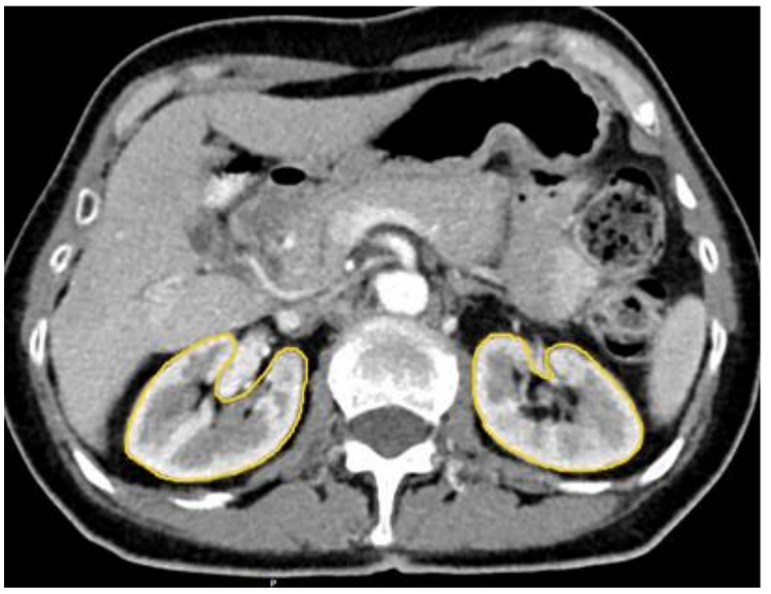


Figure 22.5.21 Kidney contouring

Spinal cord: outer contour of spinal cord, contour down to L2 (figure 22.5.22)

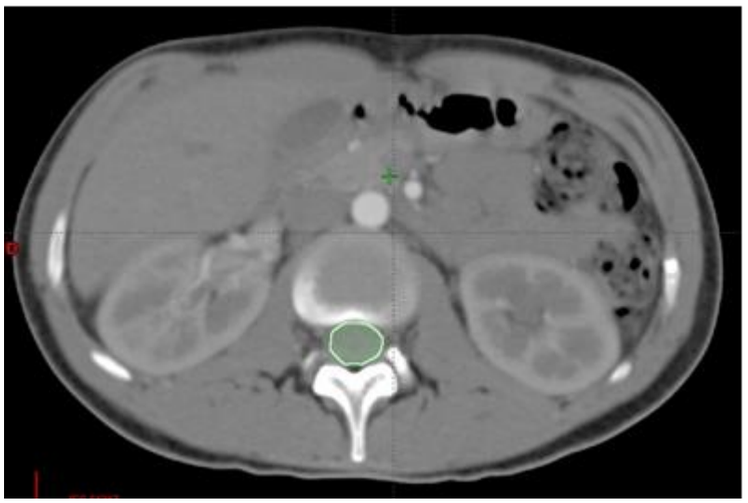


Figure 22.5.22 CT. Spinal cord

Lymph node regions to encompass	Anatomical boundaries (adapt where necessary to include all visible lymph nodes)					
	Cranial	**Caudal**	**Anterior**	**Posterior**	**Lateral**	**Medial**
Para-aortic nodes	Cranial border of L1 with a minimum of 3 cm superior to the upper border of the last positive lymph node(s)	One slice below aortic bifurcation	7 mm margin around vessels excluding bowel loops or other organs	ventro-lateral contours of vertebral bodies until connection with psoas muscle	along outer contour of psoas muscle with a minimum of 7 mm around vessels excluding bowel loops or other organs	

Common iliac nodes	One slice below aortic bifurcation	One slice below bifurcation of common iliac artery	7 mm margin around vessels excluding bowel loops	Ventro-lateral contours of vertebral bodies until connection with psoas/iliopsoas muscles excluding nerves	along outer contour of psoas muscle , up to 7 mm around vessels excluding muscle	7 mm margin around vessels excluding bowel loops
Pelvic nodes including **Internal iliac nodes** **External iliac nodes** **Obturator nodes**	One slice below bifurcation o common iliac artery	Pelvic floor (usually at the upper part of the obturator foramen, below the femoral head, where internal iliac vessels leave or enter the true pelvis)	7-17 mm ventral to external iliac vessels not extending into the abdominal wall	ventro-medial fascia of piriformis muscle/sacrospinous ligament	ventro-medial fascia of iliopsoas muscle, bony pelvic sidewall and obturator internus muscle	7 mm around vessels excluding bowel loops, bladder wall, lateral border of parametrium and mesorectal fascia
Presacral nodes	upper border S1	lower border S2	1 cm in front of S1/2	ventral border S1/2	medial borders of pelvic node compartments	
Inguinal nodes	Midfemoral head, external iliac vessels leave bony pelvis as femoral vessels	Lower edge trochanter minor, about 2 cm below junction vena femoralis/ vena saphena manga	7-10 mm margin around vessels	ventral fascia of pectineus muscle	medial fascias of ileopsoas /sartorius muscles	7 mm margin around vessels excluding, peritoneal fascia, lateral fascia of rectus abdominis muscle, latero-ventral fascias pectineus/adductor longus/brevis muscles

2704 Table 22.5.4 : Lymph nodes regions borders

2705

22.6 APPENDIX 6: MEASUREMENT AND REPORTING OF SUV

Measurement and reporting of SUV in primary tumour and lymph nodes is not mandatory in EMBRACE II, but when reported to the database, the following procedure should be used:

- In general the FDG PET/CT: EANM procedure guidelines for tumour imaging: version 2.0 should be followed (Boellaard R. et al. 2015).
- CT can be performed as either a low-dose CT-scan for attenuation correction and anatomical correlation or as a diagnostic CT-scan.
- Scans should be performed according to local guidelines with regard to fast and blood glucose levels.
- Image reconstruction should be performed according to local guidelines.
- Imaging should be evaluated using software that can display fused CT and PET data and use a SUV scale.
- Time from injection to scan start should be between 60-90 minutes.
- Reported to the database:
    - SUV_{max} of the primary tumour
    - SUV_{max} for each lymph node
    - Necrosis (yes/no) for each lymph node

22.7 APPENDIX 8: CRFS (CH 16)

This Appendix refers to a large excel file which is in principle based upon the CRF design of EMBRACE I with altogether 8 forms:

1. Registration Form
2. Status at Diagnosis Form
3. Baseline Morbidity Form
4. Status at Brachytherapy Form
5. Treatment and DVH Form
6. Follow-up Form
7. Off Study and Vital Status Form
8. Curative Salvage Treatment Form

The CRFs have been systematically reworked during the last 6 months for most of the 8 parts and still need to be finalized with about 80% already finished (estimate).

This rework has been done based on our experience with EMBRACE I and the design of the CRFs and the evaluation of parameters. In addition the design of EMBRACE II was taken into account reflecting the major (new) endpoints. As EBRT has become an additional issue of major importance in EMBRACE II, this is reflected in the respective forms. The rework has tried to follow the EMBRACE I parametrization in order to provide the basis for comparison of data between EMBRACE I (RetroEMBRACE) and EMBRACE II.

22.8 APPENDIX 9: PRINCIPALS AND STRUCTURES OF EMBRACE RESEARCH GROUP

Research work is organised based on written project proposals with a short and a long protocol version.

Research protocols are organised according to classical research proposal structure for grant applications

Research protocols have to result in minimum one major publication in a peer reviewed journal

Research funding is not available directly through the EMBRACE study

Research is organised within working groups focussing on a specific topic with a coordinator and co-workers

Milestones to be defined with time lines in a research proposal: who, what, when

Updates to be given in person on the occasion of meetings: Gyn GEC ESTRO network, midyear, annual EMBRACE end of the year

Responsibility for project plan and research performance: Working group coordinator. Working group coordinator is assigned for 2 years, can be renewed

Bilateral Agreement on this outline with main mentor/mentor group before application

Overall Agreement on all project outlines by EMBRACE Research mentor group continuously: start after 1st application round

Publication authorship (for first major publication): Working group coordinator is first author, main mentor is senior author. In case of 2 persons, co-equal authorship foreseen authors are persons with active participation in the publication project one authorship goes to one of the EMBRACE coordinators (co-mentor) provisional title of first major publication and authorship should be part of the short and long proposal version, may be adapted later

EMBRACE Research Leader group are the Study coordinators plus senior advisors

EMBRACE Research Mentor group: Richard Pötter, Kari Tanderup (coordinators)

EMBRACE Research WG Coordinator group: all workgroup coordinators,

Milestones and timelines for project progress and publication process have to be kept carefully in order to make this complex research structure feasible and to ensure our data to be handled in appropriate way .

In case of somebody going repeatedly and significantly beyond timelines not fulfilling milestones in regard to project and publication process without upfront providing a rationale to the EMBRACE research leader group, the function of the coordinator and the authorship role will be re-considered and decided by the cooperative research leader group.

Overall organisation structure: Research leader group regular 6 monthly telephone conferences. A work group coordinator or mentor may be invited, if appropriate organised by Vienna or Aarhus (RP, KT) decisions are taken by majority

The overall EMBRACE Research group, working group coordinators together with mentors and co-workers meets on the occasion of annual EMBRACE meetings and Gyn GEC ESTRO network meetings, if feasible.

Each working group and mentor group works according to its own specific working plan. Minimum actions to be taken by the working groups are telephone conference meetings in 3 months intervals (with the main mentor available) with a pre-meeting agenda and summarizing minutes (results). This is to be communicated in cc to the coordinators RP, KT.

No extra funding is at present available for the performance of the research work. Specific funds are therefore encouraged to be applied for at the regional/national/ European/international level as appropriate after discussion and agreement on the proposal with the EMBRACE RESEARCH leader group.

22.9 APPENDIX 10: PATIENT INFORMATION

Patient information needs to be adapted to the needs, legislative and ethical requirements of each country and radiotherapy department. To facilitate this process and to maintain some uniformity, parts of the following paragraphs could be included in the written patient information but this information should be adjusted according to local institutional standard treatment policies and are subject to local ethical committee approval. In addition, a study specific consent form will need to accompany the patient information form that needs to be adapted to fulfill the regulations of the local ethical committee.

Summary

You have been asked to participate in a study for patients with cervical cancer who will be treated with a combination of external beam radiotherapy, chemotherapy and brachytherapy (internal radiation).

The aim of this study is to collect exact details about:

- Radiation dose to the tumor and surrounding normal organs
- Effect of therapy on tumor control
- Side effects of treatment
- Quality of life during and after treatment

This is a study in which only details about the treatment and its effects will be registered. You will receive the same treatment if you do not participate in this study. The study is planned to include more than 1000 patients from approximately 25 different international radiotherapy departments. The radiotherapy departments who collaborate in this study all use advanced level technological methods to deliver radiation image guided, as precisely and optimally as possible, to the tumor while sparing the surrounding healthy organs. In this document you can read more information about the treatment, the possible side effects of treatment and this study.

Background

The combination of external beam radiotherapy, chemotherapy and brachytherapy is the current standard treatment for patients with locally advanced cervical cancer. The treatment starts with external beam radiotherapy together with chemotherapy. Brachytherapy (internal radiation) will be started during the last part of external beam treatment or starts when external beam treatment has ended.

In the first EMBRACE study that was completed in 2015 more than 1000 patients participated. This study focused on implementing a brachytherapy treatment method in which the radiation dose was shaped to the individual patients anatomy or position of the tumor and the healthy normal surrounding organs using MRI imaging at time of brachytherapy. Results of this and other studies indicate that in patients with small tumors high doses of radiation can safely been given resulting in a very high chance that the cancer will be cured. For these patients brachytherapy dose to normal surrounding organs can be lowered while maintaining the high chance of tumor control. On the other hand, in patients with larger tumors a higher dose of brachytherapy could be safely given with advanced brachytherapy techniques and this higher dose resulted in an improved chance of tumor control.

The current EMBRACE-II study will collect and register details from patients who have been treated with advanced brachytherapy techniques including MRI at time of brachytherapy, and with advanced external beam radiotherapy image guided techniques. Based on the results described above in EMBRACE-II:

- External beam radiotherapy will be done using intensity modulated radiotherapy, a technique that results in less radiation dose to surrounding healthy organs (bowel, bladder). Furthermore, each day patients will be positioned as accurate as possible on the treatment machine using imaging on the machine. This will increase the precision of treatment.
- For brachytherapy it will be routinely possible to adjust the devices used to deliver internal radiation to the individual anatomy and position of the tumor and surrounding healthy organs. Together with MRI imaging at time of brachytherapy, this will increase the precision of treatment. For smaller tumors this will result in less dose to healthy surrounding organs, while for larger tumors this will allow to increase the radiation dose necessary to effectively treat the tumor.

External beam radiotherapy

External beam radiotherapy is an outpatient treatment that takes approximately 20-30 minutes per day and is usually given each day (5 days a week). In total 25 external beam radiotherapy treatments are given over a period of 5-6 weeks.

Side effects of external beam irradiation

During the 5-6 week period that external beam radiotherapy is given, side effects will gradually develop, usually starting after 2-3 weeks. The side effects are most pronounced during the last 2 weeks of external beam radiotherapy and the first 2 weeks after completion. During this period the tumor will decrease in size and sometimes patients will notice a change in discharge form the vagina.

Side effects during and shortly after treatment include:

- Irritation of bowel resulting in softening of stools or diarrhea, sometimes with bowel cramps and seldom with a little blood in the stool. This results in having to go to the toilet more often for bowel movements.
- Irritation of the bladder, which leads to increased urgency or need to go to the toilet more often to pass urine, sometimes with a burning sensation.
- Irritation of the vagina.
- Loss of energy or feeling tired.

Brachytherapy

With brachytherapy radiation is given inside the tumor using an applicator. The placement of the applicator is done using a form of anesthetic (general or spinal). The applicator uses hollow tubes that are placed in the vagina and through the cervix into the cavity of the uterus (womb). It may be necessary to place additional hollow tubes or needles directly in the tumor area. Using an MRI scan with the brachytherapy applicator in position the radiation dose can be optimally shaped. During the treatment a radioactive source will be placed in the hollow tubes in the area of the tumor for some time to deliver the radiotherapy dose. How long the treatment takes and how much treatments are given depends on the equipment used and your radiation oncologist will provide more detailed information on this procedure.

Side effects of brachytherapy

In period when brachytherapy is given there usually are already side effects from external beam radiotherapy. In addition to these, there may be some bleeding from the vagina, which should stop within two days after treatment. There may be some additional soreness of the vagina or with passing urine after the procedure.

Chemotherapy

Chemotherapy will be given using the drug cisplatin that will be given on one day each week during the first five weeks of external beam radiotherapy. Cisplatin is given intravenously, in the bloodstream.

Side effects of chemotherapy

Most common side effects of this weekly cisplatin treatment include:

- Feeling sick (nausea) or having to vomit. To prevent this the treatment will be combined with medication to prevent this.
- Cisplatin can damage the kidney. For this reason additional fluid will be given together with the drug intravenously. The function of the kidney will be tested each time before the treatment is given.
- The chemotherapy temporary affects the normal blood cells. The number of blood cells will be tested each time before the treatment is given. A drop in white blood cells can result in an increased risk of infections. A drop in red blood cells can result in tiredness and shortness of breath. A drop in blood platelets can result in bruising or bleeding more easily.
- Seldom side effects include loss of taste, loss of appetite, some hearing loss, tingling or numbness in toes or fingers.

Long term side effects of treatment

Side effects that arise during or shortly after treatment usually pass away two weeks after treatment. However in the long run radiotherapy can directly damage some of the normal organ function or cause tissue to become less elastic (fibrosis). This can cause side effects that may become more apparent during the years following treatment. Your radiation oncologist will provide you with information on whom to contact in case of symptoms. These side effects may include:

- Ovaries will stop functioning. This causes infertility and causes early menopause in women that have not had their menopause.
- The vagina can become less elastic, narrower and dryer. Altogether these side effects may affect your sex life. The use of vaginal lubrication and vaginal dilators, to stretch the vagina, is recommended and you can receive more information on this subject separately.
- Parts of the bowel in the pelvic area may become less elastic and function less well. This can result in more frequent, loose stools and bowel cramps. Seldom this results in constipation or a bloated feeling.
- Due to reduced elasticity of the bladder it can not stretch as much which can give the sensation that its is full sooner.
- Swelling of the legs may be a result of fibrosis along the draining lymphatic tissue in the pelvis.
- Occasionally increased growth of small blood vessels in the mucosa of the bowel, bladder or vagina may cause bleeding.

After treatment

After treatment you will have regular outpatient visits with your radiation oncologist. These visits are used to check on the effect of treatment to control the tumor but also possible side effects. In the first year they will be every 3 months, during the second and third year every 6 moths and then yearly up to five years after treatment. During these visits a gynecological examination will be done. In addition, both at 3 months and one year after treatment a MRI scan will be made.

Quality of life investigation

Quality of life investigation is done using a questionnaire. The questionnaire is handed out before treatment starts, during treatment and at regular intervals up to 5 years after treatment. The questionnaire consists of 54 questions and will take approximately 20-30 minutes to fill in. These questions ask you about the most common symptoms (side effects) of treatment, but also ask about more general functioning such as physical activity and emotional functioning. Using these questionnaires you can provide direct information on what the consequences of treatment are for your wellbeing. The information from these questionnaires provides important results for the study. Strict privacy is enforced and the information from the questionnaires will be handled under coded.

Study participation

The treatment with expected outcome and side effects as described above is the standard treatment. You will receive the same treatment if you do not participate in this study. The aim of this study is collect and register details about the treatment, the outcomes of treatment, side effects and quality of life. You will have to decide if you will participate in this study or not. If you decide to participate you will be asked to sign the written informed consent form. It is always possible to withdraw your study participation at any point in time. Your radiation oncologist may also propose to withdraw from the study if that may benefit your situation. If you decide not to participate you will receive the same standard treatment and this will not in any way affect the relationship with your radiation oncologist. You do not have to decide immediately if you want to participate, you can discuss the study with others and are provided with enough time to consider the possible benefits and disadvantages.

In summary the main benefits and disadvantages of study participation are:

- The benefits of participating to this study are that external review and quality assurance of treatment planning and execution is part of the study and that you’re outcomes (tumor control and side effects of treatment) will be used to better understand how to improve this treatment further in the future.
- Having to fill in quality of life questionnaires may be seen as a disadvantage of participating to the study.

Confidentiality

You can be assured that all information that will be registered for this study will be handled confidential. Information that will be registered includes that of details of the treatment, details of the outcome on tumor control and side effects of treatment during the first five years after treatment. Before your data is sent to a central database anonymously, it will be coded using a unique study code. Only you're treating radiation oncologist and any personnel that is directly authorized through you're radiation oncologist will be able to see your information.

Tumor tissue

A small piece of tumor will be stored for future research. The tissue that was taken out to diagnose the cervical cancer can be used for this. This research will focus on finding alterations in the tissue that can help to better understand the outcomes of this study (effect of treatment on tumor control and side effects). The piece of tumor will be stored anonymously using you're unique study code. You will be asked separately to provide signed written informed consent for the use of the tumor tissue.

Financial support

This study receives limited financial support from Varian and Electa, both are companies that produce radiation therapy equipment. This financial support is limited and is used for administration and database management and data analysis. None of the individual persons involved in the study receive financial support from these companies.

Insurance

Since the standard treatment is used in this study, there is no separate insurance policy for this study. In case of complaints or liability issues, the standard procedure as is used for any other medical treatment or condition in your hospital will apply.

Further information

If you have any other questions about this study you can ask your treating radiation oncologist, medical oncologist or gynecologist about these. [provide contact details and phone numbers, including an independent physician].

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