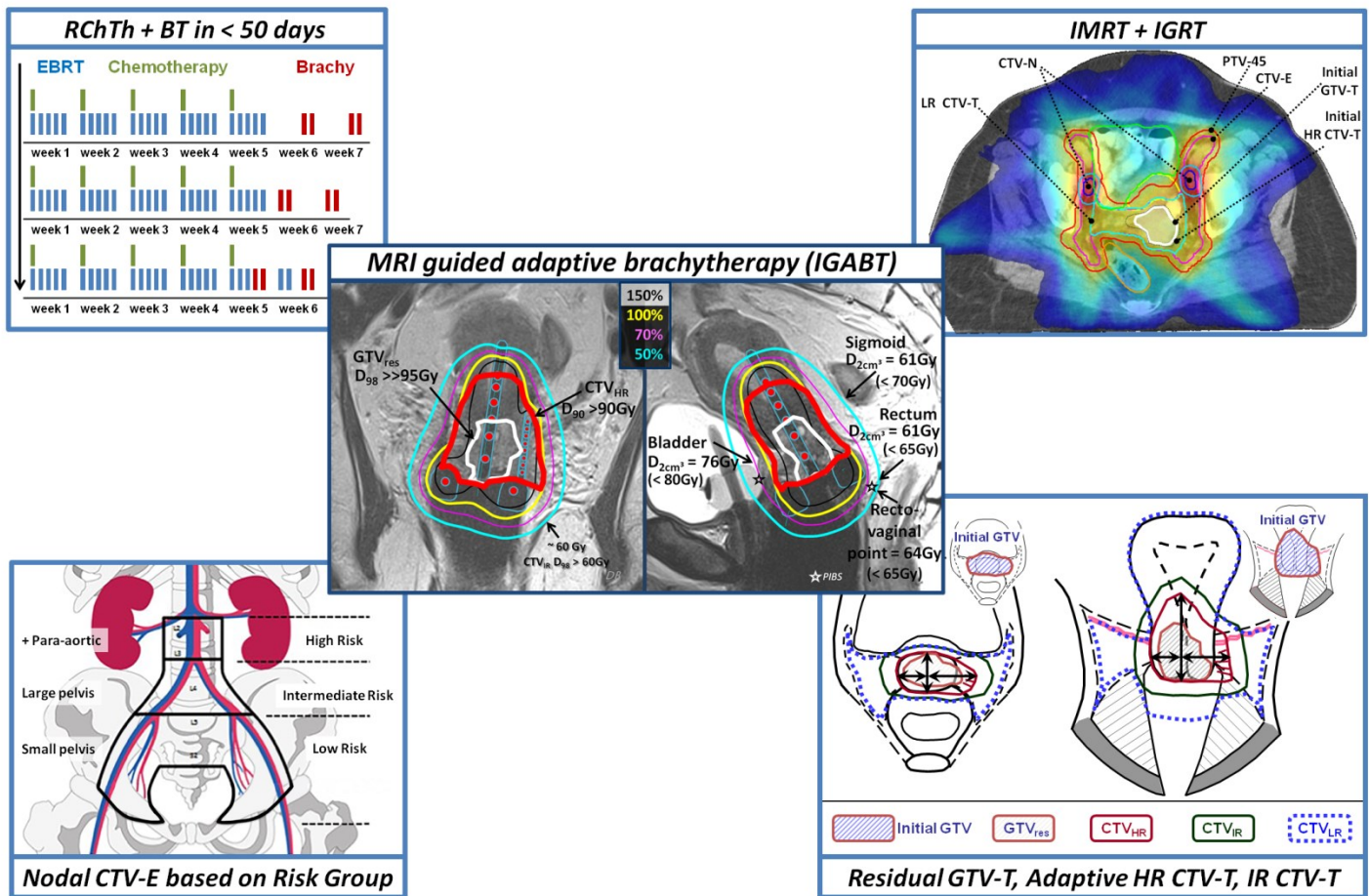


Image guided intensity modulated External beam radiochemotherapy and MRI based adaptive BRachytherapy in locally advanced CErvical cancer

EMBRACE-II



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CONTENTS

| | | |
|----|---|-----------|
| 1 | Contents | 1 |
| 2 | | |
| 3 | 1 Abbreviations | 6 |
| 4 | 2 Summary | 8 |
| 5 | 2.1 Background | 8 |
| 6 | 2.2 Interventions, aims and hypotheses | 8 |
| 7 | 2.3 Type of design | 9 |
| 8 | 2.4 Patients to be included | 9 |
| 9 | 2.5 Treatment of patients in the trial | 9 |
| 10 | 2.6 Quality assurance | 10 |
| 11 | 2.7 Outcome measures | 10 |
| 12 | 2.8 Evaluation of outcome measures | 10 |
| 13 | 2.9 Sample size and data maturity | 11 |
| 14 | 3 Introduction | 12 |
| 15 | 3.1 Background | 12 |
| 16 | 3.2 Tumor and target CONCEPTS FOR RESPONSE ADAPTED RADIOTHERAPY in cervix cancer: residual GTV-T, adaptive CTV-T_{HR} and CTV-T_{IR} | 13 |
| 17 | 3.3 Evidence from the retroEMBRACE and EMBRACE studies | 17 |
| 18 | 3.3.1 Local control and D90 to CTV _{HR} , GTV and CTV _{IR} | 17 |
| 19 | 3.3.2 Overall treatment time | 19 |
| 20 | 3.3.3 Urinary morbidity and bladder D _{2cm3} | 19 |
| 21 | 3.3.4 Rectal bleeding and rectum D _{2cm3} | 20 |
| 22 | 3.3.5 Bowel morbidity and sigmoid/bowel D _{2cm3} | 20 |
| 23 | 3.3.6 Vaginal morbidity and ICRU recto-vaginal dose | 21 |
| 24 | 3.3.7 Gastrointestinal/urinary morbidity and intermediate dose levels related to EBRT | 21 |
| 25 | 3.3.8 Patterns of spread and PROGNOSTIC PARAMETERS for nodal pelvic and para-aortic recurrences | 22 |
| 26 | 3.3.9 Administration of chemotherapy | 24 |
| 27 | 3.4 Internal target motion | 25 |
| 28 | 4 Interventions and Aims | 26 |
| 29 | 4.1 Interventions | 26 |
| 30 | 4.1.1 increased use of IC/IS technique in BT | 26 |
| 31 | 4.1.2 Reduction of vaginal source loading | 27 |
| 32 | 4.1.3 Systematic Utilisation of IMRT | 27 |
| 33 | 4.1.4 Utilisation of daily IGRT (set-up according to bony structures) | 28 |
| 34 | 4.1.5 EBRT target concept related to the primary tumour (CTV-T) and internal motion; Concepts for OAR contouring | 28 |
| 35 | 4.1.6 EBRT dose prescription and reporting | 28 |
| 36 | 4.1.7 Adaptation of EBRT nodal elective CTV according to risk of nodal and systemic recurrence | 28 |

| | | | |
|----|------------|---|-----------|
| 39 | 4.1.8 | Systematic application of simultaneous chemotherapy | 29 |
| 40 | 4.1.9 | Reduction of overall treatment time | 29 |
| 41 | 4.2 | Aims of the EMBRACE II study | 30 |
| 42 | 4.2.1 | General aims | 30 |
| 43 | 4.2.2 | Specific aims | 30 |
| 44 | 5 | Study design, endpoints and hypotheses | 31 |
| 45 | 5.1 | Study design | 31 |
| 46 | 5.2 | Estimate of patient accrual and study period | 31 |
| 47 | 5.3 | Hypotheses and endpoints | 31 |
| 48 | 5.3.1 | General hypothesis on overall survival | 32 |
| 49 | 5.3.2 | Specific hypotheses on technique, dose and volumes: | 32 |
| 50 | 5.3.3 | Specific hypotheses on clinical endpoints | 33 |
| 51 | 6 | EMBRACE Outline | 37 |
| 52 | 7 | Staging and patient work-up | 38 |
| 53 | 8 | Patient selection | 39 |
| 54 | 8.1 | Inclusion criteria | 39 |
| 55 | 8.2 | Exclusion criteria | 39 |
| 56 | 9 | External Beam Radiotherapy | 40 |
| 57 | 9.1 | Introduction | 40 |
| 58 | 9.1.1 | Aims of external Beam Radiotherapy (compare ch 3-5) | 40 |
| 59 | 9.1.2 | Nodal targets based on risk group allocation for nodal spread | 40 |
| 60 | 9.2 | Preparations for treatment planning | 42 |
| 61 | 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 | 44 |
| 62 | 9.3.1 | GENERAL Overview | 44 |
| 63 | 9.3.2 | Initial GTV and CTV related to primary tumour (GTV-T _{init} , CTV-T _{init} (HR, LR)) | 46 |
| 64 | 9.3.3 | GTV and CTV for pathologic lymph nodes (GTV-N, CTV-N) | 50 |
| 65 | 9.3.4 | CTV for nodal regions with assumed microscopic disease (CTV-E) | 50 |
| 66 | 9.3.5 | ITV (ITV-T) | 51 |
| 67 | 9.3.6 | Strategies to derive the ITV-T LR | 51 |
| 68 | 9.3.7 | Generating the ITV45 | 52 |
| 69 | 9.3.8 | PTV | 52 |
| 70 | 9.4 | Contouring of organs at risk, reference points | 54 |
| 71 | 9.5 | Contouring of Tumour, Targets and OARs based on MRI and CT | 54 |
| 72 | 9.6 | Dose and fractionation for PTV45 | 55 |
| 73 | 9.7 | Dose and fractionation for PTV-N (nodal boosting) | 55 |
| 74 | 9.8 | Technique and procedures for EBRT including daily image guidance | 56 |
| 75 | 9.8.1 | Angulation of the pelvis in relation to the lumbar spine | 57 |
| 76 | | | |

| | | | |
|-----|-------------|---|-----------|
| 77 | 9.9 | Planning aims for targets and organs at risk | 57 |
| 78 | 9.10 | Reporting of EBRT parameters | 58 |
| 79 | 10 | <i>BRACHYTHERAPY</i> | 59 |
| 80 | 10.1 | Introduction and specific aims for brachytherapy | 59 |
| 81 | 10.1.1 | Overall Schedule for EBRT and BT and chemotherapy | 59 |
| 82 | 10.1.2 | Pre-application treatment planning | 60 |
| 83 | 10.2 | Applicator insertion for brachytherapy | 60 |
| 84 | 10.3 | Imaging for brachytherapy | 61 |
| 85 | 10.4 | Applicator reconstruction and dose points for OARS | 62 |
| 86 | 10.5 | Contouring for brachytherapy: OARS, GTV_{res}, adaptive CTV_{HR}, CTV_{IR} | 64 |
| 87 | 10.5.1 | Contouring of organs at risk | 64 |
| 88 | 10.5.2 | Contouring of target volumes | 65 |
| 89 | 10.6 | Treatment planning for brachytherapy | 66 |
| 90 | 10.6.1 | Evidence obtained from retroEMBRACE and EMBRACE I | 66 |
| 91 | 10.6.2 | Planning aims and dose prescription for EMBRACE II | 67 |
| 92 | 10.6.3 | Dose optimisation for brachytherapy | 67 |
| 93 | 10.6.4 | Intracavitary treatment plans should be based on iterative steps | 68 |
| 94 | 10.6.5 | Vaginal dose de-escalation | 68 |
| 95 | 10.6.6 | PTV and dose conformality considerations in relation to brachytherapy | 69 |
| 96 | 10.7 | Dose and volume recording and reporting | 70 |
| 97 | 11 | <i>Systemic treatment</i> | 71 |
| 98 | 11.1 | Aims for chemotherapy | 71 |
| 99 | 11.2 | Concomitant chemotherapy | 71 |
| 100 | 11.3 | Adjuvant chemotherapy | 71 |
| 101 | 12 | <i>Outcome assessment</i> | 73 |
| 102 | 12.1 | Oncological outcome and salvage treatment | 73 |
| 103 | 12.2 | Morbidity | 74 |
| 104 | 12.3 | Quality of Life (QoL) | 75 |
| 105 | 13 | <i>Translational research</i> | 76 |
| 106 | 13.1 | Prognostic markers | 76 |
| 107 | 13.2 | Predictive markers for radiotherapy related morbidity | 76 |
| 108 | 14 | <i>Patient material, benchmarking, validation, evaluation and statistics</i> | 78 |
| 109 | 14.1 | Benchmark of outcome and treatment related parameters | 78 |
| 110 | 14.2 | Validation of dose and volume effects | 78 |
| 111 | 14.3 | Exploration and Evaluation of dose and volume effects | 78 |

| | | | |
|-----|-------------|--|-----------|
| 112 | 14.4 | Identification of prognostic and predictive parameters | 78 |
| 113 | 14.5 | Statistics | 78 |
| 114 | 15 | Accreditation, dummy run, data monitoring, quality assurance and continuous education | 80 |
| 115 | 15.1 | Commitment letter, compliance questionnaire and process document | 80 |
| 116 | 15.2 | Dummy run | 80 |
| 117 | 15.2.1 | Training, registration, and submission | 81 |
| 118 | 15.2.2 | Evaluation by study coordinators | 81 |
| 119 | 15.3 | Data monitoring | 81 |
| 120 | 15.4 | Continuous education | 82 |
| 121 | 16 | Patient enrollment procedure | 83 |
| 122 | 17 | Case record forms, procedures for data collection, EMBRACE II database | 84 |
| 123 | 18 | Ethical considerations | 85 |
| 124 | 18.1 | PATIENT PROTECTION | 85 |
| 125 | 18.2 | SUBJECT IDENTIFICATION | 85 |
| 126 | 18.3 | INFORMED CONSENT | 85 |
| 127 | 18.4 | ADVANTAGES AND DISADVANTAGE FOR THE PATIENTS | 85 |
| 128 | 19 | PUBLICATION OF DATA | 86 |
| 129 | 20 | Study office, Study coordinators, Study structure, communication | 86 |
| 130 | 20.1 | Study-office EMBRACE II Vienna (at present: 09/2015): | 87 |
| 131 | 20.2 | Study Coordination: | 87 |
| 132 | 21 | EMBRACE RESEARCH GRoup | 88 |
| 133 | 22 | AppendiCES | 89 |
| 134 | 22.1 | Appendix 1 Standard Clinical Diagram | 89 |
| 135 | 22.2 | Appendix 2 Gyn GEC ESTRO Recommendations I-IV, ICRU 88 | 91 |
| 136 | 22.3 | Appendix 3. Compliance questionnaire | 93 |
| 137 | 22.4 | Appendix 4. Clinical cases for contouring | 97 |
| 138 | 22.4.1 | Cases from Vienna, Utrecht and Aarhus, contouring tables | 97 |
| 139 | 22.5 | Appendix 5: EBRT contouring atlas (complement to chapter 9) | 98 |
| 140 | 22.5.1 | Introduction | 98 |
| 141 | 22.5.2 | Clinical Target Volumes related to the primary tumor | 98 |
| 142 | 22.5.3 | Fixed margin approach | 99 |
| 143 | 22.5.4 | individualized approach | 103 |
| 144 | 22.5.5 | Clinical Target Volumes for nodal metastases and nodal regions | 105 |
| 145 | 22.5.6 | Para-aortic nodes | 109 |
| 146 | 22.5.7 | Inguinal nodes | 109 |

| | | | |
|-----|-------------|--|------------|
| 147 | 22.5.8 | Planning Target Volumes (PTV) | 110 |
| 148 | 22.5.9 | nodal boost | 111 |
| 149 | 22.5.10 | Primary target contouring summary with diagnostic MRI* | 112 |
| 150 | 22.5.11 | Primary target contouring summary with an MRI in treating position | 113 |
| 151 | 22.5.12 | Contouring of organs at risk | 117 |
| 152 | 22.5.13 | For para-aortic irradiation in addition | 119 |
| 153 | 22.6 | Appendix 6: Measurement and reporting of SUV | 122 |
| 154 | 22.7 | Appendix 8: CRFs (ch 16) | 122 |
| 155 | 22.8 | Appendix 9: Principals and structures of EMBRACE RESEARCH GROUP | 122 |
| 156 | 22.9 | Appendix 10: Patient Information | 124 |
| 157 | 23 | References | 128 |
| 158 | | | |

1 ABBREVIATIONS

| | | |
|-----|---------------------|--|
| 159 | | |
| 160 | | |
| 161 | | |
| 162 | ¹⁸ F-FDG | Fluorine 18 - Fluorodeoxyglucose |
| 163 | 2/3/4D | Two/Three/Four-dimensional |
| 164 | ACT | Addenbrooke's Contouring Tool |
| 165 | ATRAB | Applied and Translational Radiobiology (Medical University Vienna) |
| 166 | AUC | Area Under the Curve |
| 167 | BL | Baseline |
| 168 | BT | Brachytherapy |
| 169 | CBCT | Cone beam computed tomography |
| 170 | CHT | Chemotherapy |
| 171 | COP | Coverage Probability |
| 172 | CR | Complete Remission |
| 173 | CRF | Case Report Form |
| 174 | CRT | Conformal Radiotherapy |
| 175 | CSS | Cancer Specific Survival |
| 176 | CT | Computed Tomography |
| 177 | CTCAE | Common Terminology Criteria for Adverse Events |
| 178 | CTV | Clinical Target Volume |
| 179 | CuSO ₄ | Copper sulphate |
| 180 | D90 | The isodose that includes 90% of the target |
| 181 | D100 | The isodose that includes 100% of the target |
| 182 | D2cm ³ | Minimum dose in the most exposed 2 cm ³ of an OAR |
| 183 | DFS | Disease Free Survival |
| 184 | DNA | Deoxyribonucleic acid |
| 185 | DVH | Dose Volume Histogram |
| 186 | EANM | European Association of Nuclear Medicine |
| 187 | EBRT | External Beam Radiotherapy |
| 188 | EMBRACE | The European and International study on MRI-guided Brachytherapy in locally Advanced |
| 189 | | Cervical Cancer |
| 190 | EORTC | European Organisation for Research and Treatment of Cancer |
| 191 | EPID | Electronic Portal Imaging Device |
| 192 | ESTRO | European Society for Therapeutic Radiology and Oncology |
| 193 | EQD2 | Equivalent dose in 2 Gy fractions |
| 194 | FIGO | Fédération Internationale de Gynécologie et d' Obstétrique |
| 195 | FTE | Full Time Equivalent |
| 196 | Fx | Fraction |
| 197 | G | (Morbidity) Grade |
| 198 | GEC | Groupe Européen de Curiethérapie |
| 199 | GFR | Glomerula Filtration rate |
| 200 | GI | Gastro-Intestinal |
| 201 | GTV | Gross Tumor Volume |
| 202 | Gy | Gray |
| 203 | HDR | High Dose Rate |
| 204 | HPV | Human Papilloma Virus |
| 205 | HR | High Risk |
| 206 | IC | Intracavitary |

| | | |
|-----|--------------------|---|
| 207 | ICH | International Conference on Harmonisation of Technical Requirements for Registration of |
| 208 | | Pharmaceuticals for Human Use |
| 209 | ICRU | International Commission on Radiation Units and Measurements |
| 210 | IMRT | Intensity Modulated Radiotherapy |
| 211 | IGRT | Image Guided Radiotherapy |
| 212 | IR | Intermediate Risk |
| 213 | IS | Interstitial |
| 214 | ITV | Internal Target Volume |
| 215 | IV | Intravenous |
| 216 | kV | Kilovoltage |
| 217 | LACC | Locally Advanced Cervical Cancer |
| 218 | LN | Lymph Nodes |
| 219 | LR | Low Risk |
| 220 | MRI | Magnetic Resonance Imaging |
| 221 | MVCT | Megavoltage Computed Tomography |
| 222 | N0/N- | Lymph Node Negative |
| 223 | N1/N+ | Lymph Node Positive |
| 224 | OAR | Organs at Risk |
| 225 | OS | Overall Survival |
| 226 | OTT | Overall Treatment Time |
| 227 | PAN | Para-Aortic Lymph Nodes |
| 228 | PDR | Pulsed Dose Rate |
| 229 | PET-CT | Positron Emission Tomography- Computed Tomography |
| 230 | PFS | Progression Free Survival |
| 231 | PI | Principal Investigator |
| 232 | PIBS | Posterior-Inferior Border of Symphysis |
| 233 | PTV | Planning Target Volume |
| 234 | QoL | Quality of Life |
| 235 | RT | Radiotherapy |
| 236 | SD | Standard Deviation |
| 237 | SIB | Simultaneous Integrated Boost |
| 238 | SPSS | Statistical Package for Social Sciences |
| 239 | SUV _{max} | Maximum Standardized Uptake Value |
| 240 | TNM | Tumor (Lymph)Nodes Metastasis |
| 241 | TPS | Treatment Planning System |
| 242 | TRAK | Total Reference Air Kerma |
| 243 | uCR | Uncomplete Remission |
| 244 | US | Ultrasound |
| 245 | VMAT | Volumetric Modulated Arc Therapy |
| 246 | WHO | World Health Organization |
| 247 | | |

248 2 SUMMARY

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250 2.1 BACKGROUND

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

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

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

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270 2.2 INTERVENTIONS, AIMS AND HYPOTHESES

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

272

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

282

283 The general aims of the EMBRACE II study are:

284

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

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- 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

298 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.

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

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305 **2.3 TYPE OF DESIGN**

306 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.

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311 **2.4 PATIENTS TO BE INCLUDED**

312 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).

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316 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.

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322 **2.5 TREATMENT OF PATIENTS IN THE TRIAL**

323 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 $\alpha/\beta = 10$ Gy for tumour effects and $\alpha/\beta = 3$ Gy for late normal tissue damage. The repair half time is assumed to be 1.5 hrs.

324

325

326 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

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331 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).
332 Maximal treatment time including both EBRT and BT is 50 days.

333 Brachytherapy is prescribed with dose escalation for advanced disease with large adaptive CTV-T_{HR} including IC/IS techniques and dose
334 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
335 the applicator in place which enables definition of the relevant volumes of interest directly on the images for treatment planning:
336 GTV_{res}, adaptive CTV_{HR}, CTV_{IR} and organ volumes. The applicator and the reference points are reconstructed in the same image series.
337 All treatment plans have to be optimized to achieve defined planning aims for dose and volume parameters for tumor (D98 for GTV_{res})
338 and target volumes (e.g. D90-95 Gy for adaptive CTV-T_{HR}) and for 2cm³ reference volumes for OARs (e.g. <80 Gy for bladder, <65 Gy for
339 rectum) and for vaginal reference points (recto-vaginal point < 65 Gy, PIBS). If the planning aims cannot be achieved, limits for the
340 finally prescribed dose levels are defined for GTV_{res}, CTV_{HR}, CTV_{IR}, point A, bladder, rectum, sigmoid bowel and vagina. Planning aim
341 doses and limits for the finally prescribed dose levels are based on the experience of the previous retroEMBRACE and EMBRACE trials.

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

344

345 2.6 QUALITY ASSURANCE

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

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

352 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
353 analysis of the results is obtained. Continuous data monitoring is performed through the study offices in Vienna and Aarhus and
354 through Utrecht for the centres in the Netherlands.

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

356

357 2.7 OUTCOME MEASURES

358 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
359 related to OAR in the pelvis and the para-artic region as well as overall survival, cancer specific survival and systemic control are the
360 primary outcome measures. All endpoints will be evaluated by actuarial statistics. Morbidity will be scored by use of the Common
361 Terminology Criteria for Adverse Events (CTCAE v3.0/4.0). QoL will also be systematically recorded in all patients.

362

363 2.8 EVALUATION OF OUTCOME MEASURES

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

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

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370 **2.9 SAMPLE SIZE AND DATA MATURITY**

371 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
372 endpoints by univariate and multivariate analysis.

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3 INTRODUCTION

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3.1 BACKGROUND

380 The standard treatment for locally advanced cervical cancer is currently radio-chemotherapy consisting of EBRT, intracavitary BT and
381 concomitant chemotherapy with Cisplatin. During the last decade, the utilisation of MRI guided brachytherapy has grown based on the
382 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
383 the cervix is among the first cancer sites where response-adaptive radiotherapy has been successfully implemented in clinical practice.
384 The novel target concepts involved in response-adaptive radiotherapy are described further in section 3.2. Acquisition of MRI at the
385 time of brachytherapy allows the brachytherapy boost to be individually tailored according to the residual tumour volume after
386 typically 40-50 Gy of external beam radiation therapy (EBRT). This approach has changed patterns of clinical practise with regard to
387 dose administration, and significant improvements in clinical outcome have been reported from mono-institutional settings with regard
388 to local control, overall survival and morbidity (Pötter R. et al. 2007, Pötter R. et al. 2011, Lindegaard JC. et al. 2013).

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

395 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.
396 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.
397 [in submission 2015](#)). Nodal and systemic control also remains challenging with levels of 87% and 77% at 5 years, respectively (all stages)
398 ([RetroEMBRACE 01/2015 work in progress](#)). Furthermore, treatment related urinary and gastrointestinal late morbidity is still a
399 significant problem with the 3 year actuarial incidence of intermediate to major morbidity ($G \geq 2$) being 30% and 29% for urinary and
400 gastrointestinal side effects, respectively, according to EMBRACE data. Major morbidity ($G \geq 3$) is seen in 7% and 8%, respectively
401 ([EMBRACE 2014, work in progress](#)). Patient reported symptoms are equally high with 30-40% of patients reporting significant urinary
402 and gastrointestinal bother according to quality of life data from the EMBRACE study ([EMBRACE 2015, work in progress](#)). Sexual side
403 effects are still poorly understood although almost 30% of patients develop significant narrowing and shortening of the vagina
404 (Kirchheiner K. et al. 2014). Further development of both BT and EBRT is needed to improve on local control, regional control as well as
405 on treatment related morbidity and quality of Life.

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

413 Advances in image guided adaptive brachytherapy include improved individualisation of brachytherapy applicators as well as
414 individualised dose optimisation. Dose optimisation using intracavitary (IC) applicators has shown to significantly decrease OAR dose
415 and morbidity (Charra-Brunaud C. et al. 2012). Dose optimisation based on IC may be used to improve target dose coverage in tumours
416 of limited size at BT, but for large residual tumours or in case of unfavourable topography, IC BT has limited possibilities to cover the
417 CTV_{HR} to doses larger than e.g. 85Gy (Tanderup K. et al. 2010). Combined intracavitary-interstitial (IC/IS) applicators have been
418 developed for targeting tumours which are not well covered by intracavitary (IC) applicators (Dimopoulos JC. et al. 2006, Kirisits C. et al.
419 2006). The IC/IS applicators allow for improved dose conformality, and target dose escalation and/or dose de-escalation in organs at

420 risk can be carried out (Fokdal L. et al. 2013). Furthermore, in the process of moving from standard loading to 3D image guided
421 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
422 previous clinical practise. However, EMBRACE data have demonstrated that dose to the ICRU recto-vaginal point correlate with the
423 probability of $G \geq 2$ vaginal morbidity (Kirchheiner K. et al. in submission 2015). This observation is a strong motivation to explore new
424 approaches to dose optimisation which spare vaginal mucosa and decreases the dose to the ICRU recto-vaginal point.

425 Pelvic EBRT is currently delivered with different techniques: 3D conformal EBRT, intensity modulated radiotherapy (IMRT), volumetric
426 arc techniques (VMAT), and tomotherapy. Application of IMRT in cervix cancer significantly reduces the volume of tissue irradiated to
427 intermediate doses such as 30-40Gy for bladder, rectum, sigmoid and bowel (Forrest J. et al. 2012). The progress from 3D conformal
428 EBRT to IMRT has demonstrated a reduction of treatment related morbidity in mono-institutional and retrospective settings (Mundt AJ.
429 et al. 2003, Xu KM. et al. 2015). Furthermore, EMBRACE quality of life data has shown a significantly lower incidence of bowel
430 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).

431 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
432 improve the possibilities to perform on board image guidance in EBRT. With imaging devices mounted on or in a fixed relationship to
433 the accelerator, it is now possible to perform daily imaging with the patient in the treatment position. The on-board images can be
434 fused with the treatment planning scan and a couch correction can be applied to correct for translational setup errors. In the case of
435 cervix cancer the daily imaging can be used for visualisation and fusion of bony anatomy. By using daily image guided set-up in cervix
436 cancer, the precision of the elective lymph node clinical target volume (CTV-E) can be significantly improved (Laursen LV. et al. 2012),
437 and thereby planning target volume (PTV45 Gy) margins can be reduced. A further step is to use daily image guidance (CBCT) to
438 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
439 motion of the primary gross tumour volume (GTV), the CTV-T and the uterus (see chapter 9). Such approaches have been developed
440 and involve adaptive EBRT where daily library plans are applied (Heijkoop ST. et al. 2014). Decrease of PTV margins as well as
441 implementation of IMRT has potential to reduce morbidity, in particular bowel morbidity.

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

451 3.2 TUMOR AND TARGET CONCEPTS FOR RESPONSE ADAPTED RADIOTHERAPY IN CERVIX CANCER: 452 RESIDUAL GTV-T, ADAPTIVE CTV-T_{HR} AND CTV-T_{IR}

453 The target concept for response-adapted radiotherapy is focussed on the primary tumour change (GTV-T) and the change of the CTV-T
454 during upfront chemo-radiation. These changes are essential for selecting the appropriate target for brachytherapy (see chapter 5.4,
455 ICRU report 88). Therefore new terms and concepts have been introduced as compared to ICRU 50, 62 and 83 which correspond to
456 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
457 further elaborated in the ICRU/GEC ESTRO report 88. Therefore, in the following, a short summary is given, taken from the recent
458 ICRU/GEC ESTRO report 88 (chapter 5):

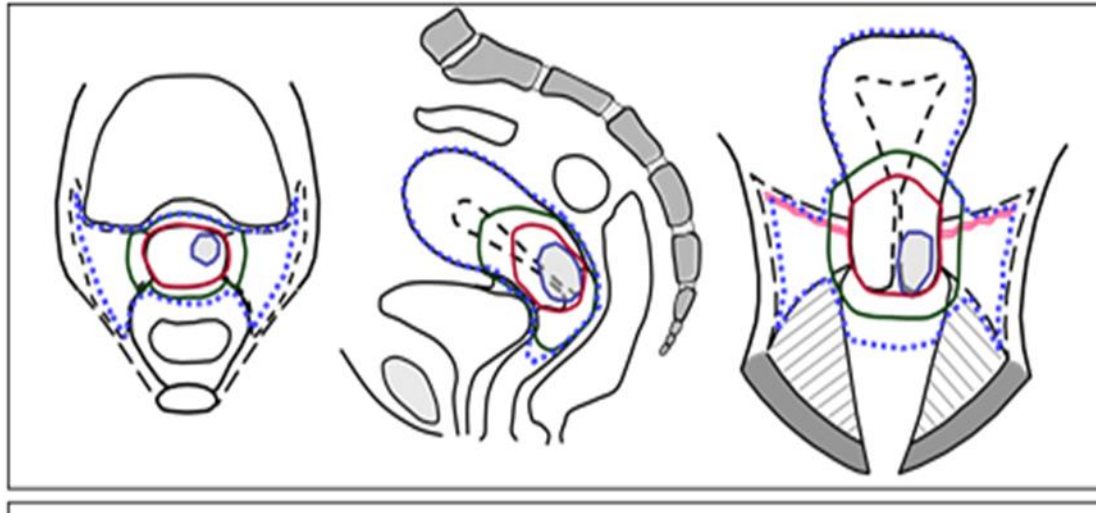
459 “Residual GTV-T (GTV-T_{res}) is defined as the residual macroscopic tumor at the time of (brachytherapy) boost after treatment assumed
460 sufficient to control microscopic disease. GTV-T_{res} still bears clinical and/or imaging characteristics similar to the initial GTV-T_{init} and may
461 represent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

| | |
|-----|--|
| 462 | 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. |
| 463 | |
| 464 | 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. |
| 465 | |
| 466 | 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.* |
| 467 | |
| 468 | |
| 469 | |
| 470 | 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. |
| 471 | |
| 472 | |
| 473 | 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) |
| 474 | |
| 475 | |
| 476 | |
| 477 | |
| 478 | * 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). |
| 479 | |

480 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.

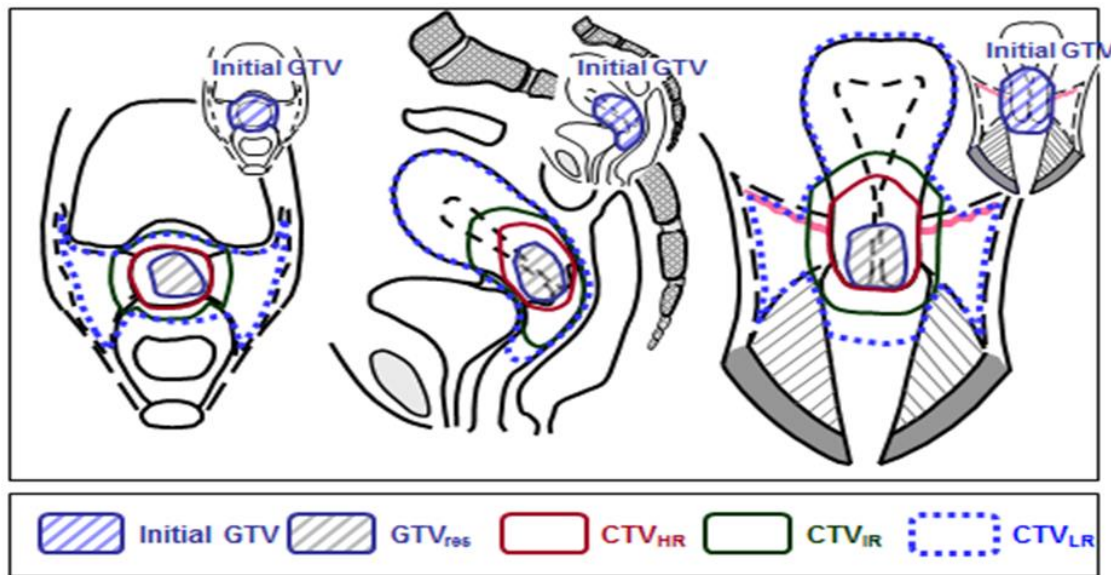
485 In the following, typical examples for contouring are given for brachytherapy in schematic diagrams for contouring of GTV-T_{res}, adaptive CTV-T HR, CTV-T IR and adaptive CTV-T LR taking into account various disease extensions and stages at diagnosis and various forms of response (taken from ICRU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

488



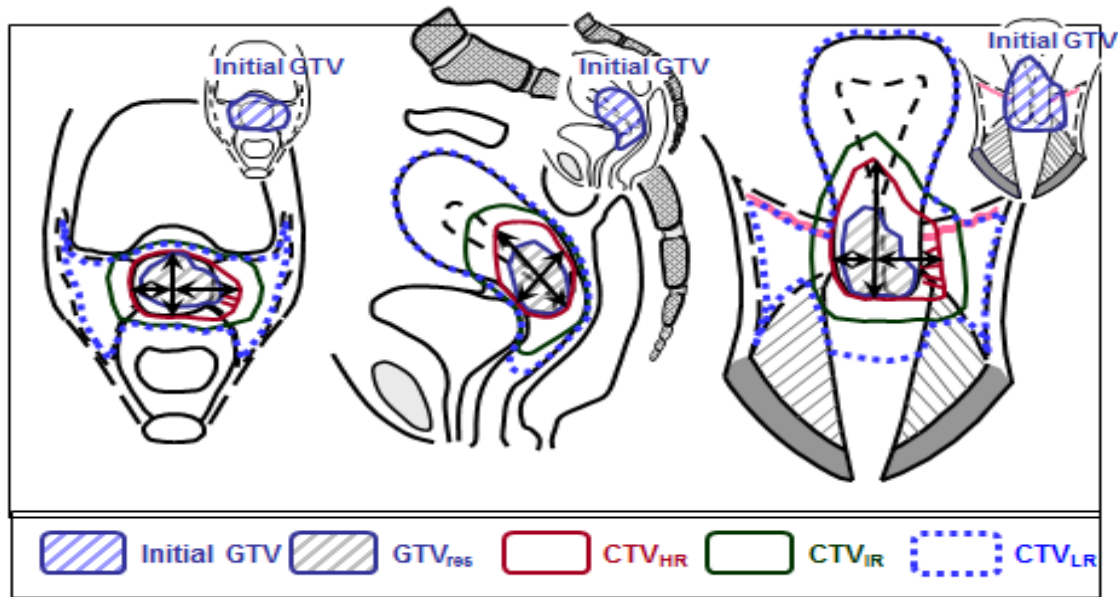
489

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



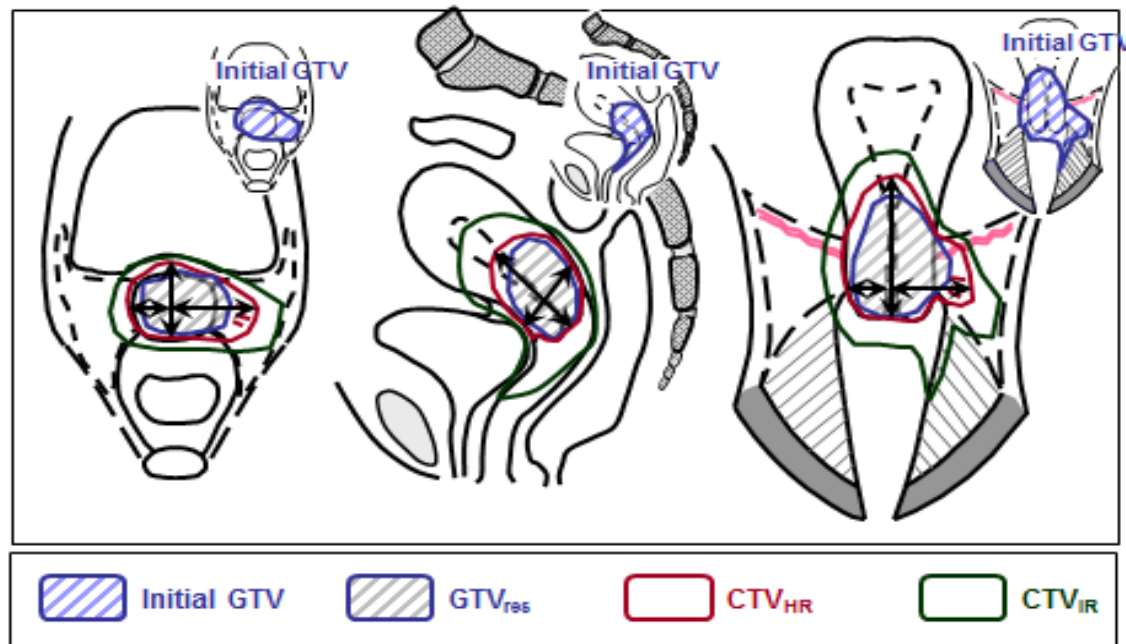
495

496 Figure 3.2 (compare figure 9.5 for EBRT). “Schematic diagram for cervical cancer, stage IB2 (bulky disease), good response after chemo-
 497 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)
 498 (GTV-T_{init} plus margins around the CTV-T HR_{adapt}) and CTV-T LR_{adapt} for adaptive brachytherapy: coronal, transversal and sagittal view
 499 (see also Appendix example 2)” (figure 5.9 from ICRU report 88 in press).



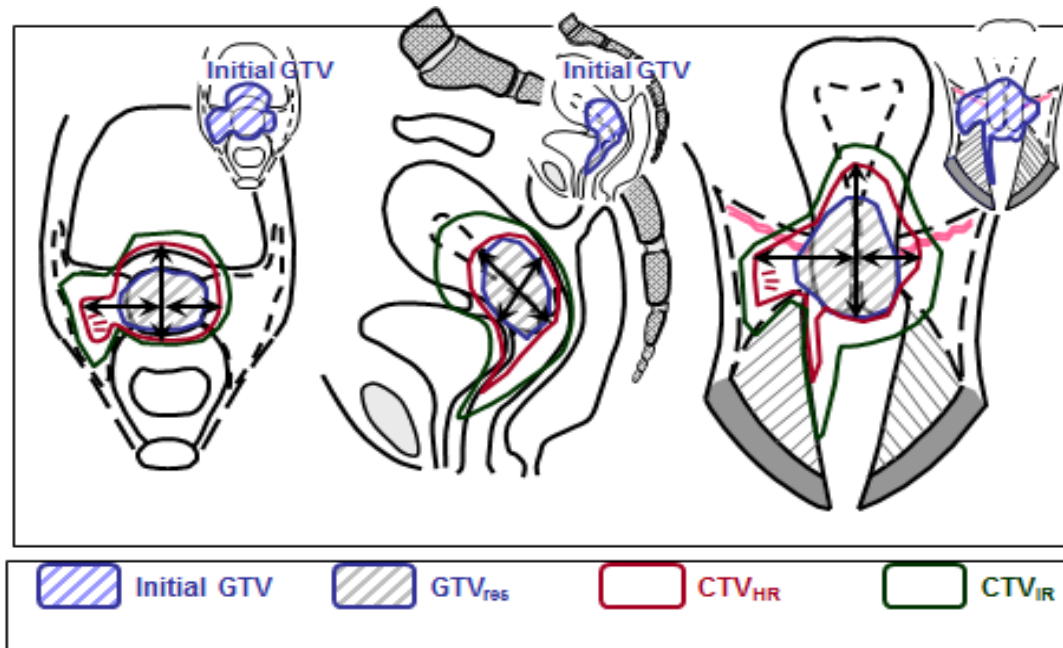
500

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).



505

506 Figure 3.4 (compare figure 9.7 for EBRT). “Schematic diagram for cervical cancer, IIB, 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).



510

511 Figure 3.5 (compare figure 9.8 for EBRT). “Schematic diagram for cervical cancer, with bladder infiltration, stage IVA, and good response
 512 after chemo-radiotherapy: large initial and residual GTV-T (GTV-T_{init}, GTV-T_{res}), extensive gray zones, residual infiltration in the posterior
 513 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,
 514 transversal and sagittal view. Maximum width, thickness and height of the HR CTV-T are indicated.” (figure 5.12 from ICRU report 88).

515

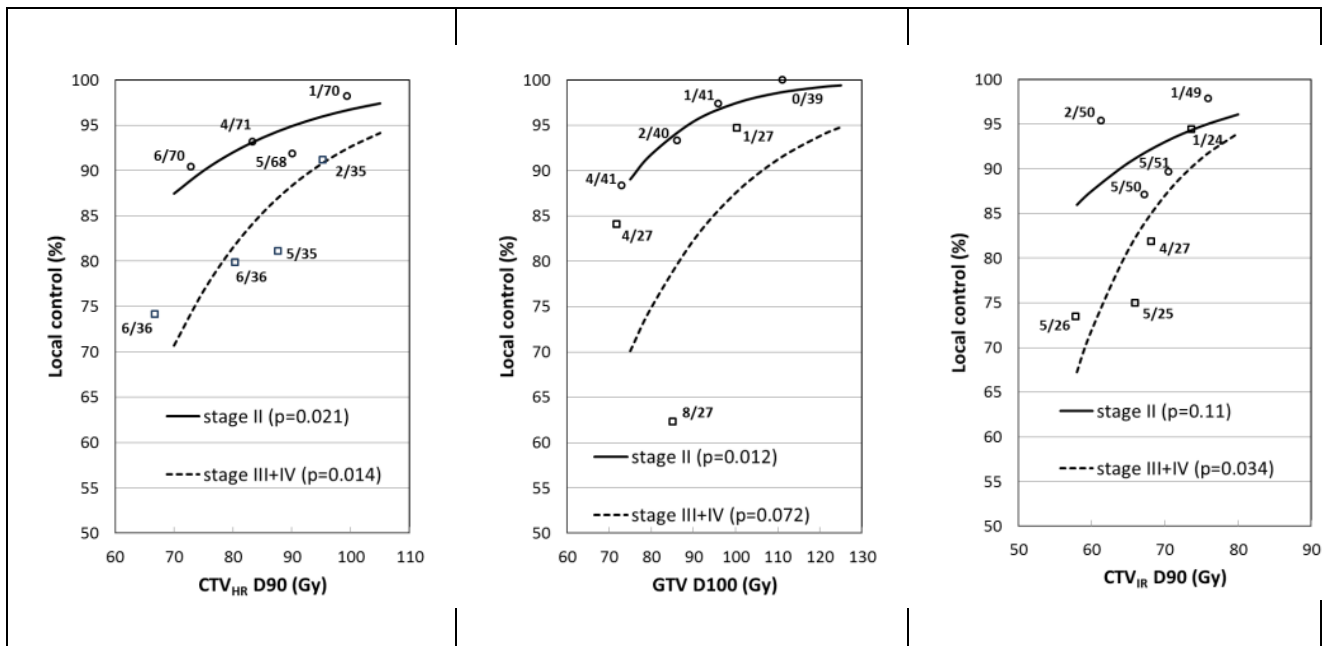
516 3.3 EVIDENCE FROM THE RETROEMBRACE AND EMBRACE STUDIES

517 When the prospective EMBRACE study was designed, there was still only limited evidence on dose and effect relations for target or
 518 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
 519 at risk (OAR). Therefore, brachytherapy dose prescription in the EMBRACE study was based on institutional practice which varied
 520 considerably with regard to total dose, fractionation, dose rate, and brachytherapy applicators. This means that a significant variation in
 521 dose prescription is present both at the institutional as well as on the patient level in the retroEMBRACE and EMBRACE studies. This
 522 heterogeneity in dose administration has provided a unique opportunity to learn about the effect of different dose levels, and a vast
 523 amount of new knowledge on dose and effect relationships is currently growing from the EMBRACE and retroEMBRACE studies for
 524 GTV_{res}, CTV_{HR}, CTV_{IR}, bladder, rectum, bowel, and vagina. Furthermore, there are a number of mono-institutional studies on dose and
 525 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
 526 published literature on dose and effect is the prerequisite of designing the EMBRACE II dose prescription protocol with dose planning
 527 aims for target and OARs. In the following sections the upcoming dose effect data from retroEMBRACE and EMBRACE is described.

528 3.3.1 LOCAL CONTROL AND D90 TO CTV_{HR}, GTV AND CTV_{IR}

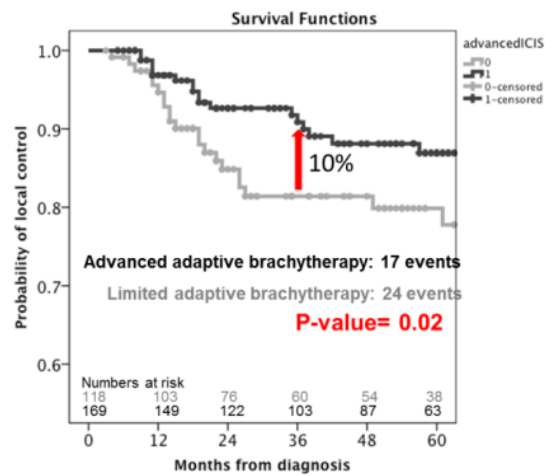
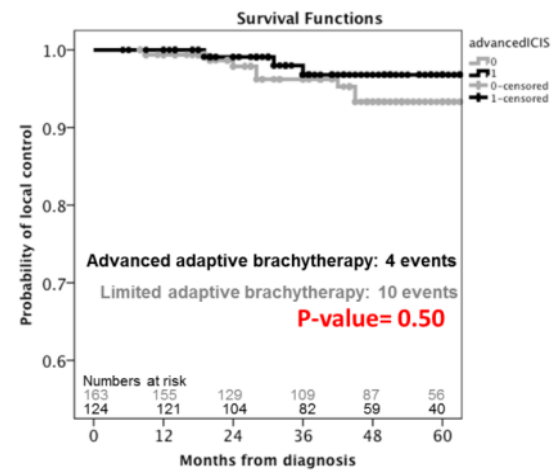
529 Relation between target dose (CTV_{HR}, GTV and CTV_{IR}) and incidence of local control was analyzed in a clinical material of 488 pts
 530 enrolled in the retroEMBRACE study from 6 institutions performing MRI guided adaptive brachytherapy. A significant dose effect
 531 relationship was found for CTV_{HR}, GTV and CTV_{IR} in stage II and stage III disease (figure 3.6). Furthermore, for HR CTV a cox regression
 532 dose response analysis showed that both CTV_{HR} volume and dose was related with local control. The data supports a dose constraint of
 533 $\geq 85\text{Gy EQD2}$ to the CTV_{HR} D90 which is predicted to lead to a 3-year actuarial local control of $>96\%$ in tumours $\leq 30\text{cc}$ and $>91\%$ in
 534 tumours $>30\text{cc}$. Dose planning aims for CTV_{IR} and GTV_{res} proposed for similar levels of local control are: CTV_{IR} D98 $\geq 60\text{Gy}$ and GTV_{res}
 535 D98 $\geq 95\text{Gy}$.

536 Utilization of combined intracavitary/interstitial (IC/IS) applicators is an essential tool for dose escalation in large tumours. In terms of
 537 dose, the IC/IS applicators can widen the therapeutic window by 5-10Gy as demonstrated by direct comparison between IC and IC/IS
 538 applicators (Fokdal L. et al. 2013). This is further supported by data from the retroEMBRACE and EMBRACE studies which demonstrate
 539 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
 540 majority of patients. In retroEMBRACE, the CTV_{HR} dose administration was larger by 10Gy in institutions systematically applying
 541 combined IC/IS applicators, while doses to OARs were not increased. The increased dose resulted in improved local control in patient
 542 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
 543 involve significant increase of dose to OARs, the incidence of morbidity was not different in the patient cohort with frequent application
 544 of IC/IS as compared to the cohort where mainly IC was applied, although there was a tendency that vaginal morbidity was slightly
 545 increased in the IC/IS cohort.



546 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)

547

CTVHR $\geq 30 \text{ cm}^3$ CTVHR $< 30 \text{ cm}^3$ 

549 gure 3.7. Local control for large (left panel) and small (right panel) CTV_{HR}, as depending on routine application of IC/IS technique.
 550 Advanced adaptive brachytherapy implies that >20% of the patients in the cohort were treated with IC/IS. Limited adaptive
 551 brachytherapy implies that the majority of patients (<20%) were treated with IC technique. Data from retroEMBRACE (Fokdal L. et al.
 552 2015, RetroEMBRACE work in progress).

553

554 3.3.2 OVERALL TREATMENT TIME

555 The effect of overall treatment (OTT) time was investigated in the same clinical material as in section 3.2.1: 488 pts enrolled
 556 in the retroEMBRACE study from 7 institutions. Multivariate Cox Proportional Hazards modelling was performed to include
 557 the effects of stage, histology, CTVHR dose, CTVHR volume, and OTT. The effect of OTT shortening by one week was
 558 equivalent to escalating CTVHR dose by 5Gy (D90), resulting in increase of local control by 1.0% for CTVHR volume of
 559 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
 560 for a treatment time of 7 weeks, and therefore if treatment time is longer or shorter than 7 weeks, the dose planning aims
 561 should in principle be adjusted by 5Gy per week for CTVHR. The data underlines the importance of keeping the OTT as
 562 short as possible, in particular for large size CTVHR, where higher dose is needed to reach >90% local control.

563

564 3.3.3 URINARY MORBIDITY AND BLADDER D_{2CM3}

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

569 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
 570 between D_{2cm³} and ICRU bladder dose as a surrogate of the D_{2cm³} location (Nkiwane KS. et al. 2015, Mazon R. et al. 2015).

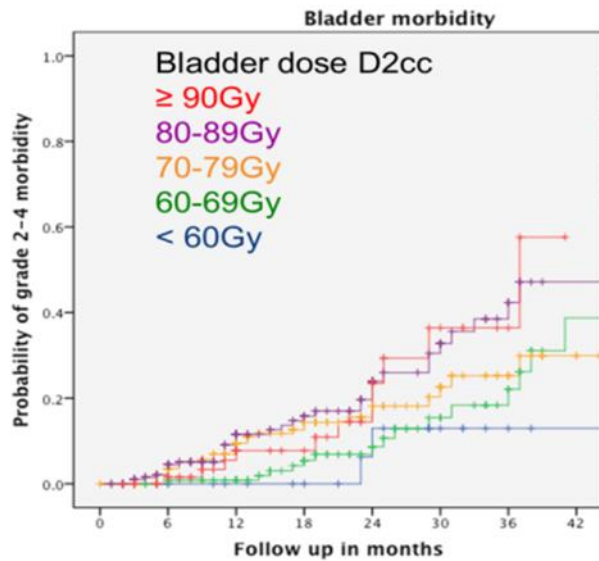


Figure 3.8. Actuarial incidence of $G_{\geq 2}$ urinary morbidity (all endpoints except ureter stenosis) grouped according to D_{2cm3} dose levels (Tanderup K. et al. 2014, EMBRACE work in progress).

571 3.3.4 RECTAL BLEEDING AND RECTUM D_{2CM3}

572 A clinical material of 701 patients from EMBRACE was analysed. Rectal bleeding (50 events) correlated significantly with dose (figure
 573 3.9). The dose response was shallow below 70Gy, and it is unclear how much clinical impact dose de-escalation below 70Gy could have.
 574 However, for doses above 70-75Gy there is a steep increase in risk of rectal bleeding. Analysis of further endpoints such as bowel
 575 control is pending.

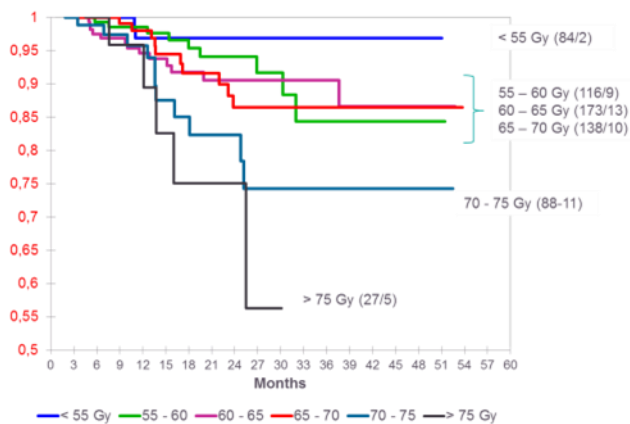


Figure 3.9. Actuarial incidence of rectal bleeding grouped according to D_{2cm3} dose levels (Mazeron R. et al. in submission 2015)

576 3.3.5 BOWEL MORBIDITY AND SIGMOID/BOWEL D_{2CM3}

577 In the EMBRACE material (701 pts) it was not possible to identify any significant relation between D_{2cm3} sigmoid and bowel dose and
 578 morbidity related to these organs. However, D_{2cm3} assessment in sigmoid and bowel is highly uncertain due to mobility of these organs.
 579 EMBRACE does not have any information recorded about the mobility of bowel/sigmoid in between BT fractions, and the EMBRACE
 580 data may therefore not be able to reveal any underlying dose response effect. In particular, if adhesions are present, the organ
 581 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
 582 sigmoid and bowel are more radiosensitive organs than rectum, doses of 60-70Gy may have an effect, in case of adherences.
 583 Furthermore, in EMBRACE there were only few patients where sigmoid or bowel D_{2cm3} exceeded 75Gy (7% and 10% of the patients,
 584 respectively), and any dose effect beyond such dose levels cannot be revealed with EMBRACE data. Therefore, although no dose

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

587 3.3.6 VAGINAL MORBIDITY AND ICRU RECTO-VAGINAL DOSE

588 Vaginal morbidity has been analysed in 754 pts in the EMBRACE material. The majority of $\geq G2$ events were vaginal stenosis (140 out of
589 181 events) which occurred mainly within the first 18 months. In a patient population of 630 pts a more detailed dose effect analysis
590 was carried out. There was a significant correlation between incidence of vaginal stenosis and the dose to the ICRU recto-vaginal point.
591 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).
592 Furthermore, there was a significant impact of EBRT dose. With lower dose ($\leq 45Gy$), the 2-year actuarial probability was 17% vs. 30%
593 with higher dose.

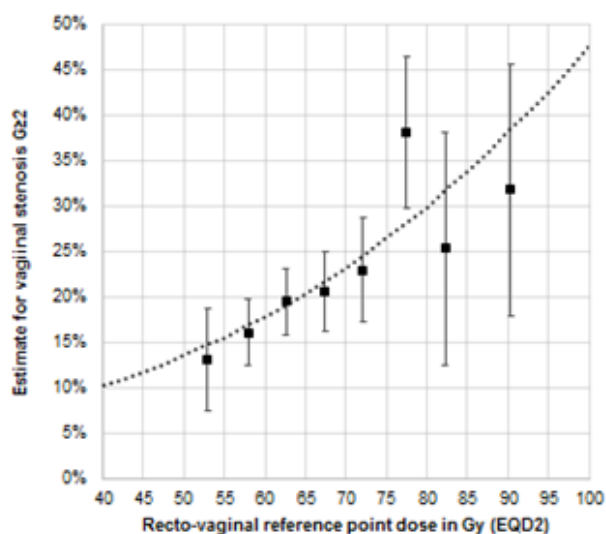


Figure 3.10. Dose effect curve based on Cox regression model of dose to the ICRU recto-vaginal point in total EBRT+BT EQD2 and vaginal shortening/narrowing $G \geq 2$. The model represents actuarial probability at 2 years (Kirchheiner K. et al. in submission 2015).

594

595 3.3.7 GASTROINTESTINAL/URINARY MORBIDITY AND INTERMEDIATE DOSE LEVELS RELATED TO EBRT

596 A number of 387 pts with >12 months of follow up were analysed. The influence of intermediate dose levels on development of GI and
597 urinary morbidity (patient reported EORTC QoL) was investigated through parameters related to EBRT: technique (IMRT/CRT) and
598 irradiated volume (43Gy and 57Gy). There was a significant relation between EBRT technique and GI and urinary patient reported
599 symptoms ("quite a bit" and "very much"). Furthermore, a relation was found between the total body (abdominal) volume which was
600 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
601 increase in diarrhea from 12% to 22%. This increase is rather shallow and likely related to the fact that the total irradiated body
602 (abdominal) volume is only a limited surrogate for the volume of bowel irradiated.

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

605

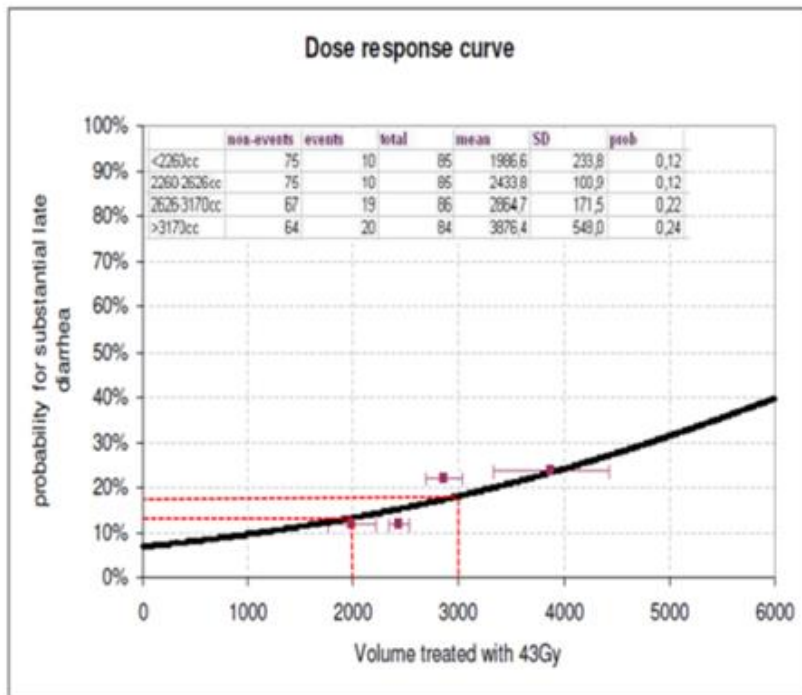


Figure 3.11. Crude incidence of diarrhea (patient reported) according to body (abdominal) volume irradiated to >43 Gy (Tanderup K., Kirchheiner K. 2014, EMBRACE, work in progress).

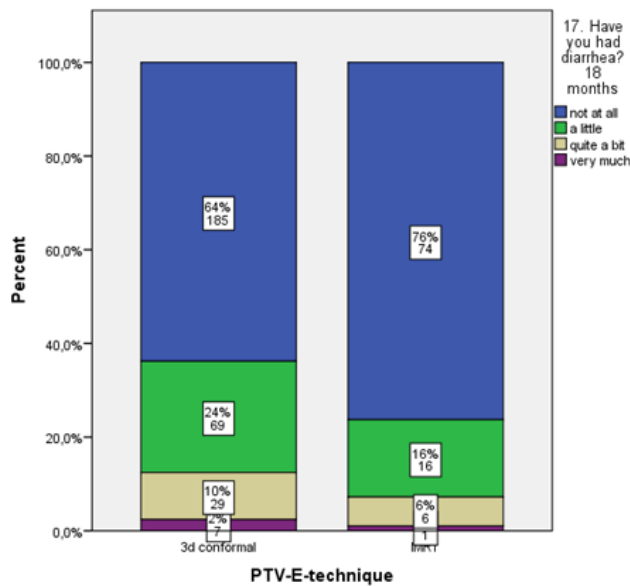


Figure 3.12. Prevalence at 18 months after treatment of patient reported outcome on the question « have you had diarrhea?» comparing IMRT and 3D conformal EBRT (Kirchheiner K. et al. 2014, EMBRACE work in progress).

606

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+

614 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
615 patients. 78% of para-aortic failures in EMBRACE were in patients who did not receive para-aortic irradiation.

616 Recently published data for node positive cervix cancer patients show promising results after extended field IMRT, not to the cost of
617 treatment related morbidity. The PAN control reported is 95 % in case of PAO negative and 89% in case of PAO positive patients at time
618 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
619 nodal disease at time of diagnosis will help increasing tumor control in the para-aortic region. Therefore, PAN irradiation will be further
620 investigated in EMBRACE II with special focus on in the group of patients with high risk features for the development of PAN and distant
621 disease which seem to be mainly location of nodes (common iliac), number of nodes (≥ 3) and also to some degree nodal size (Nomden
622 C., Fortin I. et al. EMBRACE work in progress).

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

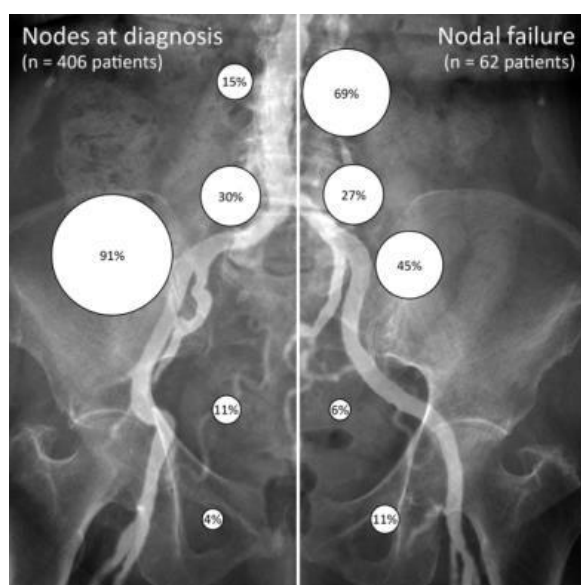


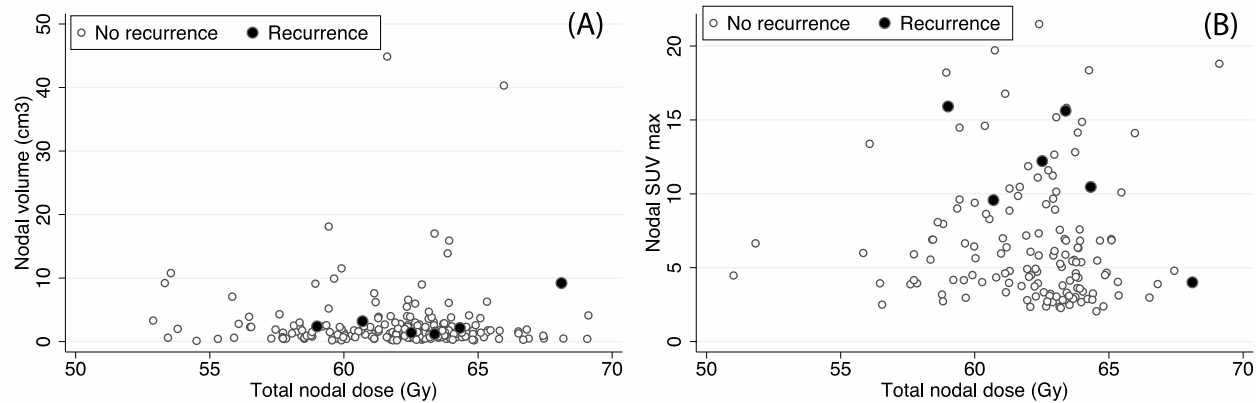
Figure 3.13. Patterns of spread for lymph node disease at time of diagnosis (left panel) and at time of first nodal failure (right panel) (Nomden C. et al. EMBRACE work in progress).

626 Nodal SUV_{max} seems to be predictive of nodal control and disease recurrence (Kidd EA. et al. 2010) in pelvic lymph nodes. They
627 measured the SUV_{max} of the most FDG avid lymph node in 83 node positive patients. No nodal boost was delivered. The average nodal
628 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
629 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
630 also had a higher risk of nodal persistent disease suggesting that these nodes might have benefitted from a more aggressive treatment.

631 Onal et al. investigated 93 patients with PET-positive pelvic or para-aortic lymph nodes. SUV_{max} was measured for the most FDG avid
632 node. A sequential boost was delivered for all enlarged lymph nodes. The mean SUV_{max} for pelvic nodes, para-aortic nodes and primary
633 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
634 SUV_{max} and between nodal and primary tumour SUV_{max} . Patients with pelvic nodal $SUV_{max} > 7.5$ had significantly larger nodes and
635 higher SUV_{max} for both primary tumour and para-aortic nodes. Ten patients had nodal recurrence. 9/10 recurred within the high SUV_{max}
636 nodal region. Patients with higher SUV_{max} had lower DFS and OS (Onal C. et al. 2015).

637 Finally a recent study by Ramlov et al. investigated 139 patients. Of these 112 had a diagnostic PET or PET/CT performed. Seventy-five
638 patients had totally 209 nodes treated with chemo-radiotherapy and a nodal boost. Total nodal dose, nodal volume and nodal SUV_{max}
639 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
640 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

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



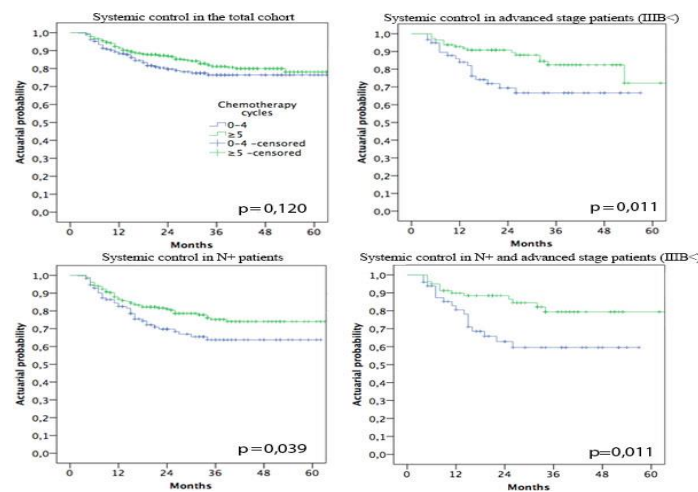
643
 644 Figure 3.14. Nodal recurrences as depending on dose and volume (left panel) and SUV and dose (right panel) (Ramlov A. et al. 2015).

645 3.3.9 ADMINISTRATION OF CHEMOTHERAPY

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

650 However the total number of cycles received during the treatment seems to play an important role in the systemic control in high risk
 651 patients (Schmid MR. et al. 2014). An early analysis from EMBRACE study performed on 753 patients shows significantly more systemic
 652 relapses in the N+ and advanced stage patients who received 4 chemotherapy cycles and less in comparison with the patients who
 653 received 5 chemotherapy cycles or more (Figure 3.14). At 24 months, N+ and advanced FIGO stage patients show a systemic control of
 654 63% vs 88% in patients having received 4 cycles and less versus 5 cycles and more, respectively. At 3 and 5 years, the distant
 655 metastases free interval was 79% and 77%, respectively in the whole cohort. These results are in line with those of Schmid et al. 2014
 656 in that the administration of 5–6 full dose cycles of chemotherapy can reduce a patient's risk of developing distant metastasis,
 657 especially in patients showing more advanced disease characteristics such as N+ and advanced FIGO stage.

658



659
 660 Figure 3.14. Impact of number of chemotherapy cycles on systemic control. Advanced stage is defined as stage III and IV (Fortin I. et al.
 661 Abstract ASTRO 2015, EMBRACE work in progress).

662

3.4 INTERNAL TARGET MOTION

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

669 Main general findings are that the motion is patient specific and that the motion of the uterus (excluding the cervix) is greater than that
670 of the cervix and these can move in independent directions. The greatest motions are observed in the anterior-posterior direction
671 followed by superior-inferior directions. Bladder filling status seems to impact more on the uterine motion and rectal filling more on the
672 motion of the cervix and upper vagina. A systematic review of organ motion in cervix cancer summarises studies on uterine and cervix
673 movements ([Jadon R. et al. 2014](#)). For the cervix, the reported mean movement ranges in the anterior-posterior direction between 2-21
674 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
675 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-
676 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
677 and superior-inferior directions. Different studies report a decrease of mean bladder volume during the course of fractionated
678 radiotherapy, while this was not found for rectal volume. There are few studies that have looked at motion of lymph node related
679 target structures, a study using MRI found mean motions ranging between 5 and 9 mm, while movement of regional vessels was
680 correlated to bladder filling status.

681 The major shortcoming in the field is that the majority of research on motion has focussed on quantifying the magnitude of the
682 movement in mm or has reported dose coverage. The direct impact of motion on dose has so far only been reported in three studies.
683 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.
684 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
685 from uterus to PTV ([Jensen NBK. et al. 2015](#)). Evaluating accumulated EBRT and BT uterus D98, it was always >45Gy. These two studies
686 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
687 shallow dose gradients. Furthermore, Assenholt et al. showed that application of a PTV margin of 5mm on pathological lymph nodes
688 boosted with SIB technique resulted always in D98 > 95% accumulated dose (40 lymph nodes) ([Assenholt M. et al. Abstract BigART
689 2015](#)).

690

691 **4 INTERVENTIONS AND AIMS**

692 **4.1 INTERVENTIONS**

693 *Based on the evidence for dose effects from the EMBRACE and retroEMBRACE studies there is a clear evidence based rationale to*
 694 *implement an overall dose prescription protocol based on a set of dose planning aims and dose constraints for the target related to*
 695 *the primary tumour (CTV-T) and the 2cm³ and reference points for OARs (see chapter 10.8). The fulfillment of these planning aims is*
 696 *hypothesized to result in improved local control and decreased morbidity.*

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

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

704 **4.1.1 INCREASED USE OF IC/IS TECHNIQUE IN BT**

705 In EMBRACE, half of the patients have been treated in institutions performing mainly IC brachytherapy (“IC centers”), where IC/IS was
 706 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
 707 + IC/IS centers”). The dose administration in the “IC” and “IC + IC/IS” cohorts differs significantly (table 4.1). In centers performing IC +
 708 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.
 709 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
 710 high percentage of patients.

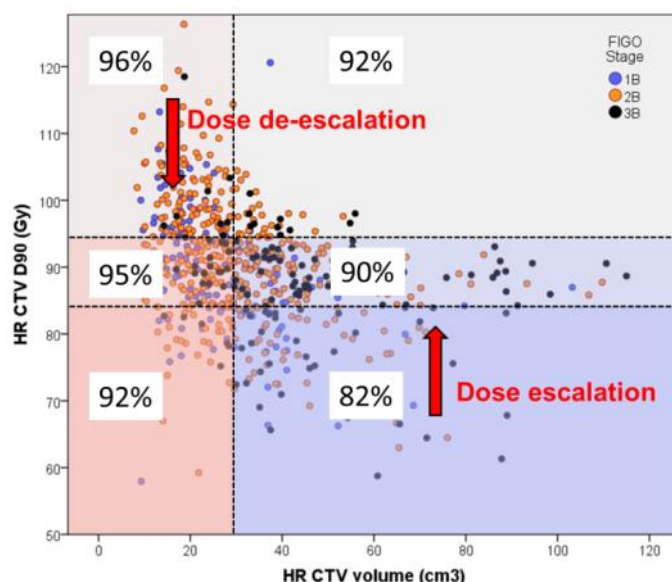
711 In most centers routinely applying IC/IS, the rate of application is normally much higher than 20% (table 4.1), since application of IC/IS
 712 can also benefit OAR sparing.

| Adaptation | HR CTV vol | Applicatio n 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 |

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

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

715 In EMBRACE II, the improved therapeutic window (through increased application of IC/IS) will be exploited for tumour dose-escalation
 716 and/or OAR dose de-escalation (figure 4.1). In tumours with large residual CTV_{HR} volumes at time of brachytherapy, dose-escalation has
 717 the potential to improve local control significantly. In limited size CTV_{HR} volumes dose-de-escalation will be performed since dose de-
 718 escalation has minor impact on local control while it has potential to reduce morbidity. The strategy of EMBRACE II is to aim for an
 719 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
 720 distribution of ~20% IB, ~50% IIB, ~20% IIIB and ~10% others. If a given patient population includes significantly higher proportions of
 721 limited or extensive disease, the threshold of 20% IC/IS applications must be adapted.



722 Figure 4.1 Principles for dose de-escalation and dose escalation in EMBRACE II. The figure shows the current distribution of CTV_{HR} dose
 723 and volume in the EMBRACE study (each point represents one patient). A number of 6 dose and volume groups are defined according
 724 to cut-points of 85Gy and 95Gy for CTV_{HR} dose and of 30cm³ for CTV_{HR} volume. For each dose-volume group the expected actuarial local
 725 control at 3 years is indicated (according to dose effect data from the retroEMBRACE study (Tanderup K. et al. 2014, RetroEMBRACE
 726 work in progress).

727 4.1.2 REDUCTION OF VAGINAL SOURCE LOADING

728 A multicenter investigation in 50 EMBRACE patients from 3 institutions (Mohamed SM. et al, in submission 2015) shows that reduced
 729 loading in ring/ovoids and increased loading in tandem (and needles when available) can be applied without compromising CTV_{HR} and
 730 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
 731 of 4±4Gy, and furthermore, bladder and rectum doses could be reduced by 2-3Gy with the same re-arrangement of loading. Similar
 732 evidence is available from a study on simulation of different intracavitary standard loading patterns in EMBRACE patients, where it was
 733 shown that limited size tumours could often be covered by tandem loading alone (Nkiwane KS. et al. 2013).

734 4.1.3 SYSTEMATIC UTILISATION OF IMRT

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

740

741 4.1.4 UTILISATION OF DAILY IGRT (SET-UP ACCORDING TO BONY STRUCTURES)

742 PTV margins of 10 mm to the elective lymph node target are currently applied in many institutions. This margin is related to set-up
743 uncertainties with patient positioning performed based on skin marks. However, currently, most institutions have in-room imaging
744 available which makes it possible to perform daily imaging and couch correction according to fusion on bony anatomy. With daily
745 imaging, bony image fusion, and couch correction, a margin reduction from 10mm to 5mm can be performed without compromising
746 target coverage ([Laursen LV. et al. 2012](#)). The 5mm margin reduction has potential to decrease the volume irradiated to 43Gy by
747 approximately 500 cm³, which is expected to decrease bowel morbidity by ~50% (Fig. 3.11).

748 4.1.5 EBRT TARGET CONCEPT RELATED TO THE PRIMARY TUMOUR (CTV-T) AND INTERNAL MOTION; 749 CONCEPTS FOR OAR CONTOURING

750 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
751 use of this novel contouring approach in conjunction with available MRI will allow to target safely the visible tumor (CTV-T) and the high
752 risk region (CTV-HR initial) while consenting for dose to a low risk region (CTV-LR initial). Anatomical changes due to bladder and
753 rectal filling variation as well as cervix and uterus position will be considered. An ITV-LR will be outlined using the planning scan and
754 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
755 only a diagnostic MRI.

756 Some new concepts will be introduced for OAR contouring. Instead of contouring the abdominal cavity, the bowel loops will be
757 outlined in one volume restricted to the outer contour of bowel loops including the mesenterium. This will allow for a better
758 approximation of the bowel loops volume and optimization of the dose constraints. Rectum and sigmoid structures will be contoured as
759 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 +
760 0,5cm PTV).

761 4.1.6 EBRT DOSE PRESCRIPTION AND REPORTING

762 There is currently a significant variation with regard to EBRT dose and fractionation in the EMBRACE study with doses ranging from
763 45Gy to 50Gy and being delivered in 25-30 fractions. Furthermore, there is a wide variety of lymph node boosting strategies. In
764 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
765 node boosting must be performed as a simultaneous integrated boost. The dose de-escalation from 50Gy to 45Gy has potential to
766 reduce morbidity. A system of reporting dose to targets and OARs is introduced in terms of dose volume parameters and a system of
767 point dose reporting for the vagina.

768 4.1.7 ADAPTATION OF EBRT NODAL ELECTIVE CTV ACCORDING TO RISK OF NODAL AND SYSTEMIC 769 RECURRENCE

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

775 Furthermore, the MD Anderson data have shown that the L5/S1 cranial border of the classical pelvic field for cervix cancer is associated
776 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
777 (personal communication).

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

780 Therefore based on the evidence from EMBRACE, RetroEMBRACE and literature findings, three categories will be defined according to
781 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
782 reduced by exclusion of the common iliac region. In the intermediate risk group the target will include the common iliac nodes with
783 inclusion of the aortic bifurcation, internal iliac, external iliac, obturator, and presacral nodal regions (and groins in case of distal vaginal
784 infiltration). In the high risk group the para-aortic region will be included in the target.

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

787 4.1.8 SYSTEMATIC APPLICATION OF SIMULTANEOUS CHEMOTHERAPY

788 According to international standard and evidence, simultaneous chemotherapy (min. 5x40 mg/m² cis Platinum) was prescribed in the
789 EMBRACE protocol for all patients, who qualify for its administration. Certain rules were given for adaption according to international
790 guidelines. Altogether, so far 90-95% of EMBRACE patients received simultaneous chemotherapy, which compares favourably with the
791 78% that received simultaneous radiochemotherapy in RetroEMBRACE, reflecting that the vast majority of EMBRACE patients received
792 chemotherapy according to the EMBRACE protocol. Most of the EMBRACE cohort is consecutive patients representing the cervix cancer
793 patient population in the respective centers. When analysing the number of patients and the number of chemotherapy cycles received,
794 about 70% received ≥ 5 cycles, while 30% received 0-4 cycles. As stated above (3.2.8), administration of chemotherapy has impact on
795 systemic control, which seems to be pronounced in high risk patients (node positive and/or stage III/IV) with a 20% difference in
796 systemic recurrence. Also a center effect has been found in the ability to administer chemotherapy with a variation from 15% and 85%
797 of the patients receiving ≥ 5 cycles of chemotherapy. In order to reach optimal outcome throughout the cervix cancer population and in
798 particular in the high risk group, the EMBRACE II protocol therefore also focusses on the appropriate administration of chemotherapy
799 according to the EMBRACE II protocol and following international guidelines (chapter 11.1).

800 4.1.9 REDUCTION OF OVERALL TREATMENT TIME

801 Several studies indicate that maintaining an overall treatment time (OTT) of ≤ 50 days is important for local control. RetroEMBRACE
802 data confirms that OTT remains of importance in the realm of IGABT. As there is significant variation of OTT across patients and
803 institutions in retroEMBRACE, the EMBRACE II study aims to reduce the OTT so that the majority of patients (>80%) will adhere to the
804 ≤ 50 day threshold. The measures to reduce OTT in EMBRACE is to systematically apply 25 fractions of EBRT including lymph node
805 boost, and furthermore to carefully plan the BT schedule, so that brachytherapy is delivered towards the end of EBRT and/or directly
806 after EBRT.

807

808 4.2 AIMS OF THE EMBRACE II STUDY

809 4.2.1 GENERAL AIMS

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

821 4.2.2 SPECIFIC AIMS

- 822 • To validate that a dose prescription protocol and increased application of IC/IS will result in:
 - 823 o Dose escalation to the GTV and CTV_{HR} in tumours with large residual volume at time of brachytherapy and increase local
 - 824 control in these tumours without increasing morbidity
 - 825 o Dose de-escalation in vagina, bladder, and rectum with regard to high doses (e.g. >50-60Gy) and improve morbidity
 - 826 without compromising local control
- 827 • To validate that vaginal source loading and dose to the vagina can be reduced without compromising GTV, CTV_{HR} and CTV_{IR} dose,
- 828 and that this can reduce vaginal morbidity without compromising local control
- 829 • To validate dose and volume effect relationships which were demonstrated in the EMBRACE/retroEMBRACE study for
 - 830 GTVres D98, CTVHR D90 and D98, volumes and local control
 - 831 CTVHR D90, CTVHR volume and systemic control
- 832 • To validate dose effect relationships for morbidity and QoL which were demonstrated in the EMBRACE/RetroEMBRACE study for
- 833 high doses in small volumes (2 cm³) or points related to brachytherapy administration: bladder, rectum, vagina
- 834 • To validate that utilisation of IMRT and daily IGRT with reduced margins can reduce the overall body volume irradiated to 45Gy
- 835 and lead to reduction of GI and urinary morbidity
- 836 • To validate that reduction of dose from 50Gy to 45Gy to the elective lymph node CTV does not compromise nodal control and
- 837 leads to reduction of vaginal morbidity
- 838 • To explore the impact of a systematic application of EBRT CTV-T concepts (with regard to the lower PTV border) on vaginal dose
- 839 and morbidity
- 840 • To demonstrate that the application of the initial CTV-T concepts as well as the ITV and PTV margins as prescribed in the protocol
- 841 does not compromise local control in the primary tumour and uterine body
- 842 • To explore dose volume effect relationships related to intermediate EBRT dose levels in bladder, rectum, vagina, bowel and
- 843 overall body volume
- 844 • To demonstrate that it is feasible to administer simultaneous chemotherapy to EBRT to reach 5 cycles of cis Platinum in the
- 845 majority of patient (in particular in high risk patients) and that this leads to improvement in systemic control
- 846 • To evaluate the prognostic significance of SUV in individual lymph nodes for lymph node control
- 847 • To explore dose and effect relationship of chemotherapy for nodal and systemic control
- 848 • To identify prognostic parameters and define groups of patients at different risk of local, nodal and systemic failure
- 849 • To evaluate the impact of continuous web-based and workshop oriented education in contouring and dose planning throughout
- 850 the study on overall quality and compliance

851

852 5 STUDY DESIGN, ENDPOINTS AND HYPOTHESES

853

854 5.1 STUDY DESIGN

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

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

869 5.2 ESTIMATE OF PATIENT ACCRUAL AND STUDY PERIOD

870 A number of 16 centers who are currently accruing patients for the EMBRACE study are expected to participate in the EMBRACE II
871 study. According to the accrual rate in 2014, these 16 centers are expected to accrue 200 patients per year for EMBRACE II.
872 Furthermore, new centers have shown interest in EMBRACE II, and it is expected that 10 new centers will be approved for participation
873 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
874 2016 to 2019, it is expected to reach a total number of patients of 1000 patients: 150 (2016), 250 (2017), 300 (2018), 300 (2019).

875 5.3 HYPOTHESES AND ENDPOINTS

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

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

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

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

888

889

890 5.3.1 GENERAL HYPOTHESIS ON OVERALL SURVIVAL

891 The sum of interventions of EMBRACE II as defined for EBRT, BT and chemotherapy will benchmark a high level of overall survival at 3
 892 and at 5 years which is assumed to be 4% superior to RetroEMBRACE. The strongest prognostic predictors for overall survival are at
 893 present stage and nodal status, and the hypothesis on overall survival is therefore stated for the overall cohort as well as for two groups
 894 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
 895 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
 896 positive patients (enlarged nodes, PET positive nodes, nodes proven by histology). In EMBRACE, patients are distributed more or less
 897 equally into these two groups: stage III, IV or N+ is 58% and stage I, II and N- is 42%.

898 Hypothesis for Overall Survival (OS):

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

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

904 5.3.2 SPECIFIC HYPOTHESES ON TECHNIQUE, DOSE AND VOLUMES:

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

909 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 CTV _{HR} D90 > 85Gy in 80% of pts CTV _{HR} D90 > 95Gy in 38% of pts | IC/IS in >30% of patients* CTV _{HR} D90>85Gy in >90% of pts: mean dose escalation of 8Gy in the group previously treated with <85Gy* 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 CTV _{HR} D90 >85Gy: 63% of pts. | IC/IS in >70% of patients* 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% Bladder D _{2cm3} <80Gy in 60% of pts Rectum D _{2cm3} <65Gy in 62% of pts | Mean vaginal loading <33%** Mean dose de-escalation**: Bladder D _{2cm3} : - 4Gy 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* |

910 *Based on current performance of advanced EMBRACE I centres

911 **Based on pilot data from the EMBRACE research group

912 ***Based on administration of 25fx (with integrated lymph node boost) as well as increased awareness of the timing of brachytherapy

913 ****Based on disease characteristics in the EMBRACE cohort

914

915 5.3.3 SPECIFIC HYPOTHESES ON CLINICAL ENDPOINTS

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

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

920 **Local control:**

921 Limited volume (CTV_{HR} ≤ 30cm³):

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

924 Large volume (CTV_{HR}>30cm³):

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

927 Improvement of local control is ~0.5% per Gy of dose escalation

928 AND

929 Improvement of local control is ~0.5-1% per day of reduced OTT.

930 **Nodal control (incl para-aortic):**

931 Stage I, II and N0:

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

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

937 Stage III, IV or N1:

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

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

948 **Systemic control (excluding para-aortic failures):**

949 Stage I, II and N-:

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

951 Stage III, IV or N+:

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

956 **Cancer specific survival:**

957 Stage I, II and N-:

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

960 Stage III, IV or N+:

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

963 **Overall survival:**

964 Stage I, II and N-:

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

966 Stage III, IV or N+:

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

968 **Morbidity:**

969 **Urinary morbidity:**

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

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

975 **Rectal morbidity:**

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

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

980 **Bowel morbidity:**

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

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

985 **Vaginal stenosis:**

986 G \geq 2 stenosis will be improved by 7% due to the combined effect of BT dose de-escalation, decreased EBRT dose (prescription
987 of 45Gy pelvic fields to all patients), as well as improved definition of the lower field border. Vaginal stenosis decreases by 0.5-
988 1% per Gy of dose de-escalation, and furthermore the incidence of vaginal stenosis is 13% less in patients irradiated to 45Gy as
989 compared to patients irradiated with 50Gy.

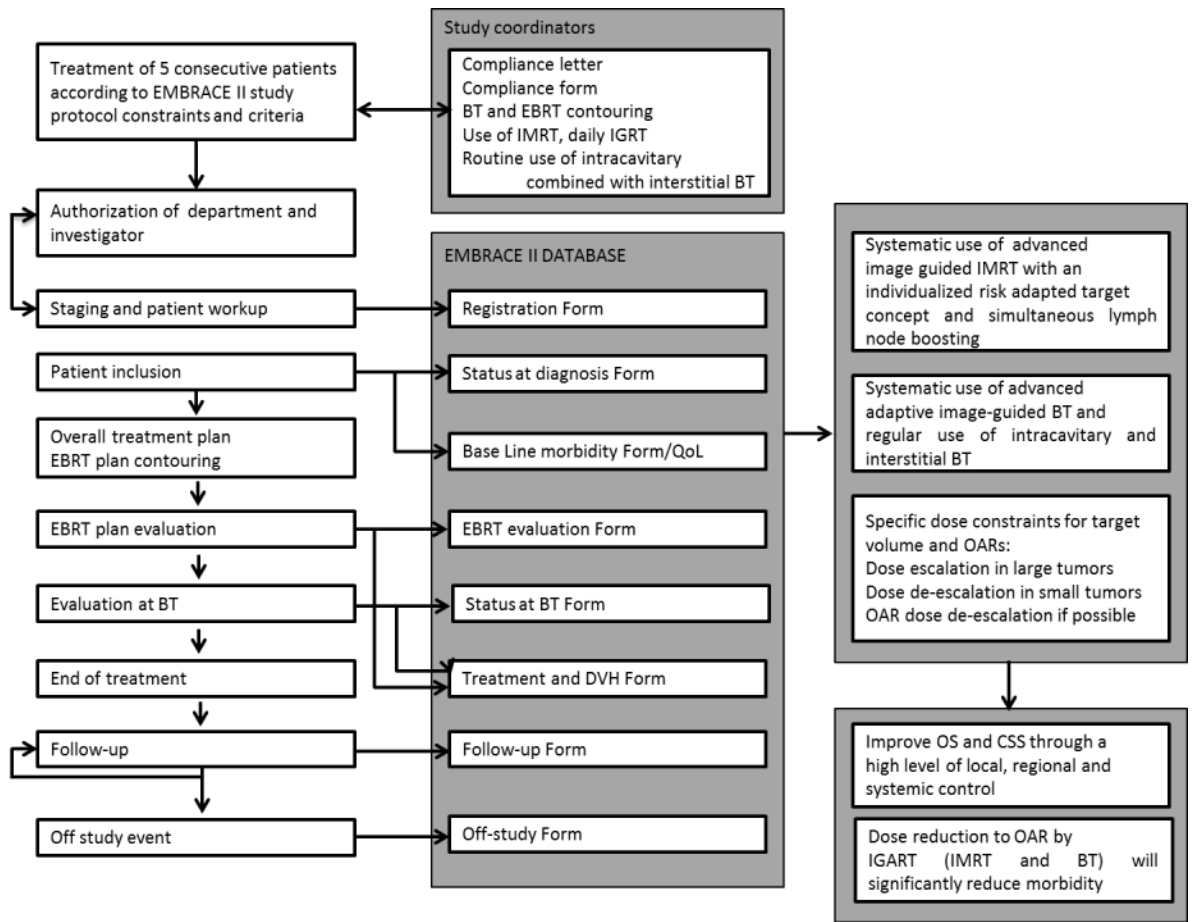
990 **Overview**

991 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
992 the retroEMBRACE and EMBRACE studies. The improvement of outcome in EMBRACE II is estimated with retroEMBRACE as baseline
993 (evaluated 9/2014) for disease related outcome and with EMBRACE as baseline for morbidity (2014/2015). Limitation: the numbers for

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

| | retroEMBRACE 3/5y | EMBRACE 3y | EMBRACE II 3y | Confidence interval* |
|--|-------------------|-----------------------------|-----------------------------|----------------------|
| Local control | | | | |
| Overall | 91/89% | 91% | 93% | 2% |
| ≤30cm ³ HR CTV | 96% | 96% | 96% | 2% |
| >30cm ³ 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% |

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



1001 7 STAGING AND PATIENT WORK-UP

1002 All examinations must be completed before treatment and no investigation should be more than 4 weeks old at the time of treatment
1003 initiation. For the purpose of including a patient in the Embrace 2 protocol the following examinations have to be performed:

- 1004 • Patient history and current status including among others information on hormonal status, co-morbidity, previous major
1005 surgery, smoking status (ch. 12, 16, CRF)
- 1006 • General physical examination, including assessment of performance status (WHO)
- 1007 • Blood tests including haemoglobin and lymphocytes
- 1008 • Gynaecological examination (supplemented by cystoscopy and rectoscopy if organ involvement is suspected) with topographic
1009 documentation on a specific cartoon (see appendix)
- 1010 • Biopsy of the primary tumour
- 1011 • Laparoscopic lymphadenectomy is recommended but not required
- 1012 • Pelvic MRI (see in detail Gyn GEC ESTRO Recommendations IV ([Dimopoulos JC. et al. 2012](#)))
- 1013 • Preferable whole body (FDG)PET-CT or at least CT scan of thorax, abdomen and pelvis
- 1014 • Assessment of SUV_{max} in primary tumour and lymph nodes is recommended but not required
- 1015 • Staging according to FIGO and TNM
- 1016 • Baseline Morbidity scoring (ch.12, 16, CRF)
- 1017 • Baseline quality of life questionnaire (ch. 12,16, CRF)

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1028 8 PATIENT SELECTION

1029 8.1 INCLUSION CRITERIA

- 1030 • Cancer of the uterine cervix considered suitable for curative treatment with definitive radio-(chemo)therapy including MRI
1031 guided BT
- 1032 • Positive biopsy showing squamous-cell carcinoma, adenocarcinoma or adeno-squamous cell carcinoma of the uterine cervix.
- 1033 • Staging according to FIGO and TNM guidelines
- 1034 • MRI of pelvis at diagnosis is performed
- 1035 • MRI, CT or PET-CT of the retroperitoneal space and abdomen at diagnosis is performed
- 1036 • MRI with the applicator in place at the time of (first) BT will be performed
- 1037 • Para-aortic metastatic nodes below L1-L2 are allowed
- 1038 • Patient informed consent

1039

1040 8.2 EXCLUSION CRITERIA

- 1041 • Other primary malignancies except carcinoma in situ of the cervix and basal cell carcinoma of the skin
- 1042 • Small cell neuroendocrine cancer, melanoma and other rare cancers in the cervix
- 1043 • Metastatic disease above and beyond the retroperitoneal para-aortic L1-L2 interspace
- 1044 • Previous pelvic or abdominal radiotherapy
- 1045 • Previous total or partial hysterectomy
- 1046 • Combination of preoperative radiotherapy with surgery
- 1047 • Patients receiving BT only
- 1048 • Patients receiving EBRT only
- 1049 • Patients receiving neo-adjuvant chemotherapy or other forms of antineoplastic treatment apart from weekly concomitant
1050 cisplatin (40 mg/2). However, adjuvant chemotherapy in the form of 4 courses of 3 weekly Carboplatin (AUC 5) and Paclitaxel
1051 (155 mg/m²) is allowed according to departmental policy.
- 1052 • Contra indications to MRI
- 1053 • Contra indications to BT
- 1054

1055 9 EXTERNAL BEAM RADIOTHERAPY

1056 9.1 INTRODUCTION

1057 External beam radiotherapy (EBRT) is an integral part of the overall treatment strategy with the primary aim of obtaining regional and
1058 nodal control. In addition, EBRT provides a basis of homogenous dose on which the steep dose gradient of brachytherapy takes off to
1059 achieve the very high dose needed to obtain local control of the primary tumour. At the same time, the dose outside of the EBRT
1060 target(s) should evidently be as low as possible. Studies comparing IMRT with 3D conformal EBRT, including results from the EMBRACE I
1061 study show that IMRT reduces the incidence of late toxicity (mainly gastro-intestinal). With the growing technical possibilities and
1062 availability of imaging, the field of image guided EBRT (IGRT) is rapidly evolving. A further decrease of treatment related toxicity is
1063 expected from IGRT approaches. For EMBRACE II, pragmatic choices have been made in order to allow safe state of the art treatment
1064 delivery within the current clinical workflows of participating centres.

1065 9.1.1 AIMS OF EXTERNAL BEAM RADIOTHERAPY (COMPARE CH 3-5)

- 1066 1. To introduce systematically MRI and CT guided IMRT for EBRT in cervix cancer with a tailored target and margin concept and
1067 defined dose prescriptions for tumour and nodal targets
- 1068 2. To control overall treatment time (90% of all patients <50 days for EBRT and BT)
- 1069 3. To maintain and improve the excellent pelvic control (local and regional)
- 1070 4. To improve para-aortic control by elective para-aortic irradiation in high risk patients (HR LN) and by elective common iliac
1071 nodal irradiation (incl. aortic bifurcation) in intermediate risk patients (IR LN) (Table 9.2, Fig. 9.1).
- 1072 5. To maintain and improve the excellent nodal control through simultaneous hypofractionated integrated boosting (SIB) and
1073 coverage probability (CoP) dose planning for treatment of pathological lymph nodes
- 1074 6. To reduce EBRT related morbidity through reduction of target volume as well as the treated and irradiated volumes:
 - 1075 • Excluding the common iliac region from the elective target volume in low risk patients (LR LN) (Table 9.2)
 - 1076 • Reducing set-up error and allowing for PTV margin reduction for the nodal CTV-E (5 mm) and the ITV-T LR through
1077 performing daily 3D IGRT with daily online couch correction based on bony anatomy (Fig. 9.9)
 - 1078 • 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)
 - 1079 • Recommending an internal target volume (ITV-T LR) approach for the primary tumour (CTV-T LR) (Fig. 9.9)
 - 1080 • Using inverse treatment planning techniques (IMRT, VMAT or Tomotherapy) applying systematically dose volume
1081 constraints for EBRT

1082 9.1.2 NODAL TARGETS BASED ON RISK GROUP ALLOCATION FOR NODAL SPREAD

1083 The risk of lymph node spread is dependent on various factors. Among the most important are the local spread (FIGO stage), histology
1084 and lymph node spread. The pattern of lymph node recurrence has two predominant areas: within the radiation field in the obturator
1085 region (in-field), at the cranial field border (marginal) and in the para-aortic region (outside radiation field) ([Verma J. et al. 2014 and](#)
1086 [EMBRACE/RetroEMBRACE work in progress](#)).

1087 In order to tailor the nodal target according to the assumed risk of microscopic nodal involvement three risk groups are introduced with
1088 three different elective nodal target volumes. The aim is to reduce morbidity in the low risk group and to improve nodal and systemic
1089 control in the intermediate and high risk group.

1090 **To summarize the indications for nodal targets based on risk group allocation for lymphatic spread (table 9.1):**

- 1091 • Small pelvis EBRT in low risk patients (LR LN)
- 1092 • Large pelvis EBRT in intermediate risk patients (IR LN)
- 1093 • Large pelvis + para-aortic EBRT in high risk patients (HR LN)

1094 Risk allocation is based on primary tumour characteristics and nodal pathology at time of diagnosis and takes into account the
 1095 probability of developing lymph node metastases in pelvic and para-aortic areas. Risk groups are defined in table 9.1, and criteria for
 1096 categorising a lymph node as pathologic are defined in table 9.2. This is a general outline, giving the major pathways for tailoring nodal
 1097 targets based on risk group allocation. Such general outline leaves some space for specific clinical situations where some outstanding
 1098 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.

1099

1100 Table 9.1: Risk groups for defining the elective clinical target volumes for lymph nodes and corresponding nodal targets defining the
 1101 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: <ul style="list-style-type: none"> • 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 <ul style="list-style-type: none"> • ≥ 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]. |

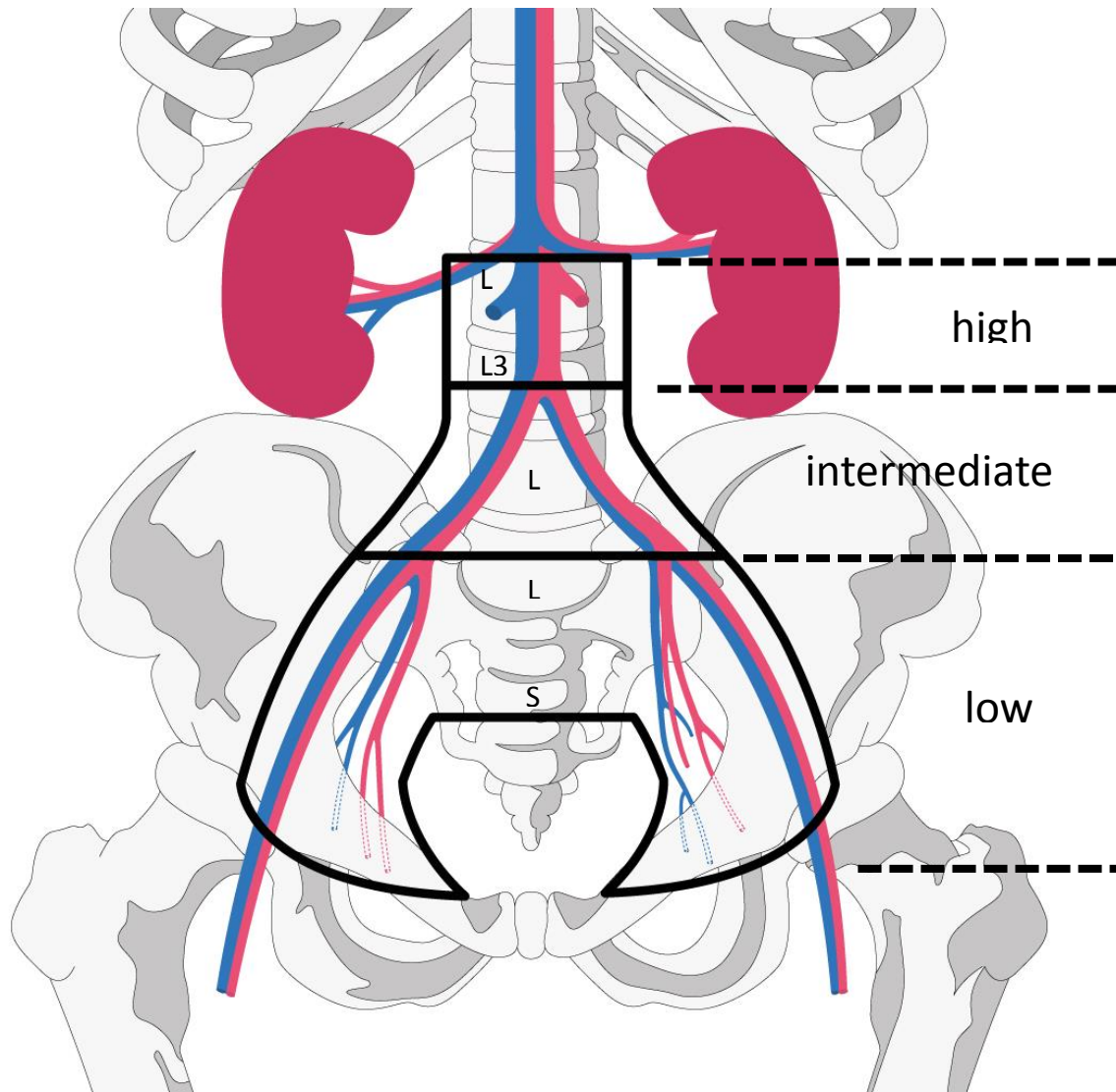
1102

1103 **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 |

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1106

1107 Fig 9.1 Schematic Diagram for lymph node elective CTVs based on risk of lymphatic spread, “Small Pelvis”, “Large Pelvis”, “Large Pelvis +
1108 para-aortic” (compare table 9.1)

1109

1110 9.2 PREPARATIONS FOR TREATMENT PLANNING

1111 Gynaecological examination with appropriate documentation on cartoons (see chapter 10), diagnostic T2 weighted MRI and a
1112 treatment planning CT in supine position are minimal requirements for target delineation and treatment planning. PET-CT is strongly
1113 recommended, but optional. Slice thickness of the treatment planning CT scan should be ≤ 3 mm. The use of intravenous contrast
1114 media for the treatment planning CT is optional but use is recommended to ease identification of structures of interest. The choice for
1115 immobilization devices is according to the clinical routine of the individual institutes.

1116 It is recommended, but not mandatory, to perform an empty bladder scan on top of the comfortably filled bladder scan. Full and empty
1117 bladder scans give information about the range of internal motion of the target volumes, and this can be exploited when defining an
1118 individualized ITV as discussed in section 9.3.3. Having multiple (diagnostic and treatment planning) imaging series available with
1119 different combinations of bladder and bowel filling, usually from different days contributes further to defining the individualized ITV.

1120 Ideally both the FDG PET-CT and MRI should be performed in treatment position, in order to enable optimal image fusion based on
1121 bony anatomy, but this is not mandatory. Thus, pertinent diagnostic-imaging sequences may be used. Further recommendations are to
1122 obtain the MRI in three orthogonal planes; to include the aortic bifurcation (cranial) and the inferior border of the symphysis (caudal) as
1123 scan borders and to limit the slice thickness to ≤ 5 mm.

1124 Minimization of internal motion at the time of dose planning scans and during treatment is difficult to achieve. The following measures
1125 have the goal to prevent taking outlier situations into account when deciding on internal organ motion and to attempt to be as
1126 reproducible as possible throughout the period of treatment.

1127 Bladder is intended to be comfortably filled on the treatment planning CT scan and throughout the treatment. Therefore a drinking
1128 protocol is mandatory with specifications on 1) timing of voiding and 2) timing and volume of fluid intake. An acceptable drinking
1129 protocol would be that the patients are asked to void 1 hour before imaging and each EBRT fraction, then drink 300-500 ml of
1130 water/clear fluid and try not to void before treatment delivery.

1131 The rectum and sigmoid should be as empty as possible. The patient is asked to empty the stools before scanning and treatment. If
1132 significant gas or filling is discovered while scanning for treatment planning (diameter of gas or filling in rectum > 4 cm maximum
1133 extension in any direction), the patient should be asked to empty the rectum or deflation with a catheter or postponing the treatment
1134 planning CT to another day could be considered. Special diets with the purpose of reducing internal motion of the gastro-intestinal
1135 system are so far ineffective and therefore currently not recommended. The same applies to the use of enemas since there is concern
1136 about related gas production.

1137

1138

1139 **9.3 TUMOR AND TARGET DEFINITION AND CONTOURING: INITIAL GTV, INITIAL HR CTV-T, INITIAL LR**
1140 **CTV-T, ITV-T; GTV-N, CTV-N, CTV-E; PTV**

1141 9.3.1 GENERAL OVERVIEW

1142 The volumes of interest are in principle defined according to ICRU 50/62/83:

1143

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.

1148

1149 Tumour and target contouring for EBRT requires an integration of the spatial information obtained at diagnosis by fused MRI, treatment
1150 planning CT, FDG PET-CT if available, and by gynaecological examination.

1151 GTV-T (GTV-N) is defined and contoured based on imaging (MRI (PET-CT)) and clinical characteristics.

1152 CTV is defined and contoured based on the extension of the GTV and the assumed microscopic spread for each specific tumour
1153 extension and its biological characteristics taking into account anatomical regions (e.g. vagina), compartments (e.g. parametrium) and
1154 borders (e.g. outer rectal wall).

1155 ITV is based on a standard or individualized margin.

1156 PTV is derived from the ITV or the CTV using an isotropic margin.

1157

1158 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.
1159 These definitions correspond to those introduced for the adaptive HR CTV-T for brachytherapy (GEC ESTRO Recommendations, ICRU
1160 Report 88):

- 1161
- 1162 • The initial HR CTV contains the initial GTV inside and outside the cervix and as a minimum the whole cervix as it presents at
1163 diagnosis.
 - 1164 • The initial LR CTV includes the initial HR CTV as starting point. A margin of 20 mm is defined towards the vagina. The whole
1165 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.)

1166 Identification of such sub-volumes for the CTV-T is important as they allow for tailored treatment with different dose prescription (HR
1167 CTV-T, (IR CTV-T), LR CTV-T (see chapter 10), and as they change during treatment.

1168 The initial HR CTV-T and LR CTV-T require different ITV margins according to the location of its borders and their specific motion
1169 uncertainties (e.g. laterally fixed parametrial borders, posterior-anterior mobile borders towards rectum and bladder, overall mobile
1170 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
1171 (individualized) ITV-T concepts. Such contouring enables to reflect the uncertainties due to different motion types at the various CTV
1172 borders when defining the ITV-T (see Appendix on EBRT Treatment Planning).

1173 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
1174 patient, which include both inter- and intra-fraction motion.

1175 The total CTV-T to PTV-T margin needs to accommodate random and systematic geometrical errors that are among others caused by:
1176 internal organ motion (ITV-T) (e.g. uterine cervix, uterine corpus; rectum, bladder filling status) and geometrical errors in positioning
1177 during the course of EBRT for the tumor and lymph node related CTVs (set-up errors). An ITV is most helpful in situations where
1178 uncertainties concerning the geometrical CTV location are greater than setup uncertainties, such as may be the case for a primary
1179 cervical tumour in a mobile uterus (ITV-T).

1180 The elective nodal CTV of the combined draining nodal regions (CTV-E) is selected according to risk of nodal spread. These nodal regions
1181 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-
1182 E) as internal organ motion seems to play no important role for the CTV-E.

1183 GTVs of pathologic lymph nodes (GTV-N) and their CTVs (CTV-N) are drawn individually. They are included in the CTV-E.

1184 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
1185 CTV-E and, if present, also the CTV-N.

1186

1187 As noted above the nomenclature for many volumes of interest follows the ICRU tradition.

1188 In addition some protocol specific nomenclature is used:

- 1189 • For the subdivision of the primary CTV-T as initial HR CTV-T and initial LR CTV (following in principle the ICRU/GEC
1190 ESTRO definitions for the adaptive CTV for brachytherapy (ICRU 88) (for clarification the suffix “initial” has to be used)
1191 and
- 1192 • For the elective nodal target, which is called “CTV-E” along the tradition of EMBRACE I (instead of CTV-N).

1193 The general definition of the different volumes is given in Table 3. The purpose is to facilitate consistent reporting between
1194 investigators and the Embrace Study Office along the lines of EMBRACE I. Target definition and contouring are described in more detail
1195 in section 9.3.

1196

1197 Table 9.3. Protocol specific nomenclature of volumes of interest.

| GTV-T_{init} | Initial Gross Tumour Volume of the primary Tumour |
|--------------------------------|---|
| CTV-T HR_{init} | Initial High Risk Clinical Target Volume of the primary Tumour |
| CTV-T LR_{init} | Initial Low Risk Clinical Target Volume of the primary Tumour |
| ITV-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 |

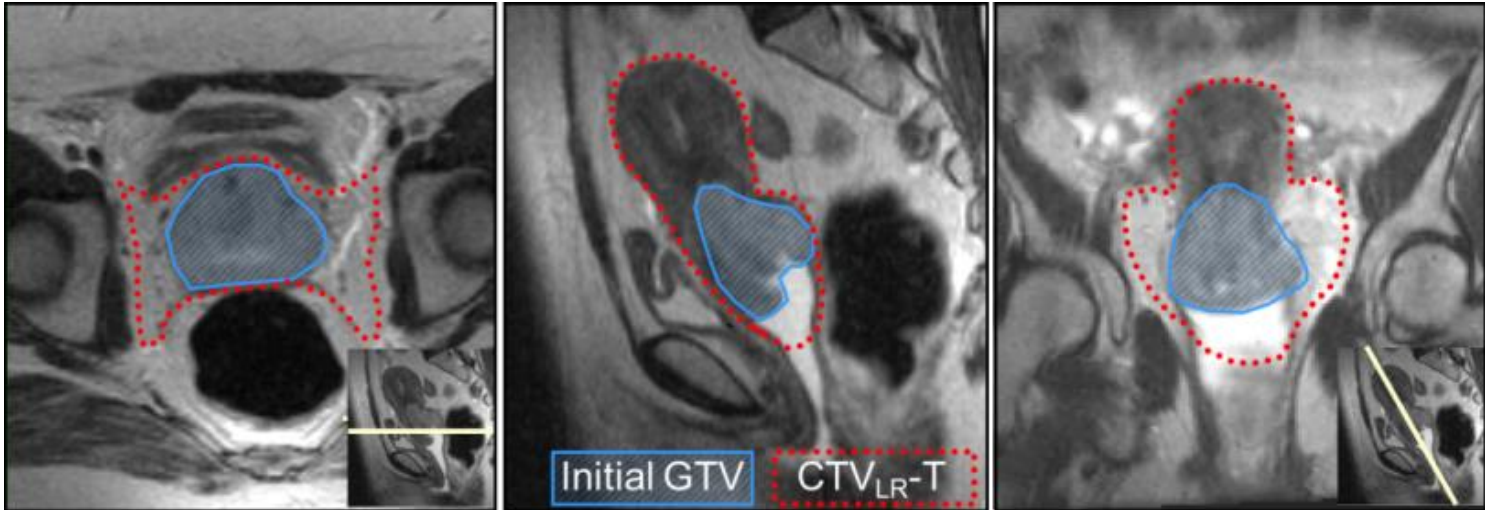
1198 To maintain consistent reporting and communication between investigators and the Embrace Study Office the protocol for contouring
 1199 AND naming of the targets (Table 9.3.) must be followed strictly.

1200 The tumour and target volumes of interest for EBRT are defined in detail in the following paragraphs.

1201
 1202 **9.3.2 INITIAL GTV AND CTV RELATED TO PRIMARY TUMOUR (GTV-T_{INIT}, CTV-T_{INIT} (HR, LR))**

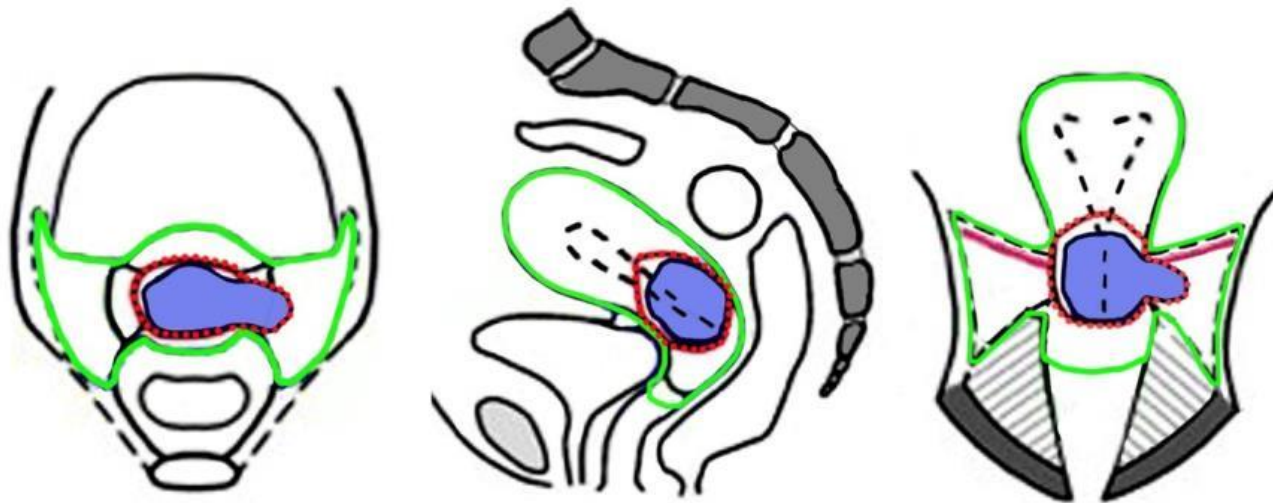
- 1203 1. GTV-T:
 1204 Extension of the primary cervix tumour (inside and outside the cervix)
 1205 (defined by T2 weighted MRI, supported by clinical investigation, FDG PET-CT information).
- 1206 2. CTV-T HR:
 1207 GTV-T and any remaining cervix not infiltrated by tumour.
- 1208 3. CTV-T LR:
 1209 a. Initial CTV-T HR
 1210 b. The complete parametria bilaterally
 1211 c. The entire uterus
 1212 d. Uninvolved vagina with a 20 mm margin measured from the most inferior position of the initial HR CTV-T, along the
 1213 vaginal axis (not starting in the fornix)
 1214 e. CTV-T HR plus a margin of about 5 mm anterior and posterior towards bladder and rectum (excluding the non-
 1215 involved walls)

- 1216 f. In case of involvement of the pelvic wall, sacro-uterine ligaments, meso-rectum or other involved structures a 20 mm
 1217 margin around the initial HR CTV-T will be extended into these structures.
- 1218 g. Any pathological lymph nodes in the parametrium may be included
- 1219



1220

1221 Figure 9.2 MRI at diagnosis (T2 weighted) of stage IIB cervical cancer with the tumour throughout the whole cervix and infiltrating both
 1222 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
 1223 parametria, upper vagina and the uterine corpus (from ICRU 88, 2015 in press)..

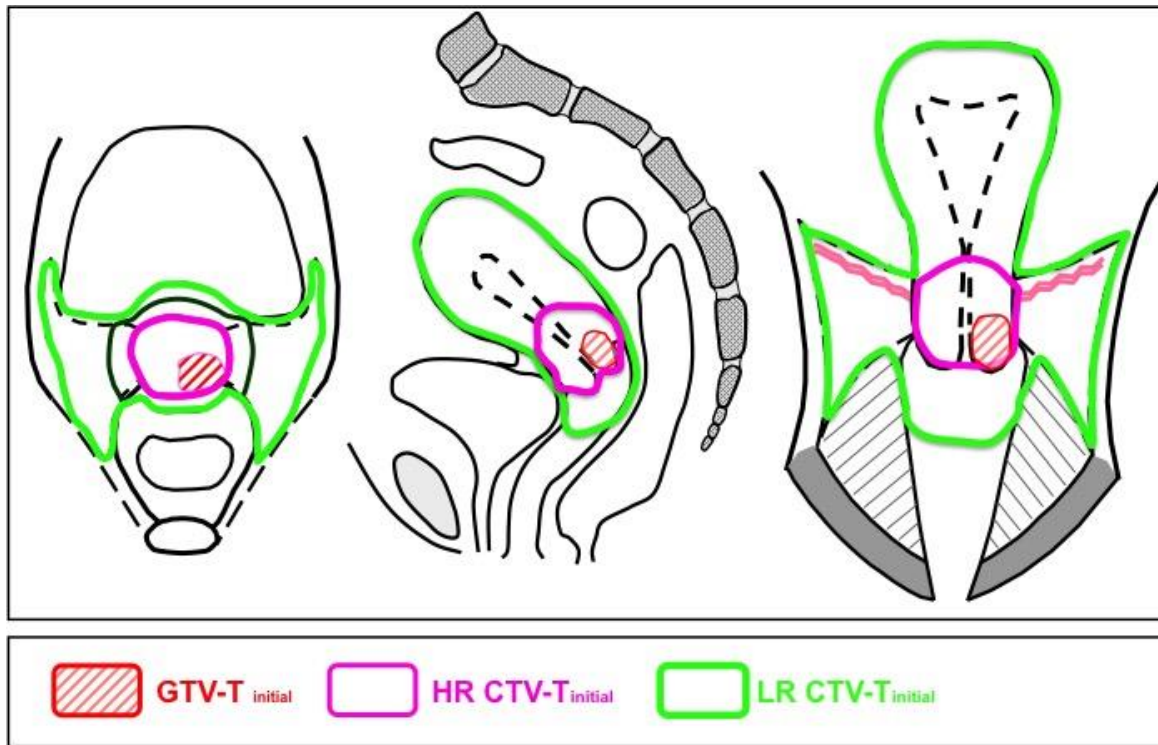


1224

1225 Figure 9.3. Schematic diagram for cervical cancer, stage IIB, invading most of the cervix with unilateral parametrial extension (at
 1226 diagnosis). The initial GTV-T (blue), the HR CTV-T (red line) and the LR CTV-T are indicated.

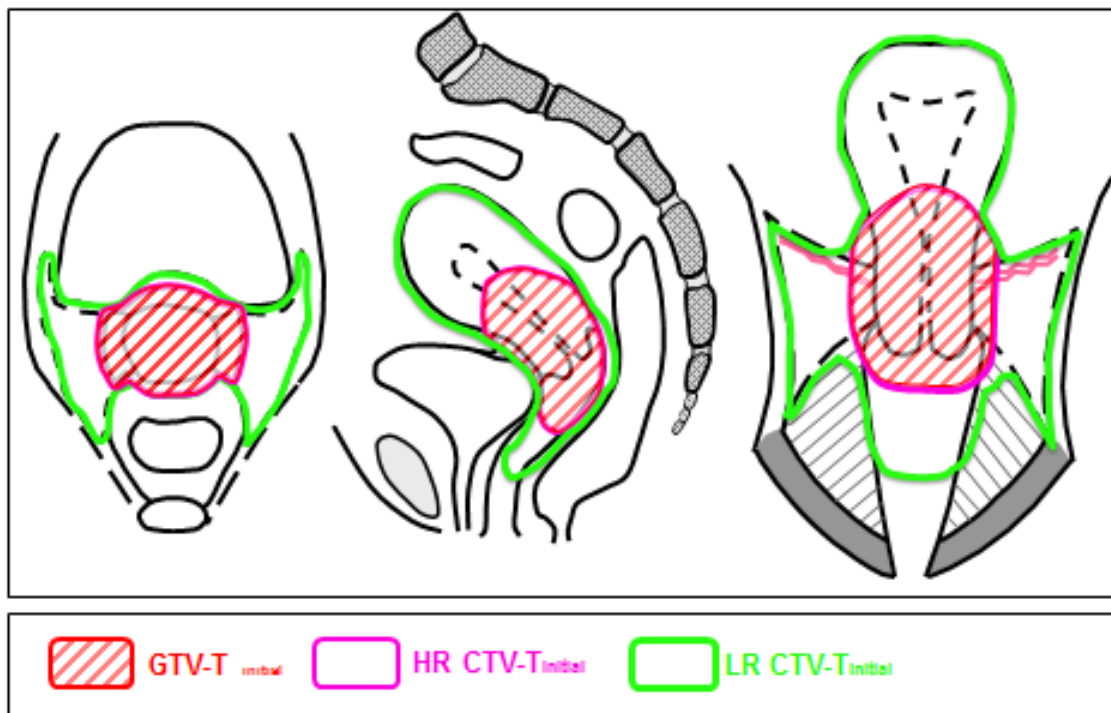
1227 In the following, typical examples for initial GTV-T, initial CTV-T HR and initial CTV-T LR for EBRT are shown for various tumor extensions
 1228 and clinical stages. These figures have been elaborated based on the initial GTV-T demonstration as shown in the figures 10.1-10.5.
 1229 They are therefore complementary to those figures taken from ICRU report 88 with typical examples for residual GTV-T, adaptive CTV-T
 1230 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
 1231 Planning (App Fig. 2-5)

1232



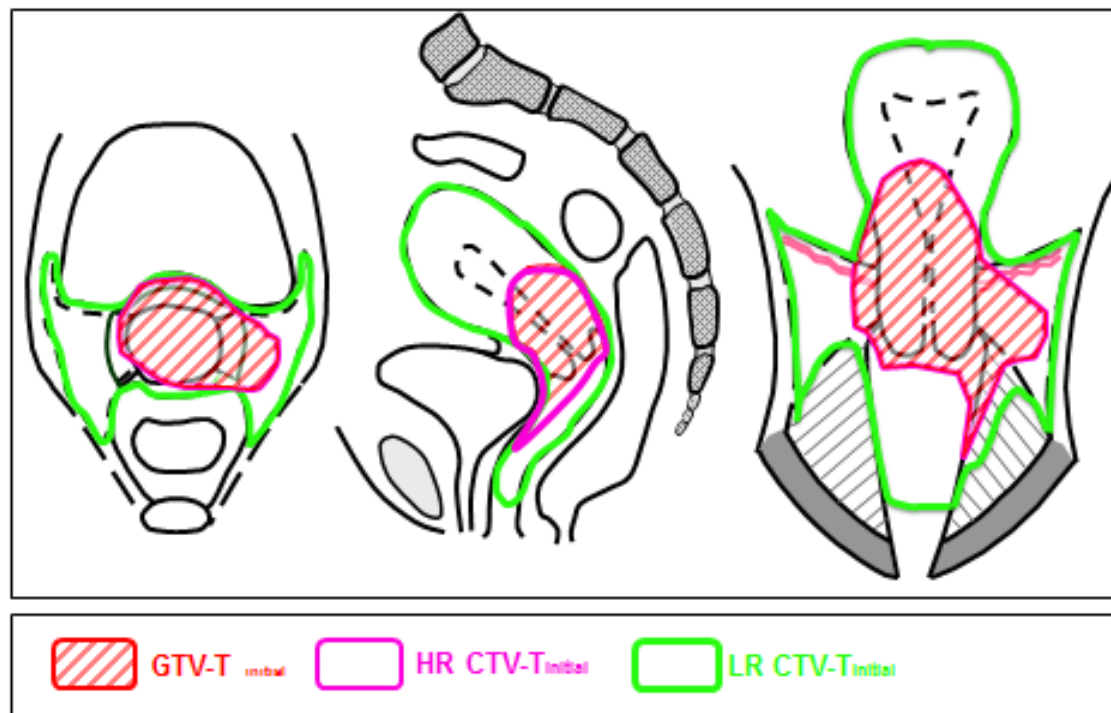
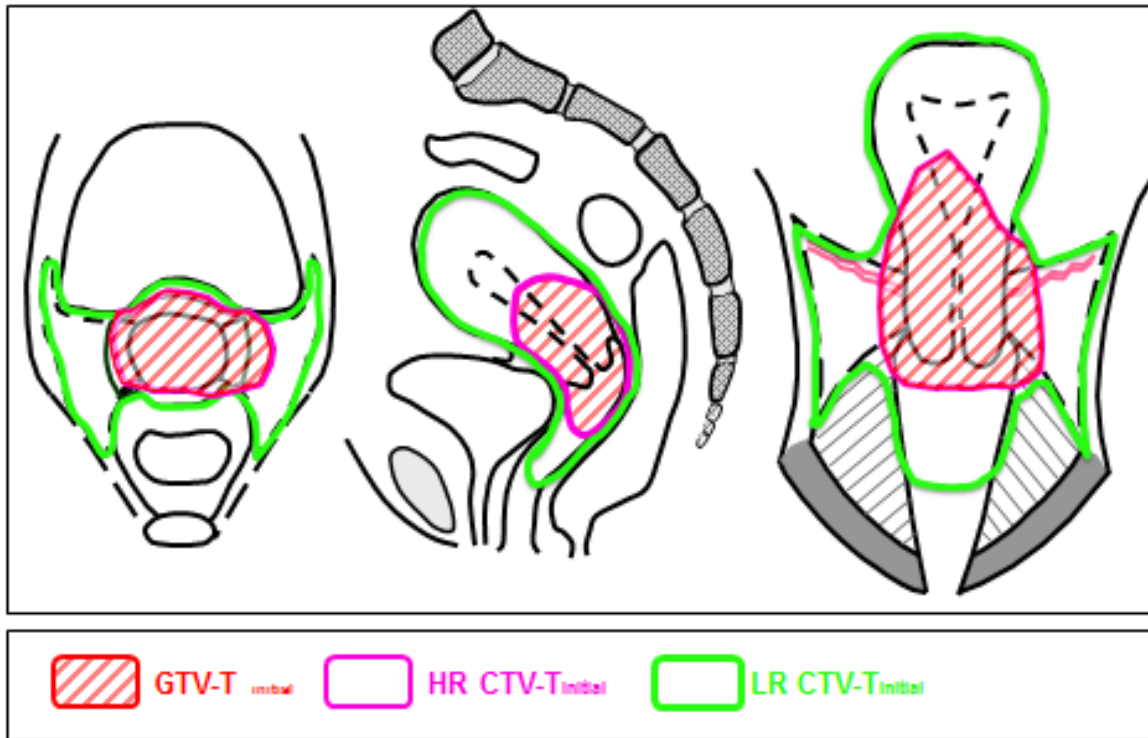
1233

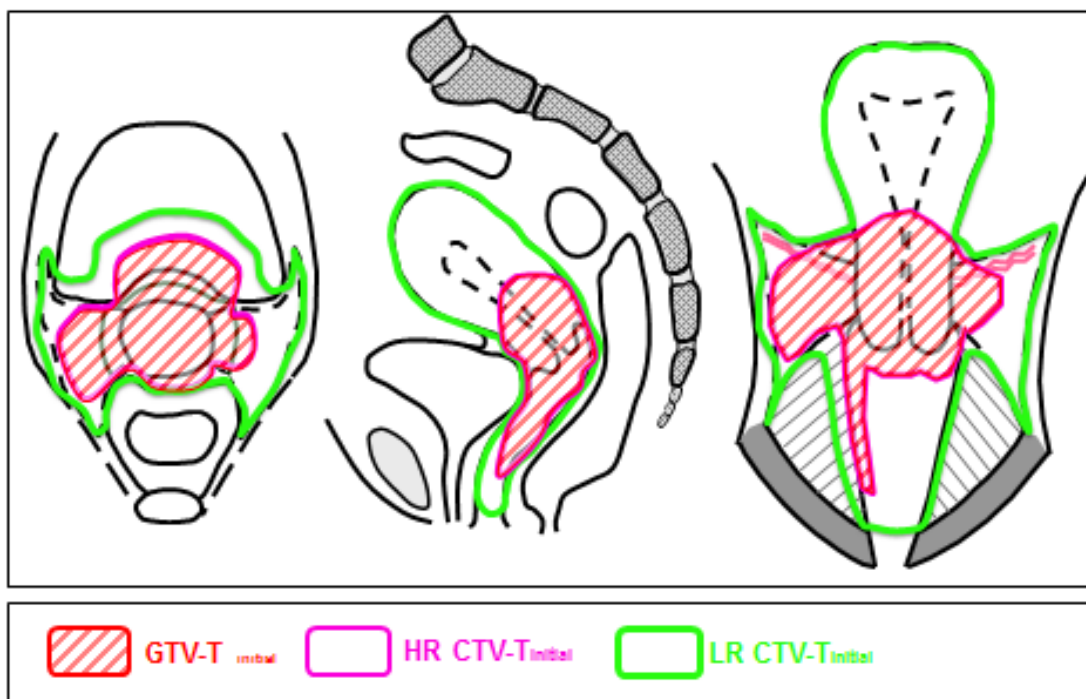
1234 Figure 9.4 (compare figure 3.1 for brachytherapy): Schematic diagram for cervical cancer, limited disease, stage IB1, with initial GTV-T,
1235 initial CTV-T HR (cervix) and initial CTV-T LR (margins for whole parametria, whole uterine corpus, upper third of vagina, utero-bladder
1236 and cervix-rectum space) for EBRT: coronal, transversal and sagittal view. (modified from Fig. 5.8 from ICRU report 88).



1237

1238 Figure 9.5: (compare figure 3.2 for brachytherapy). Schematic diagram for cervical cancer, stage IB2 (bulky disease) with GTV-T_{initial}, CTV-T
1239 H R_{init} and CTV-T LR_{init} for EBRT: coronal, transversal and sagittal view. (modified from figure 5.9 from ICRU report 88)





1247

1248 Figure 9.8 (compare figure 3.5 for brachytherapy). Schematic diagram for cervical cancer, with bladder infiltration, stage IVA, large
 1249 initial GTV-T ($GTV-T_{init}$) and CTV-T HR, initial CTV-T LR: coronal, transversal and sagittal view. (modified from figure 5.12 from ICRU
 1250 report 88).

1251 9.3.3 GTV AND CTV FOR PATHOLOGIC LYMPH NODES (GTV-N, CTV-N)

- 1252 1. GTV-N: Individual GTV-N for each pathological lymph node (defined in Table 1) is contoured (for dose reporting purposes), also
 1253 if nodal boeing is not considered. The outer-contour of the pathological node and visible (macroscopic) extra capsular
 1254 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
 1255 be used for overall guidance and not for precise delineation of the pathological nodes. In case of nodes beyond the field of
 1256 view of the pelvic MRI, individual contours should be based on PET-CT and planning CT appearance. Each GTV-N should be
 1257 numbered individually using the exact protocol nomenclature. (App Fig. 9)
- 1258 2. CTV-N: In principle CTV-N is equal to GTV-N. However, an individualized margin may be considered for each pathologic lymph
 1259 node around each GTV-N taking into account extra-capsular extension and possible progression during treatment planning
 1260 interval, avoiding bones and muscles. Furthermore, partial volume effect may lead to different appearance of the upper and
 1261 lower boundary on CT and MRI. The total CTV-N should encompass the maximum extension as visualized on both CT and MRI.
 1262 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.
 1263 (App Fig. 9).

1264

1265 9.3.4 CTV FOR NODAL REGIONS WITH ASSUMED MICROSCOPIC DISEASE (CTV-E)

1266 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
 1267 (low, intermediate, high): "Small Pelvis", "Large Pelvis", "Large Pelvis + Para-aortic" (Table 9.1, Figure 9.1 and Appendix Fig. 10-15).

- 1268 a. Nodal regions include the relevant vessels with at least 7 mm perivascular tissue including pertinent clips or lymphocysts (in
 1269 case of prior nodal resection or lymphadenectomy). For details concerning anatomical boundaries and margins see appendix
 1270 EBRT treatment planning.
- 1271 b. Any pathological node within the nodal regions must be fully encompassed.
- 1272 c. In case lymphocysts shrink extensively during ERBT, re-contouring and re-planning should be considered.
- 1273 d. In case of excessive uterine/ligamentum latum infiltration, consider to include ovaries into CTV-E.

1274 9.3.5 ITV (ITV-T)

1275 The ITV - required for optimal target coverage - depends on internal target motion and on the level of image guidance during the course
1276 of fractionated radiotherapy (IGRT). Major shifts may be expected for CTV-T LR especially in the anterior-posterior direction and have to
1277 be accounted for in ITV-T LR with appropriate margins.

1278 No ITV is defined for the elective nodal target (CTV-E).

1279 Different levels of IGRT can be recognized for image guidance and IMRT for cervix cancer EBRT:

1280 1) **Basic IGRT**: standard margins from CTV-T to ITV-T are applied to compensate for internal target motion. Daily online position
1281 verification and couch correction based on bony landmarks is required using CBCT, kV or EPID imaging to achieve the aimed decrease in
1282 set up errors and corresponding reduction of the PTV margin. CBCT may be used for daily monitoring of uterus movement to decide if
1283 re-planning would be an advantage according to the motion patterns observed.

1284 2) **Intermediate IGRT**: the CTV-T to ITV-T margin is individualized based on multiple pre-treatment imaging series that allow the
1285 assessment of the individual range of internal target motion. The different images should include different fillings of bladder, which can
1286 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
1287 more representative for the expected range of motion in the individual case. CBCT imaging is used for daily online position verification
1288 and couch correction based on bony registration. CBCT may be used for daily monitoring of uterus movement to decide if re-planning
1289 would be an advantage according to the motion patterns observed.

1290 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
1291 library plan approach has been integrated into clinical workflow in some institutions. In this situation daily CBCT is required to select the
1292 ITV-T and treatment plan that best covers the CTV-T on that day.

1293 In EMBRACE II, basic IGRT is minimally required and intermediate IGRT is recommended. Intermediate IGRT is recommended since it is
1294 expected to result in an ITV-T LR that is better representing the motion in the individual case. Advanced adaptive IGRT is allowed
1295 whenever an institution has this advanced approach clinically implemented. Furthermore, an optional sub-protocol for application of
1296 daily library plans (adaptive EBRT) will become available in EMBRACE II as an amendment to the protocol.

1297

1298 9.3.6 STRATEGIES TO DERIVE THE ITV-T LR

1299 a) **Basic IGRT, standard margin approach (Fig. 9.9.A)**

1300 The ITV-T LR includes (see also App. EBRT for Treatment Planning Figure 7):

- 1301 • CTV-T LR with the following margins:
- 1302 ○ 10 mm anterior-posterior
 - 1303 ○ 10 mm superior-inferior
 - 1304 ○ 5 mm lateral
- 1305 • At the distal vagina no additional margin along the vaginal axis in the inferior direction is applied
- 1306 • The ITV-T LR should not go into the muscle and bony boundaries of the pelvis (in particular, manual adaptation is needed in the
1307 lateral parametria)
- 1308 • In case of tumour involvement of the upper and most mobile uterus an extra 5 mm margin should be applied in all directions
1309 from the uterus body

1310 Importantly, a clinical judgment has to be made if the CTV structures as presented on the MRI and treatment planning CT are more or
1311 less in the expected average position, based on the rectal and bladder filling state. Having multiple diagnostic image sets fused with the
1312 treatment planning CT, facilitates this judgement. If the target volume is not in the average situation, this should be taken into account

1313 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
1314 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
1315 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-
1316 inferior direction. It should be kept in mind that several studies found that the average bladder volume decreases during the course of
1317 treatment. It is expected that the ITV-T LR contours are modified based on clinical judgement. Reducing the margin in one direction
1318 implies normally that the margin is increased to the same degree in the contralateral direction. The minimal required margin in
1319 anterior-posterior and superior-inferior directions is 5 mm.

1320 **b) Intermediate IGRT, individualized ITV-T approach (Figure 9.9.B):**

1321 The key difference for an individualized ITV-T compared to the standard margin approach is that pre-treatment imaging, both
1322 diagnostic and for treatment planning, is used to assess the range of motion in an individual patient. A pre-requisite is that these
1323 imaging series have different filling status of bladder and rectum. For this purpose a full and empty bladder treatment planning CT can
1324 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
1325 motion, a margin comparable or larger than that derived from standard motion range may be required.

1326 To generate the ITV-T LR, the different diagnostic and treatment planning image series should be fused to the treatment planning CT
1327 with comfortably filled bladder. The ITV-T LR margin is adapted based on the assessed range of motion within the individual patients,
1328 keeping in mind the proposed standard motion ranges (figure 9.9).

1329 The margins used under “standard margin approach” should be the starting point and individualisation can be adapted from there. ITV-
1330 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
1331 as seen on an image series with an empty bladder, since with the drinking protocol this situation is not expected during the course of
1332 fractionated EBRT. It should be kept in mind though that some studies indicate that the average bladder volume decreases during the
1333 course of treatment. If daily soft tissue verification (CBCT) is used to monitor the daily uterus position, it is possible to shrink the
1334 individualised margins further according to the thresholds defined for re-planning.

1335 **9.3.7 GENERATING THE ITV45**

1336 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
1337 also contains any CTV-N. This combined tumour and lymph node related target volume is named ITV45. This final ITV45 is required for
1338 dose reporting.

1339 **9.3.8 PTV**

1340 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
1341 considered appropriate when using daily image guidance and daily couch correction according to bony fusion (see section 9.6).

1342 The PTV45 is consequently the ITV45 with an isotropic margin of 5 mm

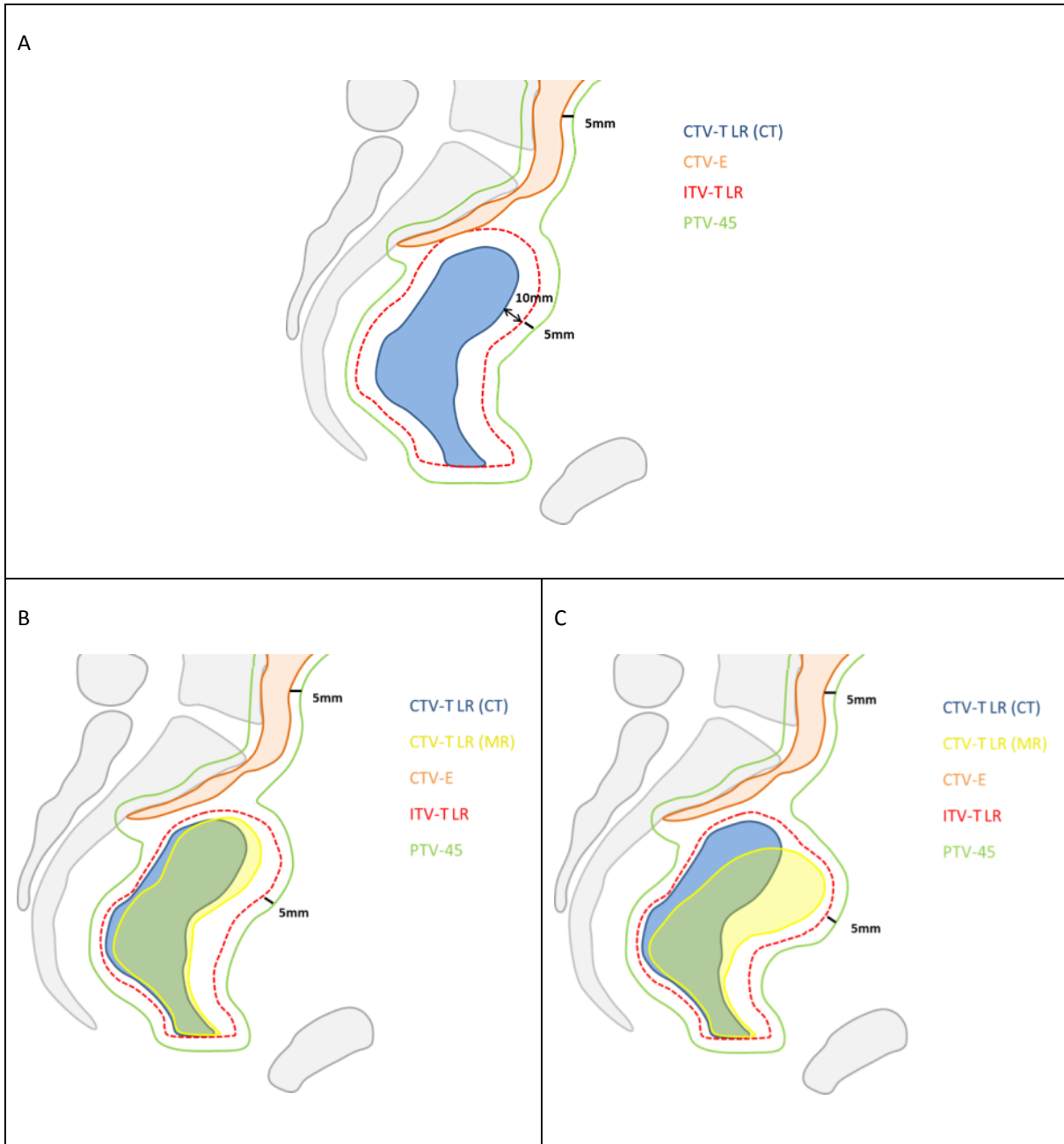
1343 For the involved nodes, PTV-N (#) is CTV-N (#) with an isotropic margin of 5 mm. Each individual pathologic node (#) will have an
1344 individual PTV-N (#). PTV-Ns are usually encompassed by PTV45. If they are not encompassed, a larger margin of e.g. 10 mm from the
1345 CTV may be considered in the specific region.

1346

1347

1348

1349



1350 Figure 9.9. Panel A shows the application of the "Standard margin" approach where the ITV is defined according to the anatomy in the
 1351 CT treatment planning scan. Panel B and C show examples of a "small mover" and "large mover", respectively, and application of the
 1352 "Individualised ITV approach". Further examples of "Standard margin" and "Individualised ITV approach" can be found the appendix 5
 1353 "Contouring Atlas for EBRT".

1354

1355

1356 9.4 CONTOURING OF ORGANS AT RISK, REFERENCE POINTS

1357 *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 \pm 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 |
|-----------------|-------------|

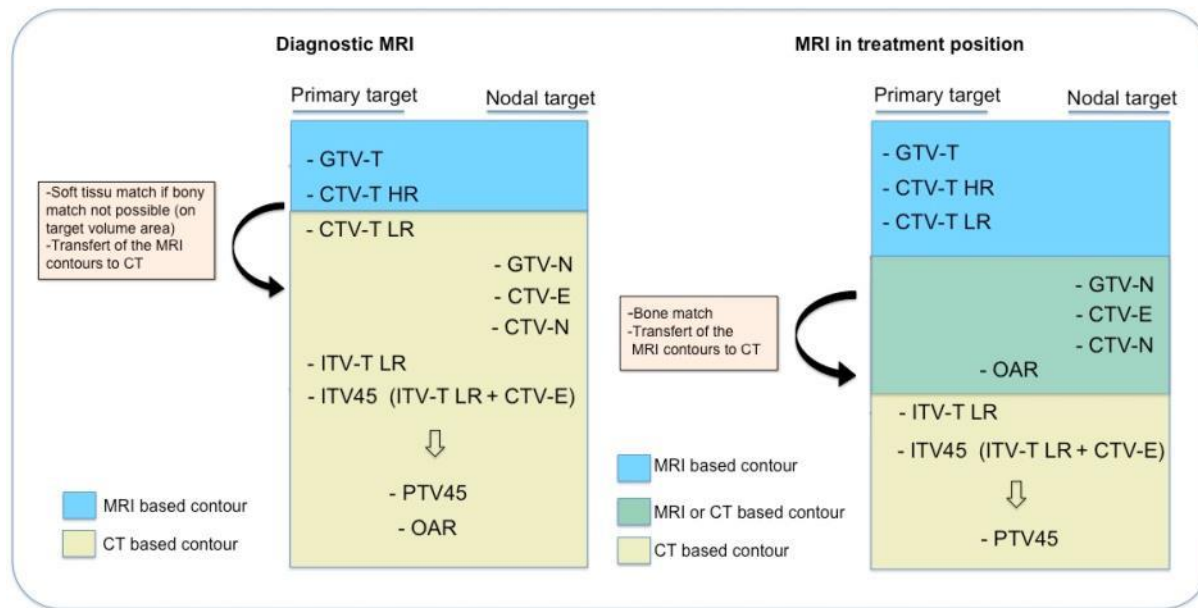
In case of ovarian transposition

| | |
|--------------|---------------|
| Ovary | Outer contour |
|--------------|---------------|

1358 9.5 CONTOURING OF TUMOUR, TARGETS AND OARS BASED ON MRI AND CT

1359 Treatment planning is performed on the treatment planning CT with a comfortably filled bladder. The T2 weighted transversal plane
1360 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
1361 filling protocol) the fusion is usually excellent and MRI can be used for contouring all targets and OAR in the whole cranio-caudal length.
1362 In these cases additional contouring on planning CT might only be needed for the para-aortic part in case of high risk disease.

1363 If diagnostic MRI scans are used, fusion may be more challenging. Priority should be set at achieving an acceptable match within the
1364 pelvis. In these cases it is preferable to use the anatomy as seen on the treatment planning CT for contouring when moving outside the
1365 area of acceptable match. It is recommended to start contouring on MRI, exploiting the superior soft tissue resolution when delineating
1366 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
1367 representative, and the next step of contouring normally proceeds on the treatment planning CT to delineate CTV-T LR, ITV-T LR, nodal
1368 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
1369 planning CT, it may be possible to perform GTV-N, CTV-E and OARs on the diagnostic MRI.



1370

1371 Figure 9.10 Schematic workflow for contouring primary target and nodal target and OARs on diagnostic MRI, MRI in treatment position
1372 and CT (see also ch. 26 on EBRT treatment planning, Appendix).

1373 9.6 DOSE AND FRACTIONATION FOR PTV45

1374 The planning aim dose and fractionation schedule for PTV45 is 45 Gy delivered in 25 fractions, 1 fraction per day and 5 fractions per
1375 week. All beams and segments involved in a given part of the treatment must be treated at each fraction. Unplanned treatment breaks
1376 (>2 consecutive treatment days) should be compensated by two daily EBRT fractions spaced by at least 6 hours. This compensation
1377 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.

1378 **Maximal overall treatment time including external beam radiotherapy, brachytherapy and concomitant chemotherapy is 50 days.**

1379 The dose to the PTV45 should be homogenous, with at least 95% of the PTV covered by the 95% prescription isodose, and dose
1380 maximum less than 107% of the prescribed dose.

1381 Special attention is needed for the OAR irradiation in close proximity to the CTV-T HR (bladder, rectum, sigmoid and bowel) where the
1382 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
1383 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
1384 contour should be less than 103% of 45Gy to avoid hotspots in OAR walls which are likely to also receive considerable BT dose.

1385 9.7 DOSE AND FRACTIONATION FOR PTV-N (NODAL BOOSTING)

1386 The decision for nodal boosting is left to the individual centre. However, all pathological nodes (with the features described in section
1387 9.3.3.) should be contoured and numbered individually.

1388 **Nodal boosting should be performed by use of a simultaneous integrated boost (SIB), with a total number of fractions of 25.** Dose
1389 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
1390 specified for dose reporting, and, if possible, (expected) contribution from BT to the total EQD2 of the specific node. Biological
1391 equivalence calculations are performed by use of the linear-quadratic formulation assuming that the alpha/beta value is 10 Gy for
1392 tumour effects.

1393 Dose from BT to each individual node can be calculated based on BT MRI information. However, the expected PTV-N dose contribution
1394 from brachytherapy can also be accounted for (Mohamed SM. et al. 2015):

1395 • 3-4 Gy EQD2: Inside true pelvis (external/internal iliac, obturator)

1396 • Negligible: Outside true pelvis (common iliac, para-aortic, inguinal)

1397 Although institutional practise for nodal boosting and dose levels can be followed, the recommendation given within this protocol for
1398 the nodal boost is that total EBRT + BT dose should preferably be in the range 55-65 Gy EQD2.

1399 Total dose to PTV-Ns of about 60 Gy EQD2 can be achieved with the following fractionation schedules:

1400 • Inside true pelvis: EBRT with SIB 25x2.2Gy= 55Gy physical dose. This schedule is equivalent to 56 Gy EQD2 EBRT + 3-4 Gy EQD2
1401 from BT which results in a total dose of ~60 Gy EQD2.

1402 • Outside true pelvis: EBRT with SIB 25x2.3Gy =57.5 Gy physical dose. This schedule is equivalent to ~59 Gy EQD2 and BT dose
1403 contribution is negligible.

1404

1405 **9.8 TECHNIQUE AND PROCEDURES FOR EBRT INCLUDING DAILY IMAGE GUIDANCE**

1406 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.
1407 This goal implies the mandatory use of IMRT, VMAT or tomotherapy based on inverse treatment plan optimisation. Photon energy of 18
1408 MV is related with increased neutron dose, and therefore lower energies (e.g. 6 MV or 10 MV) are advantageous in this respect for
1409 IMRT/VMAT. However, for higher energies the treatment plan quality is advantageous in terms of decreased low dose volumes for
1410 IMRT/VMAT. These two aspects need to be considered when deciding on photon energy.

1411 It is recommended to use coverage probability (CoP) dose planning principles for lymph node boosting. With CoP planning principles it
1412 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
1413 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
1414 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
1415 limit of 107%.

1416 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
1417 anatomy. Couch correction must be performed daily before treatment delivery according to the bony fusion between the on-board
1418 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
1419 might take nodes and elective target out of the treated volume. Soft tissue verification (evaluation of the position of uterus) based on
1420 CBCT can be performed, but is not mandatory. With soft tissue verification it is possible to evaluate if the daily uterus position is
1421 significantly different from expected and this knowledge can be used to decide that a new treatment plan would be beneficial.

1422 In case that 3D soft tissue verification imaging and monitoring shows that significant parts of CTVs are repeatedly outside the 95%
1423 isodose volume, the following should be considered:

1424 • Additional tattoos at the level of L2

1425 • Additional planning CT scan for re-planning

1426 • Redefining the ITV, taking the information acquired with CBCT into account.

1427 • Adjustment of the PTV margin (see the section on angulation of the pelvis in relation to the lumbar spine.

1428 • There is allowance for 10% under dosage in the non-involved uterus as accumulated across all EBRT treatment fractions which
1429 is equivalent to a total dose of 40Gy. Brachytherapy contributes to uterus dose normally by >5-10Gy, and the aim is to deliver a
1430 total of 45Gy EQD2 to the uterus in terms of total EBRT and BT dose (D98).

1431

1432 9.8.1 ANGULATION OF THE PELVIS IN RELATION TO THE LUMBAR SPINE

1433 With para aortic radiation, flexing of the thoraco-lumbar spine in relation to the pelvis can be a concern considering the tight PTV
 1434 margin. In case of repeated residual misalignment of more than 5mm despite daily correcting to match on bony anatomy the following
 1435 procedures should be considered: check if immobilization device is used optimally; consider additional tattoos at the level of L2;
 1436 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
 1437 residual set-up error persists.

1438 **9.9 PLANNING AIMS FOR TARGETS AND ORGANS AT RISK**

1439 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
 1440 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
 1441 definition described in chapter 9.2.3 with a 5 mm ITV to PTV margin.

1442 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: <ul style="list-style-type: none"> • V40Gy < 100cm3** • V30Gy < 350cm3** When lymph node boost or para-aortic irradiation: <ul style="list-style-type: none"> • 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 | |

1443 *In case that lymph nodes are not boosted,

***Verma J. et al. 2014

1444 **Soft constraints which can be used as optimisation constraints as they are not based on clinical evidence. The constraints are not
 1445 supposed to be fulfilled by all patients, but rather by ~70-80% of the patients.

1446 **9.10 REPORTING OF EBRT PARAMETERS**

1447 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 |

1448 *Total volume (including PTV and entire body). Depending on planning system a helper structure might be necessary (e.g. Monaco)

1449

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.

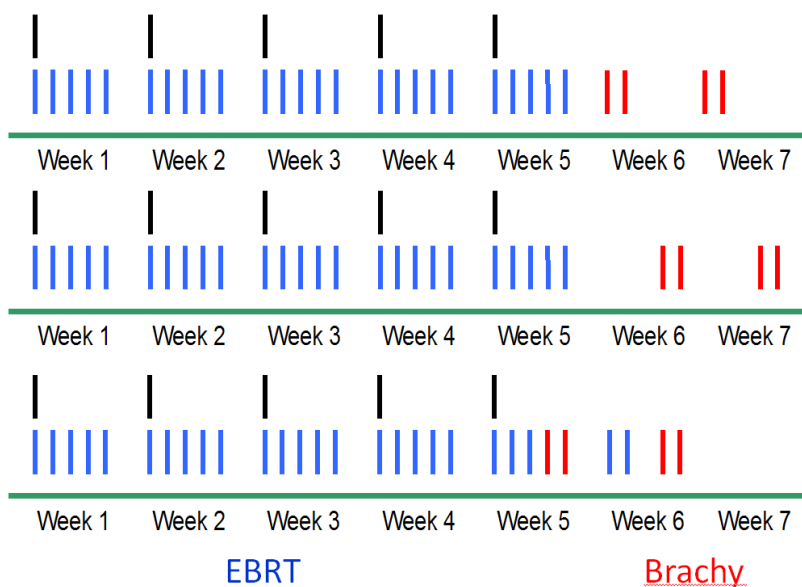


Figure 10.1: Examples of overall schedules administering 25 fractions of EBRT with or without simultaneous integrated lymph node boost (blue bars), 5 courses of concomitant cisplatin (black bars) and 4 fractions of HDR brachytherapy (red bars) within an overall treatment time of 7 weeks (upper panels)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

1475 To obtain maximal tumour regression the treatment should always be initiated with EBRT and concomitant chemotherapy for 4-5
1476 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
1477 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
1478 overall treatment time < 50 days.

1479 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
1480 OTT already during the first weekend. Concomitant chemotherapy given on the first days of the week also theoretically paves the way
1481 for sensitizing more fractions of EBRT in that week, rather than giving chemotherapy on a Friday where the sensitizing effect is expected
1482 to vanish during the weekend. There is limited data on the optimal timing of EBRT and concomitant chemotherapy on the actual day
1483 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
1484 concomitant chemotherapy later in the day to avoid problems with an overhydrated and nauseated patient during EBRT.

1485 10.1.2 PRE-APPLICATION TREATMENT PLANNING

1486 In order to arrive at an appropriate brachytherapy application for cervix cancer a pre-planning procedure is essential which allows for
1487 tailoring the application as much as possible to the vaginal anatomy and the tumour spread as it presents at the time of brachytherapy.
1488 This requires in any case a comprehensive clinical gynaecologic examination assessing the vaginal topography and the tumour response
1489 as compared to the situation at diagnosis at the cervix, in the parametria and in the vagina. This should be precisely documented on the
1490 standard gynaecologic template in three orientations including the speculum view. This examination can be supported by volumetric
1491 imaging, preferably MRI, which allows for even more precise documentation of the tumour situation at brachytherapy. Based on this
1492 assessment an individual adaptive CTV-T HR is defined with a certain width, thickness and height. Essential is the relation of these
1493 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
1494 CTV-T HR are symmetrical or asymmetrical (compare Fig. 10.2-5). Taking these dimensions into account a decision is taken about the
1495 method of application, in particular, if it can be only intracavitary or a combination of intracavitary and interstitial application. The most
1496 precise pre-treatment planning is with a tandem and vaginal applicators in place, which are only inserted for treatment planning (Petric
1497 P. et al. 2009, Fokdal L. et al. 2013).

1498 A basic preplanning procedure must be implemented routinely in gynecologic brachytherapy for a tailored application. For EMBRACE II
1499 application adaptation must be a common procedure in daily clinical practice. Systematic use of combined intracavitary and interstitial
1500 applicators (based on individual mould, ring, ovoids) is a request for appropriate dose adaptation which is dose escalation in particular
1501 for advanced parametrial disease and/or dose sparing in adjacent organs at risk. Continuous further development is necessary based on
1502 clinical and imaging information and corresponding applicator design (Dimopoulos JC. et al. 2006, Jürgenliemk-Schulz IM. et al. 2009,
1503 Kirisits C. et al. 2006). A systematic pre-application planning strategy, including a pre-procedure CTV-T, is considered important for
1504 EMBRACE II to account for the specific clinical situation, the selection and contouring uncertainties in adaptive CTV-T, and the expected
1505 geometrical and dosimetrical uncertainties (Fokdal L. et al. 2013, Petric P. et al. 2009, Tanderup K. et al. 2010).

1506

1507 10.2 APPLICATOR INSERTION FOR BRACHYTHERAPY

1508 Bowel preparation should always be used to ensure an empty rectum and sigmoid colon, which is of particular importance when using
1509 interstitial needles in addition to intracavitary treatment and also for PDR with prolonged stay in bed. Supportive treatment such as low
1510 molecular weight heparin, antibiotics and analgesics are given according to individual patient needs and institutional practice.

1511 Before placement of the BT applicator a clinical assessment of the tumour extension is performed describing tumour dimensions
1512 (width, height and thickness) as well as the possible involvement of parametria, vagina, bladder and rectum. The clinical examination is
1513 documented by drawings by use of the standard clinical diagram (see appendix 22.1).

1514 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
1515 which is suitable to correctly visualize the balloon on MRI.

1516 Each participating department should define standard rules for bladder filling which should be followed both during each imaging
1517 procedure (MRI/CT) and the subsequent BT treatments. For HDR this is usually obtained by emptying the bladder and installing a
1518 specified amount of saline in the bladder, whereas for PDR an “open catheter policy” during both imaging and treatment is usually
1519 applied.

1520 Dilatation of the uterine canal can be guided by ultrasound and the depth of the uterine cavity is measured. An MRI compatible
1521 applicator is then chosen depending on the anatomical topography of tumour, uterus, cervix and vagina and placed in close contact
1522 with the tumour and cervix. The choice of the applicator type depends on the individual anatomy and the tumour spread at the time of
1523 brachytherapy. The choice of applicator type (e.g. ring or ovoid type) is up to the decision of each centre. Additional implantation of MR
1524 compatible needles in the parametrium and/or vagina have to be used as appropriate for appropriate target coverage. Vaginal packing
1525 must be performed with gauze to push away the rectum and bladder and to fix the applicator against the cervix. The gauze may be
1526 filled with contrast medium as diluted gadolinium, US gel or saline water to distinguish the packing from the vagina.

1527 The applicator may be fixed to the patient by elastic bandages or similar. External fixation to the surgical table/board should not be
1528 used. Alternatively, an individual mould or other customized procedures may be used for fixation of the applicator according to the
1529 practice of the participating institution. Important is a fixed geometry of the applicator in relation to the target volume. In-vivo
1530 dosimetry by use of detectors can be used according to institutional practice.

1531 The patient is transferred to the MRI scanner to obtain appropriate images with the patient in the supine treatment position. With
1532 sufficient vaginal packing, there is according to available evidence so far no indication of relevant movement of the applicator relative
1533 to the CTV or to adjacent OAR.

1534

1535 **10.3 IMAGING FOR BRACHYTHERAPY**

1536 The primary imaging modality for brachytherapy treatment planning is MRI for each individual applicator insertion. Additional imaging
1537 may be performed, if possible, also for each fraction in case of fractionated HDR treatments or as a constancy check during a PDR
1538 course if planned in an individual centre.

1539 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
1540 succeeding insertions/fractions. Each applicator insertion must be followed by at least one 3D volumetric image (preferably MRI) and
1541 dose planning, while subsequent fractions using the same implant might be applied with the same treatment plan. Only in case of
1542 exceptional circumstances and if the contouring for reporting is based on an MRI performed at a time point close to the first implant
1543 also the first fraction might be planned without MRI with applicator in situ. In these exceptional cases at least one of the subsequent
1544 fractions has to be MRI based then.

1545 To ensure a reliable reconstruction of the applicator the slice thickness of MRI should be ≤ 5 mm with no interslice gap. Sequences
1546 taken parallel to the applicator, i.e. paratransversal, paracoronal and parasagittal (18) are superior to straight transversal, coronal and
1547 sagittal images with regard to both target contouring and applicator reconstruction. Marker wires of plastic with saline or solutions of
1548 CuSO_4 can be used to ease the identification of the source channel and determine any rotation of the applicators ([Dimopoulos JC. et al. 2012](#)).
1549

1550 Orthogonal X-rays is not required but may be used in the anterior-posterior and lateral projection with radio-opaque guide wires in the
1551 applicator to ensure that the spatial 2D relation between applicator and target and OAR is satisfying. Dose points must be defined
1552 directly in the 3D imaging set used for contouring and treatment planning and should not be defined in 2D on the radiographs (see
1553 below).

1554

1555

1556 10.4 APPLICATOR RECONSTRUCTION AND DOSE POINTS FOR OARS

1557 Uncertainties of 4% (k=1) due to applicator reconstruction are assumed when reporting dose parameters for cervix brachytherapy
1558 (Kirisits C. et al. 2014). This uncertainty level can only be reached by an appropriate step-by-step quality assurance program in each
1559 center (Hellebust TP. et al. 2010):

1560 Step 1: The first step is to define the source path (which is subsequent dwell positions of the actual source inside the applicator) in
1561 relation to the applicator. This is usually defined or at least checked during commissioning of applicators and afterloaders. The source
1562 path can be related to the outer dimensions of an applicator or to marker wires or other indicators placed inside the applicator. A usual
1563 way is to perform auto-radiographs to visualize the dwell positions. Such commissioning procedure should result in drawings of the
1564 essential dimensions or even applicator templates which can be integrated into treatment planning systems.

1565 Step 2: The accuracy of applicator reconstruction is depending on the resolution of the 3D image set. Appropriate imaging has to be
1566 performed, either by reducing the slice thickness, by combining different image orientations (e.g. oblique orientations in transverse,
1567 sagittal and coronal) or by using dedicated 3D sequences (e.g. isotropic voxel size). Each department must ensure that the applicator
1568 reconstruction can be performed with an uncertainty of < 2 mm. This includes the overall deviation of the planned dwell position to the
1569 finally realized dwell position on an anatomical situation as visualized on the planning MRI (or CT). This includes deviations due to
1570 source path definition (commissioning), equipment performance (constancy checks) and the reconstruction process in the treatment
1571 planning system.

1572 Step 3: For CT reconstructions library plans or direct reconstruction based on CT, markers may be the optimal solution. For MRI
1573 reconstructions library plans are the optimal method. Fusion of CT to MRI is most often not helpful for applicator reconstruction; as
1574 such fusion techniques have to be based on the already reconstructed applicator in both image modalities. In certain situations the
1575 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
1576 registering MRI with CT via the intracavitary applicator and then use CT for needle reconstruction. However, this depends on the
1577 individual settings and MRI can also be sufficient, even for complex implantation geometries.

1578 The dose points for brachytherapy are defined directly in the volumetric imaging study (MRI or CT). In addition, the point of expected
1579 dose in a specific organ may be determined and used for in vivo dosimetry for instance if rectal diodes are used (optional).

1580 The following dose points should be defined directly in the 3D imaging study:

- 1581 • The ICRU bladder point
- 1582 • The ICRU recto-vaginal point
- 1583 • Vaginal point doses at level of sources (lateral at 5 mm)
- 1584 • Lower and mid-vagina doses (PIBS, PIBS ± 2 cm)

1585 Definition of the point A, the recto-vaginal, the bladder and the PIBS reference points on CT and MRI has to be strictly followed
1586 according to the ICRU88/GEC ESTRO report. Point A is strictly related to the applicator. Practically a coordinate system is rotated and
1587 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
1588 vaginal applicators. When defining the recto-vaginal and bladder reference points the image orientation is essential. Both points are
1589 defined according to the patient coordinate system - on anterior-posterior lines, which are strictly perpendicular to the longitudinal axis
1590 of the patient. The location of the PIBS points is estimated best on sagittal image orientations, again taking into account the image
1591 orientation to define PIBS on a straight anterior-posterior line perpendicular to the patient axis. From PIBS, PIBS+2 and PIBS-2 are
1592 defined via ruler function in the TPS or entering coordinates in a correct adjusted patient coordinate system.

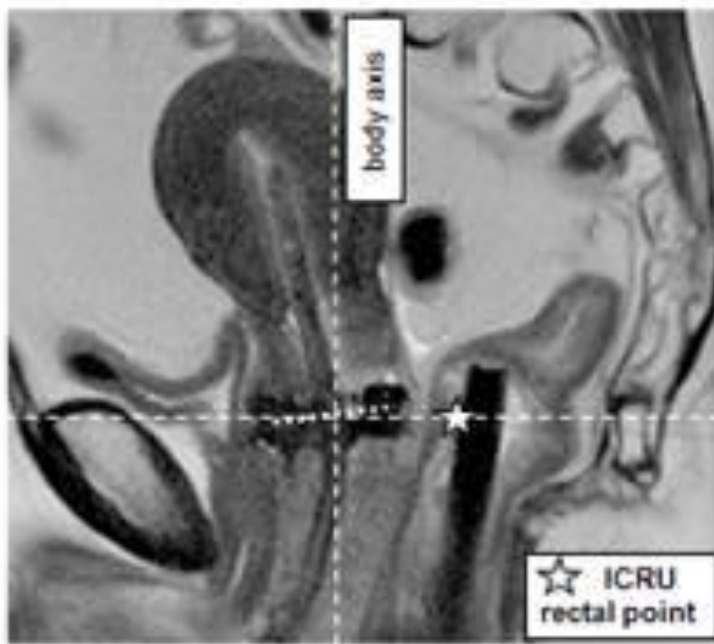
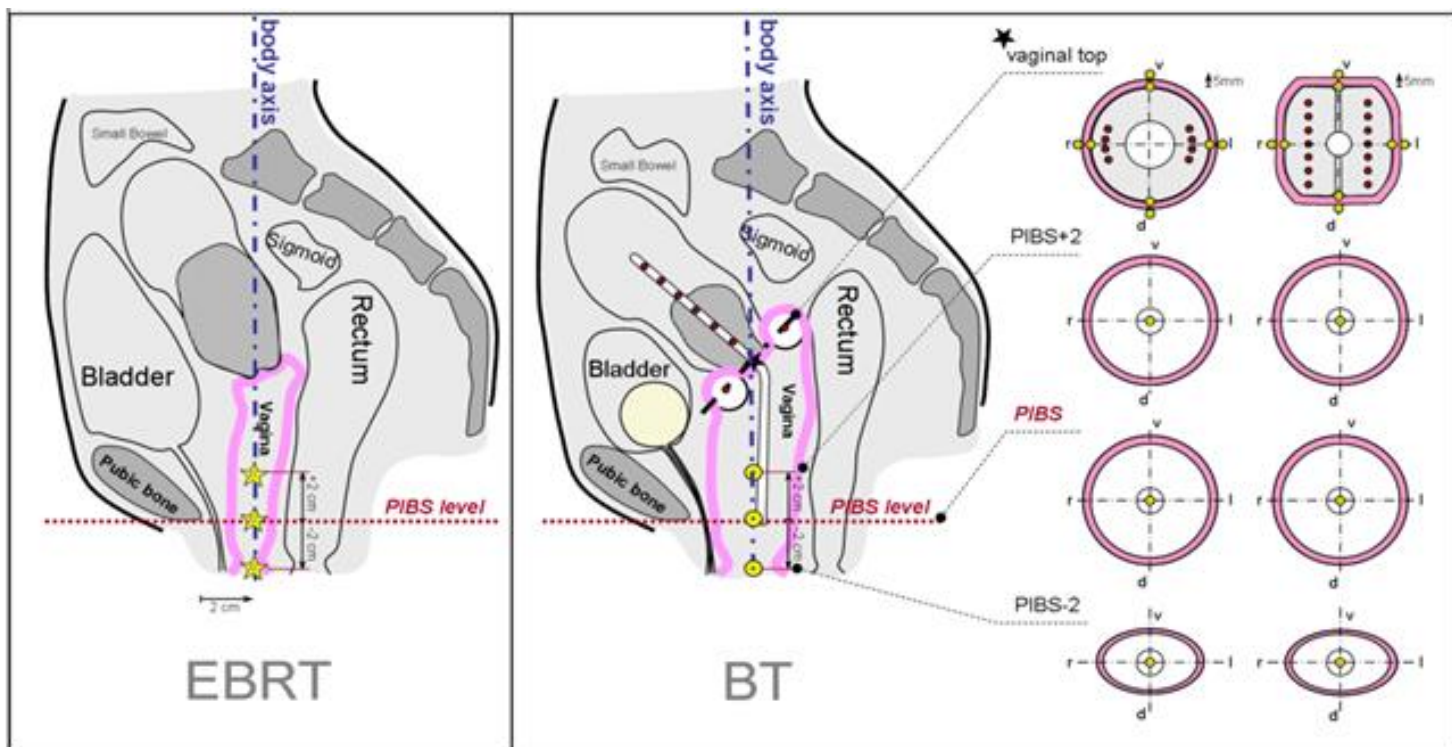


Figure 10.2: The recto-vaginal dose point inserted according to the ICRU/GEC ESTRO report 88 (image from Kirchheiner K. et al. in submission 2015)



1593

1594 Figure 10.3. Sagittal views showing the vagina at time of EBRT and at brachytherapy with an intracavitary applicator in place. At the
 1595 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.
 1596 Three additional points are defined along the central axis of the vagina in the cranio-caudal direction. The PIBS vaginal-dose point was
 1597 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
 1598 applicator tandem. From there, two additional points 2 cm up and down along the vaginal axis, are defined with PIBS+2 representing
 1599 the mid of the vagina and PIBS-2 representing the introitus level (Westerveld H. et al. 2013).

1600

1601 10.5 CONTOURING FOR BRACHYTHERAPY: OARS, GTV_{RES}, ADAPTIVE CTV_{HR}, CTV_{IR}

1602 Contouring for both tumour and OAR is performed for each insertion/implant of BT applicators by contouring on T2 weighted (para)-
1603 transversal MRI sequences in a dedicated 3D brachytherapy dose-planning system according to the GEC ESTRO Recommendations and
1604 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
1605 in the process of contouring on CT, if for subsequent fractions of brachytherapy only CT can be used with the applicator in place.

1606 To maintain consistent reporting and communication between investigators and the EMBRACE Study Office the protocol for contouring
1607 AND naming of targets and OAR must be followed strictly.

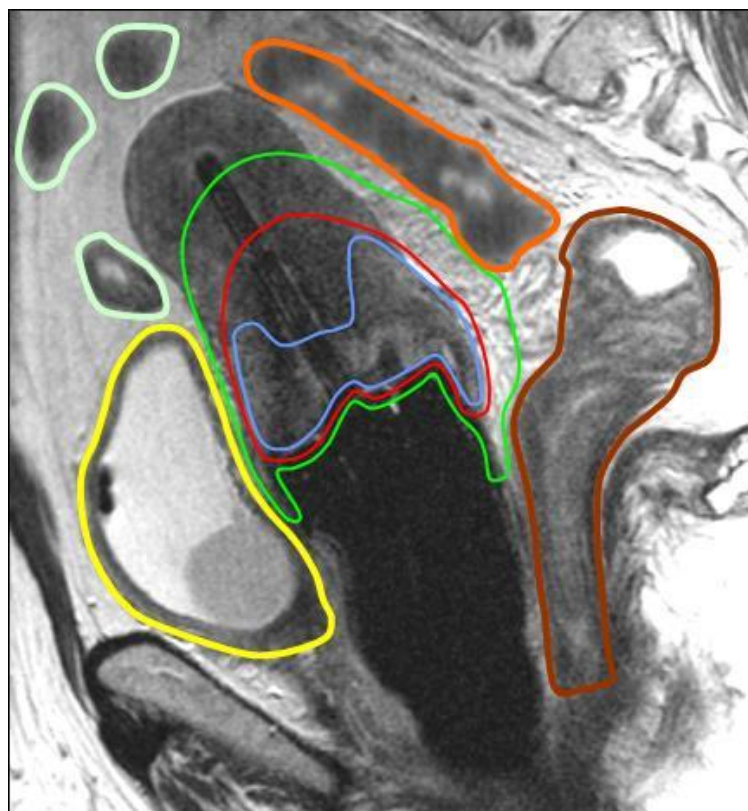
1608 10.5.1 CONTOURING OF ORGANS AT RISK

1609 The following organs are contoured (from at least 2 cm below the IR-CTV to 2 cm above the uterus):

- 1610 • Bladder: Outer bladder wall including the bladder neck
- 1611 • Rectum: Outer rectal wall from the anal sphincter to the transition into the sigmoid
- 1612 • Sigmoid: Outer sigmoid wall from the recto-sigmoid flexure to at least 2 cm above the parametria and the uterus
- 1613 • Bowel loops: Outer contours of loops positioned within 3-4 cm to the uterus and applicator

1614 For cases with significant vaginal involvement it is advised also to contour the urethra separately to be able to assess the dose to this
1615 structure. There is no specific DVH constraint known so far for the urethra.

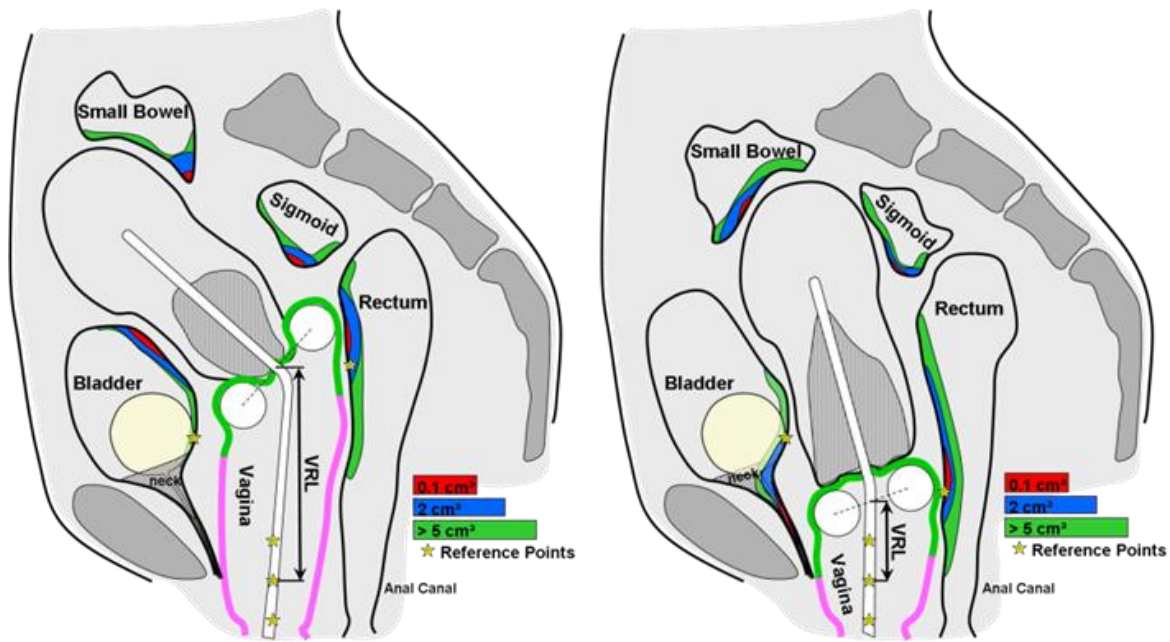
1616 If the anatomical transition from rectum to sigmoid is immediately in vicinity of the applicator it is advised to move the transition up or
1617 down to avoid that the D2cm³ for one or the other will be too low.



1618

1619 Figure 10.4: The outer contour of bladder (yellow), rectum (brown), sigmoid (orange) and bowel (light green) shown in the sagittal
1620 plane (Petric P. in Viswanathan et al. 2011).

1621



1622

1623 Figure 10.5. “Schematic anatomical diagrams (sagittal view) showing two different positions of the vaginal part of the utero-vaginal
1624 applicators, the cervix tumor, the uterus and the reference volumes of OARs in two different patients. The most irradiated-tissue
1625 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
1626 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
1627 reference volumes in the adjacent OARs (modified from GEC ESTRO Recommendations II, Pötter R. et al. 2006; see also Westerveld H.
1628 et al. 2013). Reference points are indicated for the bladder (ICRU Report 38), the rectum and upper vagina (ICRU Report 38), and the
1629 mid and lower vagina (PIBS ± 2 cm). Figure: Schematic drawing showing the position of the volumes related to the DVH analysis and
1630 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)
1631 The points are in a sagittal image containing the intrauterine applicator except the bladder point, which could be in a parallel plane
1632 before or behind this plane, according to the location of the bladder balloon.

1633

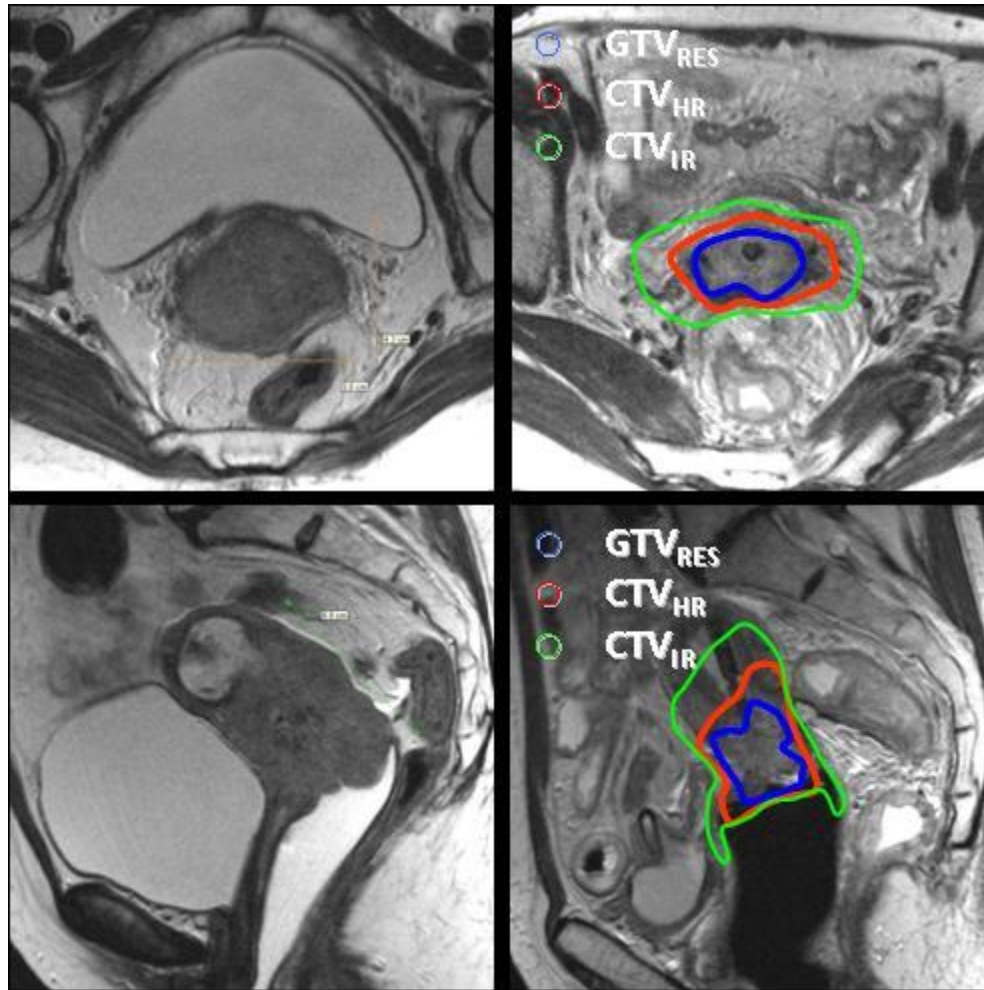
1634 10.5.2 CONTOURING OF TARGET VOLUMES

1635 Accurate tumour and target contouring requires that the contouring physician has performed the gynaecological examination that has
1636 to be done prior to insertion of the applicator and that information including clinical drawings from gynaecological examination at
1637 diagnosis as well as MRI at diagnosis and MRI at time of brachytherapy with the applicator in situ are available at the contouring station
1638 (Figure 10.6).

1639 The following targets should be contoured for brachytherapy:

- 1640 • GTV_{res}: Residual (high signal) Gross Tumour Volume of the primary Tumour
- 1641 • CTV_{HR}: Adaptive High Risk Clinical Target Volume of the primary Tumour
- 1642 • CTV_{IR}: Intermediate Risk Clinical Target Volume of the primary Tumour

1643 The targets are primarily contoured on the para-axial sequence, but para-coronal and sagittal sequences should be inspected during the
1644 process to ensure target consistency also in these sequences.



1645

1646 Figure 10.6: MRI at diagnosis (left panels) and at time of brachytherapy with the applicator in situ (right panels). The brachytherapy
 1647 targets (blue: GTV_{RES}, red: CTV_{HR}, green: CTV_{IR}) are contoured in the para-axial slide (upper right panel) and here inspected for
 1648 consistency in the sagittal sequence (lower right panels). The MRI at diagnosis (left panels) is used to identify grey zones and to ensure
 1649 that the CTV_{IR} contour fully covers the primary tumour extension. [By courtesy of Primoz Petric.](#)

1650

1651 10.6 TREATMENT PLANNING FOR BRACHYTHERAPY

1652 10.6.1 EVIDENCE OBTAINED FROM RETROEMBRACE AND EMBRACE I

1653 The D90 constraints for the CTV_{HR} are based on dose-response curves for retroEMBRACE. In an analysis of 766 cases from EMBRACE in
 1654 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
 1655 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
 1656 available. Taking into account the ratios of D98 to D90 and D100 for physical dose, and EQD2 conversion for a PDR schedule of 40
 1657 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
 1658 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
 1659 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
 1660 review of clinical practice within EMBRACE and by taking into account the historical French experience. The 60 Gy volume should
 1661 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
 1662 dose for the point A is a safety measure. Conformal adaptation of dose to very small target volumes, probably related to contouring
 1663 uncertainties, should not result in too small brachytherapy contributions. The planning aim of 65 Gy, which is based on expert review of

1664 the existing practice within EMBRACE, should warn in case of such small brachytherapy dose values. The dose levels proposed as
 1665 constraints for OAR are based on analysis from EMBRACE. For the sigmoid/bowel no clinical evidence is available so far to define
 1666 constraints by now. However, suggestions for planning aims and prescribed dose are given, with a clear remark that these constraints
 1667 are only valid in case subsequent fractions or pulses are always related to the same most exposed volume of this organ. The constraints
 1668 have been tested within a database of EMBRACE. While the proposed planning aims for rectum and bladder were achieved already in
 1669 ~60%, the constraints for the recto-vaginal point were achieved in 53% and for sigmoid in 80%. The limits for prescribed dose were
 1670 reached in >90% of cases, except for the recto-vaginal point (84%).

1671 **10.6.2 PLANNING AIMS AND DOSE PRESCRIPTION FOR EMBRACE II**

1672 The D90 for the CTV_{HR} should be between 90-95 Gy, while D_{2cm³} for bladder should be below 80 Gy, D_{2cm³} for rectum below 65 Gy, for
 1673 the ICRU vaginal recto-vaginal point dose below 65 Gy, for the D_{2cm³} for sigmoid/bowel* below 70 Gy and for D98 for the GTV above 95
 1674 Gy (planning aim ~ soft constraints). Taking into account the individual patient case and possibilities in application and dose
 1675 optimization, deviations of these planning aims are allowed. However, for the vast majority of patients, the D90 for the CTV_{HR} should be
 1676 higher than 85 Gy and the D98 for the GTV higher than 90 Gy, while D_{2cm³} for bladder should be below 90 Gy, D_{2cm³} for rectum below 75
 1677 Gy, the ICRU vaginal recto-vaginal point dose below 75 Gy and the D_{2cm³} for sigmoid/bowel* below 75 Gy (limits for prescribed dose ~
 1678 hard constraints). Deviations from these constraints are only allowed in special cases with detailed explanation. For OARS there are also
 1679 two levels with planning aims 5 - 10 Gy lower than the maximum limits for the prescribed dose.

1680 Table 10.1: Planning aims (soft constraints) and limits for prescribed dose (hard constraints) for treatment planning in Embrace II. The
 1681 EQD2 is calculated using $\alpha/\beta=10$ for targets, $\alpha/\beta=3$ for OAR and a repair halftime of 1.5h. The EQD2 include 45 Gy/25 fractions
 1682 delivered by EBRT.

1683

| 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 _{2cm³} EQD2 ₃ | Rectum D _{2cm³} EQD2 ₃ | Recto-vaginal point EQD2 ₃ | Sigmoid D _{2cm³} EQD2 ₃ | Bowel D _{2cm³} 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* |

1684 * for the sigmoid/bowel structures these dose constraints are valid in case of non-mobile bowel loops resulting in the situation that the
 1685 most exposed volume is located at a similar part of the organ

1686 **10.6.3 DOSE OPTIMISATION FOR BRACHYTHERAPY**

1687 Dose optimisation is performed by optimising the implant geometry, the dwell time distribution and the fractionation. The use of
 1688 implant geometries with interstitial needles in addition to an intracavitary applicator is seen essential for unfavourable topography
 1689 (either larger target volumes or unfavourable relation between target and OARs). It is assumed that at least 20 % of a representative
 1690 cohort of cervical cancer cases needs such implant techniques to fulfil the planning aims and prescription limits.

1691 10.6.4 INTRACAVITARY TREATMENT PLANS SHOULD BE BASED ON ITERATIVE STEPS

1692 Preferably, a loading resulting in standardized pear shaped isodose distributions normalized to point A should be used as a starting
 1693 point for optimisation. This is usually achieved by certain loading patterns in the intrauterine and vaginal applicator parts. In a stepwise
 1694 procedure the loading pattern and the dwell times are optimized until the planning aims are fulfilled. The same procedure should be
 1695 used in case of combined intracavitary/interstitial application geometries. The loading and dose contribution from the needles is added
 1696 to the intracavitary dose distribution. This ensures that the dose levels and dose gradients around the implant geometry stay
 1697 comparable to intracavitary plans and not interstitial plans, where each applicator has a similar weighting. This should ensure to avoid
 1698 hot spots and cold spots in any areas not directly controlled via dose points or dose-volume relations. The contribution of the TRAK
 1699 resulting from the interstitial components to the overall TRAK varies on each situation, but is usually between 5-20 % (Trnkova P. et al.
 1700 2009).

1701 10.6.5 VAGINAL DOSE DE-ESCALATION

1702 Recent EMBRACE data demonstrates that vaginal stenosis is correlated to the brachytherapy dose delivered in the upper vagina (ICRU
 1703 recto-vaginal point), and there is significant potential to reduce vaginal morbidity by dose de-escalation. Vaginal dose de-escalation can
 1704 be performed by decreasing dwell times in ovoid/ring and increasing the loading in tandem/needles. With the use of combined
 1705 intracavitary-interstitial applicators, it is possible to increase the width of the 85Gy isodose volume by loading the needles, and it is not
 1706 necessary to heavily load the vaginal sources. Furthermore, limited size tumours often do not need extensive vaginal loading in order to
 1707 reach a dose of 85Gy EQD2, since they can be reached mainly by loading the tandem (Nkiwane KS. et al. 2013).

1708 Vaginal loading can be monitored by vaginal dose points, vaginal TRAK or by visually evaluating isodose curves. The major priority when
 1709 performing vaginal dose de-escalation is to decrease the ICRU recto-vaginal point dose according to the dose planning aim of 65Gy,
 1710 since this is based on clinical evidence.

1711 In a multicenter study by Mohamed et al. it was demonstrated that vaginal dose de-escalation could be performed without
 1712 compromising target dose. In this study, reduction of the vaginal loading was attempted such that the 140% isodose would be located
 1713 as close to or within the applicator at the lateral aspect - as judged from visual inspection. The 140% isodose refers to the physical
 1714 fractional dose which corresponds to 85Gy. E.g. for a fractional schedule of 7Gy in 4 fractions, 140% corresponds to $140\% * 7Gy = 10Gy$.
 1715 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
 1716 possible to limit the vaginal TRAK to a mean of 30% which should be compared to typical classical loading patterns (Paris and Fletcher)
 1717 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)
 1718 could be reduced to <85Gy EQD2 (total EBRT and BT dose) (Mohamed SM. et al. 2015, in submission).

1719 Table 10.2: Parameters and constraints for vaginal dose control

1720

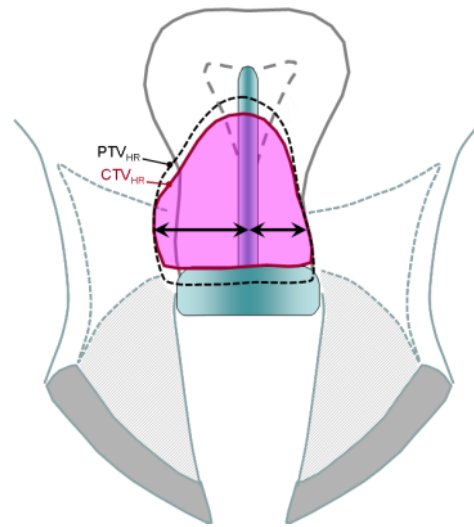
| | Aim | Priority |
|--|---|-----------|
| 1721 ICRU recto-vaginal point dose | <65Gy EQD2 (EBRT+BT) | Primary |
| The ratio of vaginal TRAK and total TRAK | <30-40% | Secondary |
| Vaginal lateral dose points at 5mm | <85Gy EQD2 (EBRT+BT) | Secondary |
| Visual inspection of the 140% isodose | Intruding as little as possible into vaginal tissue, and preferentially located within the applicator | Secondary |

1722 10.6.6 PTV AND DOSE CONFORMALITY CONSIDERATIONS IN RELATION TO BRACHYTHERAPY

1723 Planning Target Volume (PTV-T) assures that the dose prescribed to the CTV-T is actually applied and has been developed within the
1724 frame of external beam radiotherapy (EBRT). The PTV-T margin around the CTV-T takes into account geometric and dosimetric
1725 uncertainties and is considered essential in EBRT. In brachytherapy the dosimetric characteristics with sources inside the target volume,
1726 the variations and the uncertainties are different from those in EBRT. A PTV-T margin in brachytherapy, selected after implantation of
1727 the applicator, may contribute to dose escalation throughout the target. PTV margins should not be used to compensate for
1728 uncertainties in 3D image guided intracavitary brachytherapy (Tanderup K. et al. 2010). This applies to intracavitary and interstitial
1729 brachytherapy in cervix cancer. Internal target motion is considered minimal when the applicator is fixed by an intra-vaginal
1730 tamponade.

1731 However, geometric uncertainties (reconstruction and contouring) may occur, in particular in the longitudinal direction along the
1732 tandem. As margins along the longitudinal axis of the tandem have limited impact on the dose throughout the target, longitudinal
1733 margins along the axis of the tandem maybe used to compensate for these set up variations. Addition of margins orthogonal to the
1734 tandem axis leads to a dose increase throughout the entire target and are therefore not recommended.

1735 When planning the absorbed dose distribution there is no specific aim for target conformality in the cranial direction. Normally a
1736 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
1737 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
1738 fulfilled) is not decreased to reach a conformal situation. By this the dose is kept high in a region which is prone to contouring
1739 uncertainties and possible systematic uncertainties in the applicator location (shifting of the applicator in caudal direction) as shown in
1740 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.



1741

1742

1743 Figure 10.7 " Longitudinal margins for set up uncertainties in intracavitary image guided adaptive brachytherapy. Margins are added to
1744 compensate for uncertainties only in the longitudinal direction, whereas no margins can be added in the orthogonal direction.
1745 Therefore a PTV_{HR} may be delineated in the cranio-caudal direction. This may also apply within a planning procedure before the
1746 applicator insertion, resulting in a guiding PTV, which may guide the necessary length of the tandem to compensate for set-up
1747 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
1748 compromise OAR exposure.

1749

1750 **10.7 DOSE AND VOLUME RECORDING AND REPORTING**

1751 Recording and reporting follows the recommendations of ICRU/GEC ESTRO Report 88, where all parameters included in level 1 and level
 1752 2 of the reporting standards are included: The physical doses should be reported to the database NOT the EQD2!

1753 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 | |

1754 * Lymph nodes which were pathologic at diagnosis (in case of complete regression at time of BT, a representative dose should be
 1755 estimated for the region where the node was). If the node is not covered by the MRI performed for brachytherapy it is assumed that
 1756 the dose contribution from brachytherapy to such a node is negligible.

1757 ** if PIBS-2cm is outside the MR image object assign a representative dose

1758

1759

1760 11 SYSTEMIC TREATMENT

1761 11.1 AIMS FOR CHEMOTHERAPY

- 1762 • To improve systemic and nodal control and to improve survival
- 1763 • To apply systematically simultaneous chemotherapy (minimum 90% of patients who qualify as able to undergo
- 1764 chemotherapy);
- 1765 • To apply full dose of chemotherapy (5 cycles) in the vast majority of patients (80% of those patients who receive
- 1766 chemotherapy).

1767 11.2 CONCOMITANT CHEMOTHERAPY

1768 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).
1769 Cisplatin is to be given intravenously at a dose 40 mg/m² once a week for a total of preferably 5-6 cycles according to institutional
1770 practice. In EMBRACE I para-aortic and distant control was inferior when less than 5 cycles of cisplatin monotherapy had been
1771 administered. Other chemotherapeutics and schedules might carefully be considered if monotherapy cisplatin cannot be given due to
1772 patient related factors, like co-morbidity or early cisplatin related morbidity and must be reported. Treatment with Cisplatin should
1773 be withheld at the discretion of the center. Several guidelines on chemo-radiation protocols exist for cisplatin withhold (Rose PG. et al.
1774 2011, Keys HM. et al. 1999, Pearcey R. et al. 2002). Leucocytes and granulocyte numbers are used as constraints for withhold of
1775 cisplatin. Therefore we suggest to use either leucocyte or granulocyte counts as constraints. Guidelines for withhold vary for leucocytes
1776 counts around 2.500 or for granulocytes counts between <1,5 to 1.0 X 10⁹ cell/L. For platelets guidelines for constraints vary
1777 between < 100 to < 50 X 10⁹ cell/L platelets. Cisplatin can be resumed in the next cycle once the blood counts exceed these limits.
1778 The dose of Cisplatin should be reduced to 30 mg/m² if two consecutive cycles of chemotherapy have been given at dose zero. Cisplatin
1779 dose should also be reduced to 30 mg/m² in case of febrile leucopenia. Cisplatin should be totally discontinued if blood tests remain
1780 unacceptable or febrile leucopenia recurs despite dose reduction. Cisplatin should also be abandoned in case significant auditory
1781 problems (tinnitus, deafness) or neuropathies > grade 2 develops.

1782 Measurement or calculation (Cockroft-Gault) of GFR is performed before treatment and repeated after 3 cycles. Treatment with
1783 Cisplatin is abandoned if GFR < 50 ml/min. Haemoglobin should be monitored during treatment. Corrections by transfusion according to
1784 institutional guidelines are allowed and have to be reported.

| Agent | dose/day | Route | Frequency |
|-------------|---------------------|-----------------|-----------------------|
| Cisplatinum | 40mg/m ² | i.v. in 3 hours | Weekly for 5-6 cycles |

1785

1786 11.3 ADJUVANT CHEMOTHERAPY

1787 According to poor outcome in high risk patients, in particular for systemic recurrence, there is in some centers a practice to apply
1788 adjuvant chemotherapy, in particular in the high risk patient group with Carboplatin and Taxol as applied in the OUTBACK trial.
1789 Therefore, the EMBRACE II protocol allows for applying this combination in high risk patients based on a center decision.

1790 If decision for adjuvant chemotherapy for the high risk group is made for patients feasible for it, the centre should in general stick to
1791 this choice throughout the whole study inclusion period. Stratification for yes or no adjuvant chemotherapy will be performed for
1792 treatment outcome analysis.

1793 Adjuvant chemotherapy should in principal be administered according the protocol of the treating centre. In order to achieve a certain
1794 level of agreement global recommendations should be followed as given in the protocol of the ongoing clinical OUTBACK trial
1795 (<https://www.anzdog.org.au/uploads/ANZGOG%20Trial%20-%20Outback.pdf>).

1796 Four cycles of adjuvant therapy with carboplatin and paclitaxel should be given at 3 weeks intervals, starting 4 weeks after completion
1797 of all radiotherapy (EBRT and BT). Before starting adjuvant chemotherapy the toxicities of the concomitant chemoradiation should be
1798 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/m ² | i.v. in 3 hours | 1, 22, 43, 64 |
| Carboplatin | AUC 5 (calculated AUC) | i.v. in 3 hours | 1, 22, 43, 64 |

1799 Carboplatin dose is to be calculated according to the Calvert formula:

1800 Dose (mg) = target AUC x (GFR +25)

1801 with AUE being area under curve, GFR calculated according to Cockcroft-Gault formula.

1802 Maximum carboplatinum dose (mg) = target AUC (mg/ml x min) x 150 ml/min.

1803 Maximum allowed dose of carboplatin is AUC 5 = 750 mg

1804 Pre-treatment neutrophil count should be $\geq 1/5 \times 10^9/L$ and pre-treatment platelet count $\geq 100 \times 10^9/L$. If counts are below these
1805 levels treatment should be postponed for a maximum of 2 weeks. If counts have not resolved after 2 weeks reduced dose levels should
1806 be administered or adjuvant chemotherapy should be omitted. Decisions for dose reduction or omission of adjuvant chemotherapy
1807 cycles because of hematologic or non-hematologic morbidity is in principle left to the decision of the treating centre but should be
1808 preferable follow the recommendations as described in the OUTBACK trial protocol:

1809 (<https://www.anzdog.org.au/uploads/ANZGOG%20Trial%20-%20Outback.pdf>).

1810 Pre- and post-hydration procedures, the use of anti-emetics and otherwise medication as well as treatment of eventual allergic
1811 reactions are left to the decision of the treating centre.

1812

1813 **12 OUTCOME ASSESSMENT**

1814 Outcome in terms of survival, disease control, morbidity and Quality of Life (QoL) must be assessed prospectively for 5 years by
 1815 scheduled follow-up according to this table:

1816 ¹

| 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 | • | • | • | • | • | • | • | • | • | • | • | • | • |

1821 ²Base Line, ²Week 4 during EBRT, ³At the end of radiotherapy including BT

1822

1823 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
 1824 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
 1825 response should be send. However, no further request should be send if there is no response.

1826 Unplanned follow-up due to suspicious of recurrence and/or development of morbidity should be performed in the same manner as
 1827 regular follow-ups and reported to the database

1828 Gynaecological examination must include recto-vaginal exploration. General anaesthesia is recommended at 3 month and also if a local
 1829 recurrence is suspected in order to maximise the possibility for evaluating local tumour control, take biopsies and to reopen vaginal
 1830 adherences if present.

1831 MRI of the pelvis and retro-peritoneum should routinely be performed at 3 month and at 12 month after end of radiotherapy. It is
 1832 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
 1833 should be performed according to the clinical needs when a recurrence (local, nodal, systemic) is suspected. Every effort should be
 1834 made to confirm recurrences by biopsy.

1835

1836 **12.1 ONCOLOGICAL OUTCOME AND SALVAGE TREATMENT**

1837 The predictive value of the time/volume response of the primary tumour (GTV-T) during radiotherapy will be assessed by comparing
 1838 the volume of GTV-T contoured on MRI for EBRT and on MRI for each BT implant.

1839 The GTV-T response will be measured according to clinical and imaging criteria for residual disease. The dimensions/volumes are
 1840 registered in the CRFs.

1841 The investigators categorize in addition according to the following schedule. This is of particular importance for patients with very good
 1842 response and to assess the patients with complete and uncertain complete remission. This is an area of much uncertainty and the aim
 1843 of EMBRACE II is to have a more precise assessment of GTV volume response in order to build upon this experience further
 1844 stratification into risk groups for future trials (both for local and general outcome):

1845

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

1846 Table 12.1 Categorization of remission (in addition to measurements)

1847 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
1848 this will be categorised as persistent local disease. If uncertainty exists at this time point despite MRI and gynaecological examination
1849 which are not resolved by biopsies, PET-CT scan or other measures, then the patients should be followed closely at least with
1850 gynaecological examination and MRI and/or PET-CT at the subsequent follow-ups until the questions has been resolved. The patient will
1851 be categorised as having obtained local control at 3 months, if later follow-up then shows continuous local control. On the other hand if
1852 this does not happen and the tumour eventually progresses this will be categorised as persistent disease at 3 months. Salvage
1853 hysterectomy should be performed when relevant/possible in case of persistent or recurrent local and central disease.

1854 Pathological nodes are numbered consecutively (N1, N2,...N10) at diagnosis. If persistent or recurrent nodal disease is found on imaging
1855 during follow-up bioptical verification should be attempted. The relevant images should then be matched with the pre-treatment scans
1856 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
1857 nodes should be evaluated with regard to the PTV45 as inside, marginal or outside. Salvage radiotherapy +/- surgical removal of
1858 previously unirradiated nodes should be attempted if there are no signs of systemic recurrences.

1859 Oligometastases in previously unirradiated volume should also be evaluated with regard to the possibility of salvage treatment
1860 (surgery, stereotactic body radiotherapy etc.).

1861 The oncological outcome of intended curative salvage treatment (local, regional, systemic) should be reported in the database.
1862 Palliative treatments are not reported but the vital status should be updated at least quarterly.

1863 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.

1864

1865 12.2 MORBIDITY

1866 Physician assessed morbidity will be scored prospectively with the Common Terminology Criteria for Adverse Events (both CTCAE v3.0
1867 and CTCAE v4.0, NCI 2003 and 2009) on a priori selected, clinical relevant endpoints regarding gastro-intestinal, genito-urinary, vaginal
1868 and several unspecific symptoms (See table above).

1869 Both early morbidity (per definition within the first 90 days after begin of treatment) and late morbidity will be assessed. Early
1870 morbidity will be assessed with a short version of the overall morbidity assessment with selected endpoints.

1871 The morbidity endpoints for EMBRACE 2 were selected after a consensus based on yearly interim comprehensive analyses of the
1872 EMBRACE 1 material, covering inter alia: longitudinal analyses on manifestation pattern of symptoms, evaluation of the open text

1873 reports of the EMBRACE 1 database, cross-validation with the patient reported symptoms from the quality of life assessment, literature
1874 research and joint clinical discussions.

1875 Case report forms are available for download at the EMBRACE 2 website.

1876 Analyses: Morbidity outcomes will be analysed if baseline and at least one follow-up assessment have been recorded. Morbidity will be
1877 censored at time of any recurrence (local, nodal, systemic) and baseline morbidity will be taken into account in any analysis in order to
1878 differentiate between tumour-related and treatment-related symptoms.

1879 Endpoints will be evaluated both for the overall organ at risk (bowel, rectum, bladder, vagina etc.) and for individual symptoms with
1880 prevalence rates, crude and actuarial incidences (Kaplan Meier time to event method). For selected endpoints, a dose effect relation
1881 will be investigated based on Cox proportional hazard models; independent risk factors for morbidity will be taken into account by
1882 multivariate modelling.

1883 12.3 QUALITY OF LIFE (QOL)

1884 QoL will be assessed prospectively with the internationally established and validated questionnaires of the European Organization for
1885 Research and Treatment of Cancer ([EORTC](http://groups.eortc.be/qol); <http://groups.eortc.be/qol>).

1886 The basic module EORTC QLQ-C30 is of general use for all cancer sites and consists of five functional scales (physical, emotional, social,
1887 role and cognitive functioning), a global health status/QoL scale and several symptom scales commonly reported by cancer patients
1888 ([Aaronson NK. et al. 1993](#)). The cervical cancer module EORTC QLQ-CX24 covers typical disease and treatment related symptoms and
1889 items regarding sexuality ([Greimel E. et al. 2006](#)). In addition, 6 clinically relevant items of the endometrial module EORTC EN-24 will be
1890 added with the permission of the EORTC QoL group ([Greimel E. et al. 2011](#)).

1891 All questionnaires are available for download at the EMBRACE 2 website in all translations available. The time points of assessment are
1892 scheduled according to the morbidity assessment.

1893 Analyses: In QoL reports, patients with baseline and at least one additional EORTC QLQ follow up will be included. In patients with local
1894 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
1895 outcomes will be calculated and linearly transformed according to the scoring manual of the EORTC QoL group; results reported in
1896 mean scores (ranging from 0-100) with standard deviation and/or 95% confidence interval ([Fayers PM. et al. 2001](#)). Results will be
1897 analysed regarding differences in subscales over time in EMBRACE 2 patients and differences between the reference general population
1898 and EMBRACE 2 patients.

1899

1900 13 TRANSLATIONAL RESEARCH

1901 13.1 PROGNOSTIC MARKERS

1902 Despite the improved loco-regional control with definitive radio(chemo)therapy in high-risk patients, distant metastasis are still
1903 frequent and - in absence of effective systemic therapy options - have a large impact on cancer specific and overall survival. Tumor type
1904 (squamous versus adenocarcinoma), FIGO stage, tumor size and (extent) of lymph node involvement are well-established prognostic
1905 factors for distant metastasis. When considering the inclusion criteria of current ongoing trials that investigate the value of adjuvant
1906 chemotherapy in addition to definitive radio(chemo)therapy, there may be considerable overtreatment. Several promising (epi) genetic
1907 molecular markers (e.g. HPV-type, hypoxia markers, tumor infiltrating lymphocytes) have been identified, but none have been
1908 compared prospectively in a larger patient cohort nor are they currently applied in clinical practice.

1909 The aim of the translational tumour research project is to establish the value of molecular prognostic markers for local and regional
1910 recurrence as well as distant metastasis in relation to well-described clinical and pathological prognostic factors. Better selection of
1911 patients at high risk of distant metastasis or recurrence will allow for a highly personalized treatment approach. While comparing tumor
1912 samples from the primary tumor with that of primary involved lymph nodes and to those at time of recurrence will help understand
1913 which factors contribute to disease progression and therapy resistance. EMBRACE II will include a large cohort of patients treated with a
1914 uniform protocol and therefore offers a unique opportunity to make progress in this field.

1915 Paraffin embedded tumor tissue derived from biopsies of the primary tumor and available lymph node metastasis at the time of
1916 diagnosis will be collected from all consenting patients.

1917 In addition, paraffin embedded tumor tissue derived from biopsies of local and regional recurrences or distant metastasis, if performed,
1918 will be collected. DNA will be extracted and a tissue microarray will be constructed from these paraffin embedded tissue samples,
1919 allowing for high throughput analysis. All study samples will be stored in the patient's treating center, coded under study number, until
1920 DNA extraction and tissue micro array assembly, which will be done centrally at time of study closure under pseudonymized conditions.

1921 A pilot sub-study is envisioned for collaborating centers with facilities to perform and store snap frozen tumour tissue samples, and
1922 collect blood and serum samples (liquid biopsies). The aim of the sub-study is to apply more advanced techniques in a limited number
1923 of patients as a discovery set for novel markers of tumour sensitivity and response. Based on available evidence at the time of study
1924 closure, a more targeted approach will be undertaken, aiming to validate the most promising markers in the large cohort of patients.
1925 For this validation study, preferably more conventional techniques (i.e. hotspot mutation analysis) will be used, facilitating eventual
1926 broader clinical implementation.

1927

1928 13.2 PREDICTIVE MARKERS FOR RADIOTHERAPY RELATED MORBIDITY

1929 In EMBRACE II treatment related morbidity, both clinician-assessed and patient reported, as well as health related quality of life, will be
1930 assessed prospectively in a large cohort of uniformly treated patients. This offers a unique opportunity for intensive translational
1931 research into the identification of biomarkers for the manifestation of (late) treatment-related morbidity. A sub-study is envisioned for
1932 collaborating centres with the aim to improve future individualisation of follow-up strategies and eventually treatment protocols. For
1933 this, early markers indicative of the individual patient's risk to develop treatment-induced (late) morbidity will be identified and
1934 characterised. This will also allow the development of pathomechanism-based interventions for the prevention, mitigation or
1935 amelioration of morbidity ("biological morbidity targeting").

1936 Furthermore, indicators of treatment-related morbidities (morbidity biomarkers), assessed pre- or early within the treatment can
1937 facilitate the selection of patients with a high individual risk for (severe) treatment complications, with whom less toxic treatment
1938 strategies may be discussed with the patient to avoid excessive morbidity and to improve post-treatment HR-QoL. Compared to

1939 outcome predicting biomarkers, much less work has been done in this field, particularly in relation to radiation dose/dose distributions
1940 ([Bentzen SM. et al. 2010](#)).

1941 Some of the most promising morbidity biomarkers for the associated OAR include:

- 1942 • Urinary bladder – urine: Urothelial degradation products, inflammatory markers, and immune response markers ([Gibson RJ. &](#)
1943 [Bowen JM. 2011](#)).
- 1944 • Large bowel - faeces: Inflammatory markers, calprotectin and lactoferrin ([Hille H. et al. 2009](#), [Varela E. et al. 2009](#)) and immune
1945 response markers ([Gibson RJ. & Bowen JM. 2011](#), [Henson CC. & Ang YS. 2012](#)).
- 1946 • Vagina - vaginal smears: Cell morphology, differentiation markers, inflammatory markers, and immune response markers
1947 ([Gibson RJ. & Bowen JM. 2011](#), [Shield PW. 1995](#)).
- 1948 • Various OAR - blood: Growth factors (various OAR), immune cells (immune system and others), immune response markers
1949 (epithelia, bone marrow), citrulline (small bowel), other serum proteins (intestine) ([Lutgens LC. et al. 2003](#), [Lacombe J. et al.](#)
1950 [2011](#), [Chai Y. et al. 2015](#), [Onal C. et al. 2011](#)).

1951
1952 Although many promising morbidity biomarkers have been identified over the years, none has been validated in large datasets, and
1953 none has therefore been entered into routine clinical use. Translational (morbidity) research within EMBRACE II will establish and/or
1954 optimize the respective analytical procedures, in samples from an initial (small) test population of patients. The most promising
1955 candidates for each OAR morbidity endpoint will be defined and the respective analytical procedures will be established in the section
1956 for applied and translational radiobiology (ATRAB) in Vienna. Subsequently these candidates will be analyzed in a larger cohort of
1957 patients from participating centers. Collection and storage of biological samples will be standardized to avoid center effects.

1958 One essential prerequisite for the morbidity biomarker studies is the precise assessment and documentation of early and particularly
1959 late morbidity. This will be standardized within EMBRACE II (see “morbidity and QoL”).

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1970 14 PATIENT MATERIAL, BENCHMARKING, VALIDATION, EVALUATION AND STATISTICS

1971 14.1 BENCHMARK OF OUTCOME AND TREATMENT RELATED PARAMETERS

1972 EMBRACE aims at improving outcome of locally advanced cervical cancer through well-defined interventions of advanced EBRT
1973 (IMRT/IGRT), IGABT and systematic application of chemotherapy in a limited overall treatment time (section general aims 4.2.1).

1974 EMBRACE II will be benchmarked against the outcome of the retroEMBRACE and EMBRACE cohorts and reports from literature as
1975 appropriate. The benchmark will include evaluation of overall survival, cancer specific survival, local control, pelvic control, nodal
1976 control (regional, para-aortic), distant control, morbidity (various organs and morbidity endpoints), patient reported outcome and
1977 quality of life. The prognostic characteristics of the patient populations may change over time and the evaluation will take into account
1978 major prognostic factors through stratification and/or other statistical methods such as propensity score weighting. The general
1979 hypothesis on survival (section 5.3.1) and the specific hypotheses on specific clinical endpoints (section 5.3.3). will be tested.

1980 Treatment related factors (“interventions” section 4.1) will be benchmarked and compared with those recorded in the EMBRACE and
1981 RetroEMBRACE cohort: target selection, tumor and target volumes, EBRT techniques (IMRT/IGRT) and BT techniques (adaptive
1982 intracavitary/interstitial), irradiated volumes, target doses, organ doses, chemotherapy administration, and OTT. Change of practice
1983 compared with EMBRACE with regard to technique, dose and volume will be quantified, and the specific hypotheses described in
1984 section 5.3.2. will be tested (table 5.1).

1985 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,
1986 the performance with regard to the major EMBRACE II interventions will be monitored: BT technique and dose prescription, reduction
1987 of vaginal loading, utilization of IMRT/VMAT, utilization of daily IGRT and limited margins, EBRT target concepts related to the primary
1988 tumour, EBRT dose prescription and fractionation, selection of elective EBRT target volume, and application of concomitant
1989 chemotherapy.

1990 14.2 VALIDATION OF DOSE AND VOLUME EFFECTS

1991 EMBRACE II validates dose and volume effects as found in RetroEMBRACE and EMBRACE I (section specific aims 4.2.2). In EMBRACE I
1992 and RetroEMBRACE, dose-effect relationships related to the BT high dose regions have been found for different endpoints (section
1993 introduction 3.3). These dose-effect relationships will be validated in the EMBRACE II cohort.

1994 14.3 EXPLORATION AND EVALUATION OF DOSE AND VOLUME EFFECTS

1995 EMBRACE II explores and evaluates dose effect relationships related to intermediate EBRT and BT dose and volume levels in the
1996 EMBRACE II cohort comparable to RetroEMBRACE and EMBRACE I for BT high dose regions. Finally, dose and effects of chemotherapy
1997 administration will be evaluated.

1998 14.4 IDENTIFICATION OF PROGNOSTIC AND PREDICTIVE PARAMETERS

1999 EMBRACE II will test beside dose and volume various prognostic and predictive parameters for disease outcome, morbidity and quality
2000 of life and compare with EMBRACE and literature reports as appropriate.

2001 14.5 STATISTICS

2002 Data will be reported with mean and standard deviation / 95% confidence interval or median and interquartile range, depending on the
2003 distribution. Proportions will be evaluated as number of patients with and without the characteristic and as a percentage.

2004 Time-to-event data will be analyzed using the actuarial Kaplan Meier method; time will be calculated with the date of diagnosis as the
2005 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
2006 will be treated as censored observations.

2007 Local control will be defined as absence of disease in the cervix, uterus, upper vagina and parametria on clinical examination, imaging,
2008 and biopsy. Pelvic control will be defined as absence of local and nodal disease within the pelvis. Nodal control will be defined as
2009 absence of nodal disease within the pelvis and within the para-aortic nodes. Systemic control will be defined as absence of any organ
2010 recurrence and extra-pelvic and extra-aortic nodal recurrence.

2011 Overall survival will be defined as death from any cause and cancer specific survival as death from cervical cancer (disease progression
2012 or treatment-related morbidity).

2013 Morbidity outcomes will be analyzed for organs and specific endpoints within one organ if baseline and at least one follow-up
2014 assessment have been recorded. Morbidity will be censored at time of any recurrence (local, nodal, systemic) and baseline morbidity
2015 will be taken into account in any analysis in order to differentiate between tumor-related and treatment-related symptoms.

2016 Serious late morbidity will be defined as grade 3 (severe), 4 (life-threatening) or 5 (death) complications present at or after 91 days
2017 from completion of treatment. Morbidity analyses will also be performed on grade 1 (mild) and grade 2 (moderate) complications.

2018 Endpoints will be evaluated both for the overall organ at risk (bowel, rectum, bladder, vagina etc.) and for individual symptoms with
2019 prevalence rates, crude and actuarial incidences (Kaplan Meier method).

2020 Several a priori chosen, clinically relevant patient-, disease- and treatment characteristics (prognostic and predictive factors) will be
2021 evaluated as risk factors for outcome events in uni- and multivariable analyses (Cox proportional hazards model). Hazard Ratios (HR)
2022 and 95% confidence intervals (CI) will be estimated.

2023 Cox proportional hazards model estimates will be used to evaluate several dose and volume effect relationships with regard to selected
2024 endpoints, such as local control and morbidity. Dose parameters will be normalized to 2Gy per fraction (EQD2) using the linear-
2025 quadratic model with α/β ratio of 3Gy.

2026 Advanced modeling studies and studies for comparing various cohorts using advanced statistical methods (e.g. propensity score) are
2027 foreseen.

2028 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
2029 applied. All statistical analyses will be performed using the Statistical Package for the Social Sciences IBM SPSS (Armonk, NY: IBM Corp).

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2033 **15 ACCREDITATION, DUMMY RUN, DATA MONITORING, QUALITY ASSURANCE AND CONTINUOUS**
2034 **EDUCATION**

2035 EMBRACE II accreditation includes an evaluation of the current practice of each centre through a “compliance questionnaire” on
2036 brachytherapy, external beam radiotherapy and chemotherapy. Furthermore, participation in a dummy run on contouring, treatment
2037 planning, and reporting is required. These procedures will ensure that the centre has the infrastructure and expertise needed to comply
2038 with the protocol requirements of EMBRACE II.

2039 It is the responsibility of the study coordinators to evaluate and approve participation. Approval requires a successful dummy run with
2040 an individual assessment of the performance of each participating centre. Approval of the institution/investigator must be
2041 accomplished prior to any patient enrolment in the protocol.

2042 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
2043 analysis of the results is obtained. Continuous quality assurance during the study is projected. The procedure will include a monitoring
2044 of the treatment planning parameters of interest for this study and an overall check of the CRFs.

2045 A continuous education programme focussing on contouring will be set up and will give access to online education throughout the
2046 study period. Continuous education may be extended to include morbidity assessment and scoring.

2047 **15.1 COMMITMENT LETTER, COMPLIANCE QUESTIONNAIRE AND PROCESS DOCUMENT**

2048 Each institution has to submit a Commitment Letter to the study coordinators. The centres are also required to complete a web based
2049 compliance form which documents the current practice of the centre demonstrating that the centre in question will be able to meet the
2050 requirements of the protocol with regard to number of patients as well as EBRT and brachytherapy treatment techniques.

2051 The compliance criteria are:

- 2052 • Treatment of >10 patients per year qualifying for enrolment in EMBRACE II
- 2053 • Both EBRT and BT are performed in the centre
- 2054 • Routine use of IMRT or VMAT
- 2055 • Routine use of daily IGRT with bony fusion
- 2056 • Routine use of MRI guided IGABT with applicator in situ (at least for first fraction)
- 2057 • Routine use of the combined intracavitary-interstitial technique when needed (~20-50% of patients)

2058

2059 **15.2 DUMMY RUN**

2060 Based on evaluation of the compliance questionnaire, the study coordinators will decide if the centre is ready to proceed with the
2061 Dummy Run. The Dummy Run will ensure that the contouring and treatment planning is consistent with the protocol requirements. The
2062 Dummy Run will include a training and registration phase as well as submission of contouring and dose planning for evaluation. Based
2063 on this, the study coordinators will evaluate if the centre is ready to participate in EMBRACE II.

2064

2065 **15.2.1 TRAINING, REGISTRATION, AND SUBMISSION**

- 2066 • Contouring training for EBRT and BT: self-assessment by each physician who will be contouring for EMBRACE II
- 2067 • EBRT planning exercise: self-assessment by each institution (physicists/physicians)
- 2068 • Registration of 5 consecutive patients in a registration database within 6 months: self-registration
- 2069 • Submission of EBRT and BT contours: one set of contours is submitted per institution for evaluation by study co-ordinators
- 2070 • Submission of an EBRT dose plan: documentation of one case with dose and volume reporting as well as isodose screenshots is
- 2071 submitted per institution for evaluation by study co-ordinators

2072 Contouring training for BT and EBRT will be available online using the Addenbrooke’s Contouring Tool (ACT). Contouring will be
2073 performed by each physician according to the EMBRACE II guidelines as outlined in chapters 9 and 10. Instructions, case descriptions,
2074 diagnostic information and contouring guidelines will be available online in ACT. Tools for self-assessment of the training contours will
2075 be available.

2076 An EBRT planning exercise will be downloadable from the EMBRACE website for training of dose planning. IMRT or VMAT dose planning
2077 is performed according to the EMBRACE II guidelines in chapter 9. A reporting sheet will be available for DVH reporting and the results
2078 can be compared to an “expert plan”.

2079 When contouring and dose planning training has been performed, the centre can proceed with registration of 5 consecutive patients in
2080 a registration database (within 6 months). The registration database will be a copy of the EMBRACE II database with on-line reporting of
2081 1) Status at diagnosis, 2) Status at brachytherapy and 3) Treatment and DVH parameters. Furthermore, screen dumps of EBRT and BT
2082 contours and dose plans are required, as well as cartoons documenting clinical examination at diagnosis and at BT.

2083 After the registration phase, a final submission of EBRT and BT contouring and dose planning has to be performed through the ACT tool
2084 (one submission per institution). Specific instructions will be available on the EMBRACE web site.

2085 **15.2.2 EVALUATION BY STUDY COORDINATORS**

2086 After all information is fully available, the study coordinators will evaluate:

- 2087 • The submitted EBRT and BT contours
- 2088 • The submitted EBRT plan
- 2089 • The completed 5 registered patients

2090 Centres already participating in EMBRACE and having accrued at least 25 patients during the whole EMBRACE period are not required
2091 to enter the registration phase of 5 consecutive patients or to complete brachytherapy contouring training.

2092

2093 **15.3 DATA MONITORING**

2094 Continuous data monitoring throughout the study will be based on reviewing of data reporting, clinical cartoons and
2095 contouring/treatment planning screen dumps. The data monitoring will be performed by the EMBRACE II study office.

2096 A committee for patient safety and data monitoring will be established consisting of representative(s) from radiation oncology, medical
2097 physics and statistics as appropriate. This committee will meet regularly in large intervals to check the relevant respective issues in the
2098 on-going EMBRACE II study.

2099 **15.4 CONTINUOUS EDUCATION**

2100 Based on ACT, cases will be available for continuous training along the same principles of the dummy run. Annual contouring workshops
2101 will be performed at the annual EMBRACE meetings. MDs who are not attending the annual EMBRACE meeting must perform the
2102 annual contouring remotely.

2103

2104

2105 16 PATIENT ENROLLMENT PROCEDURE

2106 Patients' registration will only be accepted from authorized investigators in the Vienna study office. A patient can be registered after
2107 verification of eligibility by the EMBRACE 2 study office according to the registration form, which includes details on inclusion and
2108 exclusion criteria. In addition, the following information must be provided:

- 2109 • Patients' centre ID (made up of the centres' acronym and the following patient number)
- 2110 • Patients' initials
- 2111 • Patients' birthday
- 2112 • Date of scheduled treatment start

2113 If the patient is included in the study, a number will be allocated to the patient (patient sequential identification number). This number
2114 has to be recorded by the investigator. For future communication between the investigator and the EMBRACE 2 database or the study
2115 coordinators, the patients' centre ID should be used. After successful registration of a patient, the investigator informs the centre that
2116 the data of this patient can be entered in the database. The registration form will be saved electronically by the study office.

2117 **Patients must be registered and accepted before any treatment procedures are initiated.**

2118

2119

2120 17 CASE RECORD FORMS, PROCEDURES FOR DATA COLLECTION, EMBRACE II DATABASE

2121 Patient data will be collected by web based CRF system. The CRFs must be completed and reported according to the time table below.

2122 **It is the responsibility of the investigator to check that all CRFs are completely, correctly and timely filled out.**

2123 The following CRFs will be used:

- 2124 • Registration Form: To be reported before treatment.
- 2125 • Status at diagnosis Form: To be reported at start of treatment
- 2126 • Base Line Morbidity Form: To be reported at start of treatment
- 2127 • Status at BT Form: To be reported within 4 weeks after treatment completion
- 2128 • Treatment and DVH Form: To be reported within 4 weeks after treatment completion.
- 2129 • Follow-up Form: To be completed within 4 weeks after each regular follow-up. Visits not scheduled should also be reported
- 2130 within 4 weeks if they concern an event of interest such as recurrence or morbidity
- 2131 • Vital status Form: In case of any event, this part should be updated frequently.
- 2132 • Off study Form: Should be reported within 4 weeks after the off-study occurs.
- 2133 • Curative salvage treatment Form: should be reported within 4 weeks after salvage treatment completion.

2134 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
2135 specific portfolio including a paper copy of the registered CRF data for each patient.

2136 At the EMBRACE 2 website the study protocol, appendices, quality of life questionnaires, patient information folders and any other
2137 pertinent information in relation to the study will be available.

2138 The EMBRACE 2 database will be placed at the Aarhus University Hospital, Denmark. The Danish Board of Registry has approved the
2139 database (pending). Access to the database can be gained through the EMBRACE 2 website, by providing a valid username and
2140 password. Entering of all data will be carried out over the Internet using a standard web-browser.

2141 All data will be encrypted before transmission. A number of validation procedures will be installed in order to ensure a high data
2142 quality. There will be sent out reminders of all follow-up visits and examinations, and data from these will also be entered via the
2143 Internet.

2144 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
2145 of included patients for own centre as well as for the entire study population. The database will allow for data extraction in Microsoft
2146 Windows Excel and the Statistical Package for the Social Sciences IBM SPSS (Armonk, NY: IBM Corp).

2147

2148 18 ETHICAL CONSIDERATIONS

2149 18.1 PATIENT PROTECTION

2150 This study will be conducted in agreement with the Declaration of Helsinki. The protocol has been written, and the study will be
2151 conducted according to the ICH Harmonized Tripartite Guideline for Good Clinical Practice. The protocol will be approved by the local
2152 Research Ethics Committee in accordance with national guidelines and legislation in the participating centres.

2153 18.2 SUBJECT IDENTIFICATION

2154 To ensure patient privacy, the name of the patient will not be asked for nor recorded at the Study Office. A sequential identification
2155 number will be automatically attributed to each patient registered in the trial. This number will identify the patient and must be
2156 included on all case report forms. In order to avoid identification errors, patient's initials (maximum of 4 letters) and date of birth and
2157 local chart number (if available) will also be recorded, only on the registration form.

2158 18.3 INFORMED CONSENT

2159 Patient information forms will be produced in all the relevant languages, an English version is included as Appendix 10. All patients will
2160 be informed by the radiation oncologist of the aims and registration process of the study, the possible adverse events, the procedures
2161 and possible hazards to which they will be exposed. The radiation oncologist will hand out the written patient information form, and
2162 before deciding to participate, the patient will be offered enough time for consideration the study.

2163 The consent form will include study participation and subject registration, processing and recording of data, participation to quality of
2164 life investigation and collection and storage of a paraffin embedded tumour tissue sample under study code for future research.
2165 Patients will be informed as to the strict confidentiality of their patient data, but that their medical records may be reviewed for study
2166 purposes by authorized individuals other than their treating physician.

2167 It will be emphasized that the participation is voluntary and that the patient is allowed to refuse further participation in the protocol
2168 whenever she wants. This will not prejudice the patient's subsequent care. Documented written informed consent must be obtained for
2169 all patients included in the study before they are registered at the Study Office. This must be done in accordance with the national and
2170 local regulatory requirements.

2171 For European Union member states, the informed consent procedure must conform to the ICH guidelines on Good Clinical Practice. This
2172 implies that "the written informed consent form should be signed and personally dated by the patient or by the patient's legally
2173 acceptable representative".

2174 18.4 ADVANTAGES AND DISADVANTAGE FOR THE PATIENTS

2175 The radiation oncologist will inform the patients about the possible risks and side effects connected to the involved treatments. At
2176 present the standard treatment for patients with locally advanced cervical cancer is EBRT, concurrent chemotherapy with Cisplatin and
2177 brachytherapy. Although these same treatment modalities will be used, EMBRACE II aims are to implement an image guided risk
2178 adapted dose and volume prescription protocol according to interventions specified in chapter 4. All or some of these advanced
2179 technological interventions will be implemented as standard treatment in participating centres, but there may be deviations in the
2180 extent to which the standard treatment differs from the study protocol per participating institution. Nonetheless, it is expected that
2181 minor deviations between the study protocol and the standard treatment in a centre will not alter the chance of tumour control and
2182 treatment related morbidity for a given individual patient. The written patient information should be adapted if necessary to
2183 accommodate the institutional standard treatment policy and needs subsequent approval by the local ethics committee.

2184 Advantages of study participation include external review and quality assurance of the treatment planning and execution, and
2185 knowledge that the individual patient data will contribute to the understanding and future improvement of treatment for locally
2186 advanced cervical cancer. A possible disadvantage of study participation may be the additional time involved in filling out quality of life
2187 questionnaires.

2188

2189 19 PUBLICATION OF DATA

2190 1. The major authors of a manuscript consist of the core research group, which substantially prepared and performed the
2191 research in agreement with the coordinators of the EMBRACE 2 study and the EMBRACE 2 research group. It usually covers the
2192 first author as major contributing scientist, 1-2 active co-workers and 1-2 supervising seniors, according to input.

2193

2194 2. The coordinators of the EMBRACE 2 study and the EMBRACE 2 research group are appropriately represented (minimum 2
2195 persons: Richard Pötter, Kari Tanderup, Jacob Lindegaard, Christian Kirisits).

2196

2197 3. The principle investigators of the centers, who contributed the majority of patients, are listed as co-authors. The principal
2198 investigator (PI) may indicate another person from the institution to replace him or her, if appropriate. This co-authorship
2199 should be minimum 5 centers in addition to Vienna and Aarhus (as represented by the EMBRACE 2 coordinators). The total
2200 number of co-authors based on patient numbers depends on the individual journals requirements.

2201

2202 If manuscripts cover certain sub-cohorts of the overall EMBRACE 2 patients recruited, the number of patients for the specific
2203 analysis of the manuscript is calculated per center, a ranking of the centers is performed according to these numbers.

2204

2205 4. Some journals allow for inclusion of a 'collaborative group', with associated names, which may even be tagged in PubMed. If
2206 possible, such a 'collaborative group' should be included. The number of collaborators should be graduated, according to the
2207 overall recruiting rate of the center: the PI and 1-2 persons designated by the PI (one physicist as appropriate).

2208

2209 20 STUDY OFFICE, STUDY COORDINATORS, STUDY STRUCTURE, COMMUNICATION

2210 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
2211 study office (including follow-up of EMBRACE I). The infrastructure of the study office and the communication with centres follows the
2212 experience as gained in EMBRACE. E.g. the weekly EMBRACE meeting in Vienna (about 90 minutes) with review of cases and
2213 participation of study office, medical physicists, radiation oncologists, clinical and research fellows is to be continued. Regular review of
2214 cases will require as in EMBRACE I about 0.5 academic FTE.

2215 In addition, the responsibilities for guiding the brachytherapy and the EBRT branch of EMBRACE II are shared: Vienna will guide the
2216 brachytherapy part and Aarhus the EBRT part.

2217 In addition, there will be one regional centre in Utrecht, which takes the responsibility for guiding all centres in the Netherlands in close
2218 cooperation with Vienna and Aarhus.

2219

2220

2221 **20.1 STUDY-OFFICE EMBRACE II VIENNA (AT PRESENT: 09/2015):**

2222 Ian Dilworth (0.5 FTE), Thomas Liederer (0.5 FTE), Eva Weisz (1.0 FTE), academic position (0.5 FTE)

2223 Department of Radiotherapy, Medical University of Vienna, Vienna, Austria

2224 Telephone: +43 1 40 400 2720; E-mail: @akhwien.at

2225 Aarhus-office: 0.5 FTE academic position

2226

2227 **20.2 STUDY COORDINATION:**

2228 **Principal Investigator:**

2229 Richard Pötter, Vienna, Austria: Richard.Poetter@akhwien.at

2230

2231 **Overall coordinators:**

2232 Richard Pötter, Vienna, Austria: richard.poetter@akhwien.at (overall and BT)

2233 Kari Tanderup, Aarhus, Denmark: karitand@rm.dk (overall and EBRT)

2234 Christian Kirisits, Vienna, Austria: christian.kirisits@akhwien.at (overall and BT)

2235 Jacob Lindegaard, Aarhus, Denmark: jacolind@rm.dk (overall and EBRT)

2236

2237 **Regional coordinators in the Netherlands:**

2238 Ina Juergenliemk-Schulz, Utrecht (for all participating centres in the Netherlands)

2239 Astrid de Leeuw, Utrecht (for all participating centres in the Netherlands)

2240

2241 **Continuous Education:**

2242 Li Tee Tan, Cambridge University

2243

2244 **Senior advisors:**

2245 Christine Haie-Meder (christine.haiemed@gustaveroussy.fr), Erik Van Limbergen (erik.vanlimbergen@uz.kuleuven.ac.be)

2246

2247 **Statistician:**

2248 NN, Vienna

2249 Søren Møller Bentzen, Maryland, Baltimore, USA (sbentzen@som.umaryland.edu)

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2251 **Communication**

2252 All coordinators, the senior advisors and the study secretariat communicate regularly (at least twice per year) on relevant questions of

2253 the EMBRACE study and take joint decisions.

2254 Each year an annual meeting is held, where the current activities are reported, discussed and future developments discussed and
2255 decided (following the annual EMBRACE meetings, which took place from 2008-2015 in Brussels (2008) and then in Vienna). All
2256 participating centres are invited for this meeting, including all centres which participated in EMBRACE I.

2257 This meeting forms the body of the study committee: one member of each participating centre, all coordinators, senior advisors,
2258 statistician, study office

2259 The major form of continuous communication is through internet, direct e-mailing and the EMBRACE webpage which has an open
2260 access and a password protected access part.

2261

2262 **21 EMBRACE RESEARCH GROUP**

2263 In order to take advantage of the large prospective collection of data as established in EMBRACE (and RetroEMBRACE, >2000 patients
2264 with cervix cancer) a multi-disciplinary EMBRACE Research Group has been established in 12/2012. Structures and Principles and
2265 Responsibilities for Research have been set up. Regular physical meetings have been held in addition to research visits through
2266 researchers in particular going to Vienna, Aarhus and Utrecht and additional much internet communication.

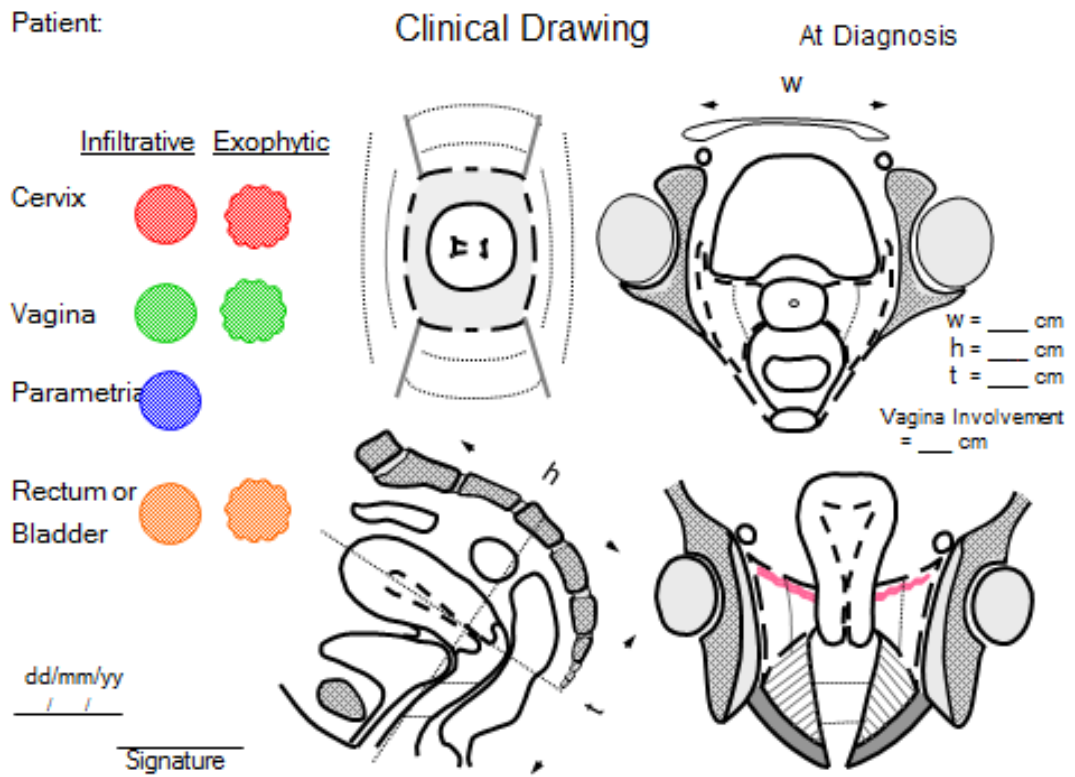
2267 Each centre participating in EMBRACE can also participate in the EMBRACE Research Group according to possibilities of the person
2268 interested and the respective centre. On request, also fellows not working in EMBRACE centres can join this Research Group which has
2269 been successful so far in several cases.

2270 The aim of this EMBRACE research group is to build up a large scientific body of clinical evidence based on the large database of
2271 EMBRACE, RetroEMBRACE and the upcoming EMBRACE II study. The topics of research are widespread and related to the whole field of
2272 areas investigated in the EMBRACE studies. So far, 13 publications on various aspects of EMBRACE and RetroEMBRACE could be
2273 published in leading international journals and 4 more are in the submission process. This ongoing process is planned to be followed
2274 and extended in parallel to the implementation of EMBRACE II and will benefit from the maturation of data from EMBRACE I and the
2275 upcoming data of EMBRACE II.

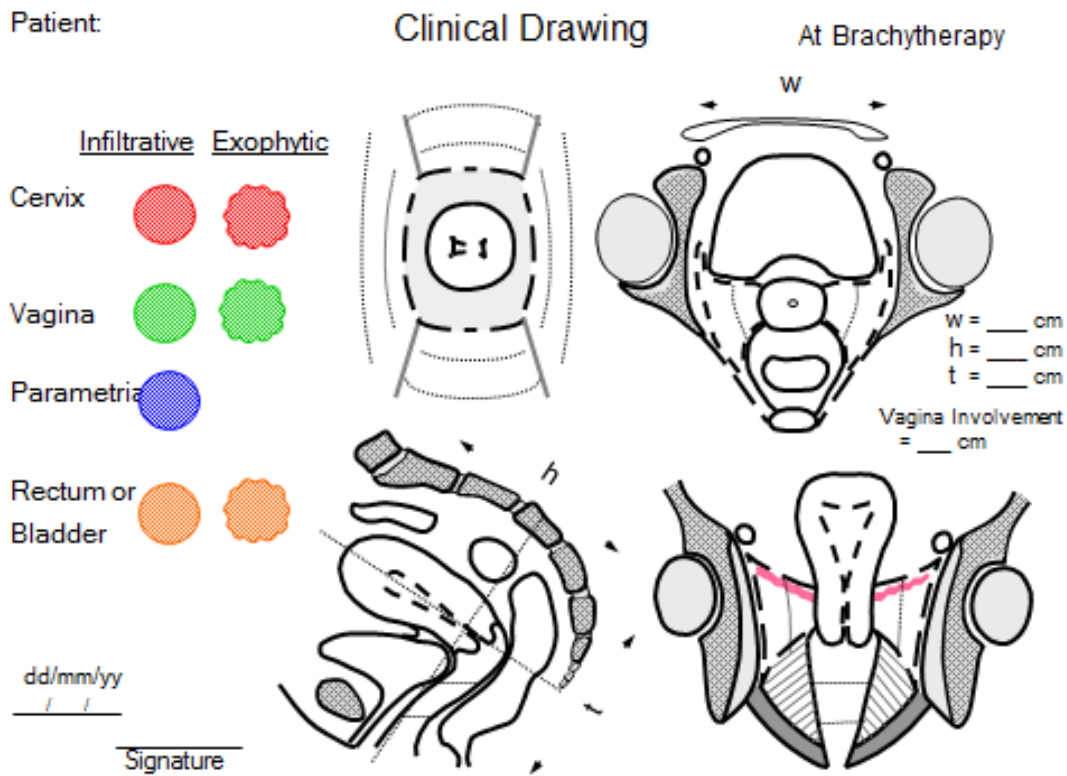
2276 The coordination of this EMBRACE research group is the group of coordinators of the EMBRACE I and II studies (n=6) with the principal
2277 coordinators Kari Tanderup and Richard Pötter.

2278 So far, there is only limited specific sponsoring for this EMBRACE Research Group (travel and accommodation support for group
2279 meetings).

2280



2283 #



2284

2285 Clinical drawings have traditionally been used to depict the extent of disease based on clinical examination. Tumour that is visible
2286 or palpable is drawn manually, usually on paper templates. With the advent of image-guided brachytherapy in cervical cancer, an
2287 argument can be made to also incorporate disease findings from imaging examinations into these “clinical drawings”.

2288 We aim to develop standardized methods for the creation of these clinical drawings, that would hopefully, eventually, lead to some
2289 level of standardization of clinical drawings across different physicians, across different centres, across time, and ultimately, across
2290 multiple tumour sites as well.

2291 “At Diagnosis” or “At Brachytherapy” should be marked on each drawing. Treatment received to date, including any external beam
2292 radiotherapy (EBRT) delivered to date, should be noted.

2293 Four different views or planes are illustrated: **Specular, Axial, Coronal, and Sagittal**. Dotted lines of the vagina represent a virtual
2294 division in thirds. Dotted lines in the parametria represent a border between the proximal and distal half of the parametria. A pink
2295 line in the coronal view represents uterine artery.

2296 Tumour dimensions: **height (h), width (w), and thickness (t)** should be documented. Height, defined on the sagittal view, is
2297 measured along the long axis of the uterus. Thickness, defined on the sagittal view, is measured perpendicular to the height. Width,
2298 measured on the axial view, represents the greatest lateral diameter. Vaginal extension of tumour is specified separately.

2299 The date of the evaluation should be recorded. The drawing should be signed.

2300 Manual colour drawing: There are three basic options for the drawing of uniform and reproducible universal clinical drawings. A
2301 **first option** utilizes coloured marker pens and a colour legend. Four different, specific colours are used. In addition, tumour can be
2302 identified as exophytic in nature by changing the border as outlined in the legend. There are certain advantages to coloured marker
2303 approach, such as straightforward and quick implementation, and immediately recognizable distinctions of different anatomical
2304 areas of involvement. However, the incorporation of up to four specifically coloured markers into routine clinical practice in clinics
2305 and operating rooms may be a challenge to do consistently. Ensuring the consistent availability of the markers in multiple work
2306 environments, with multiple caregivers, may not be practical.

2307 Manual line drawing: A **second option** uses a legend that requires only a single pen to convey the same amount of information.
2308 Different anatomical areas of involvement are demonstrated using simple line patterns, with a specific pattern for each anatomical
2309 site according to the legend. Again, any exophytic tumour can be delineated with a special border. Unlike the colour approach,
2310 consistent availability of a pen at any location or with any caregiver should not be an issue. A drawback is that the drawings may
2311 appear less readily discernible. However, after a brief learning curve, practitioners should be able to draw and read such drawings
2312 with ease. This approach seems the most practical and reliable, and could be adopted widely.

2313 Electronic drawing: Finally, a **third option** involves a computer-based method to create the clinical drawings. This method involves
2314 electronic versions of the colour or background lines templates, with electronically modifiable tumour cartoons. The cartoons can
2315 be modified for the individual patient by way of a Powerpoint[®] type of application, using relatively simple tools (Figures 3, 4).
2316 Clinical drawings can be stored and transmitted electronically. Drawings for physical medical chart record-keeping would have to
2317 be printed. Advantages of an electronic approach include the consistency and clarity of the drawings produced. In addition, the
2318 electronic format facilitates the storage, access, and distribution of the drawings. Electronic templates could be made available on
2319 the internet for clinical use. However, logistical issues such as the availability of a local computer with the appropriate software, the
2320 availability of a local (colour) printer for generation of hard copies, and the clinician’s familiarity with the software tools needed,
2321 may preclude this electronic method’s widespread adoption.

2322 Electronical drawing tools will be available for download at the website.

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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.

2380 **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;**
2381 **Gynaecological (GYN) GEC-ESTRO Working Group. Recommendations from Gynaecological (GYN) GEC-ESTRO Working Group:**
2382 **considerations and pitfalls in commissioning and applicator reconstruction in 3D image-based treatment planning of cervix cancer**
2383 **brachytherapy. Radiother Oncol. 2010 Aug;96(2):153-60.**
2384

2385 Abstract

2386
2387 Image-guided brachytherapy in cervical cancer is increasingly replacing X-ray based dose planning. In image-guided brachytherapy the
2388 geometry of the applicator is extracted from the patient 3D images and introduced into the treatment planning system; a process
2389 referred to as applicator reconstruction. Due to the steep brachytherapy dose gradients, reconstruction errors can lead to major dose
2390 deviations in target and organs at risk. Appropriate applicator commissioning and reconstruction methods must be implemented in
2391 order to minimise uncertainties and to avoid accidental errors. Applicator commissioning verifies the location of source positions in
2392 relation to the applicator by using auto-radiography and imaging. Sectional imaging can be utilised in the process, with CT imaging being
2393 the optimal modality. The results from the commissioning process can be stored as library applicators. The importance of proper
2394 commissioning is underlined by the fact that errors in library files result in systematic errors for clinical treatment plans. While the
2395 source channel is well visualised in CT images, applicator reconstruction is more challenging when using MR images. Availability of
2396 commercial dummy sources for MRI is limited, and image artifacts may occur with titanium applicators. The choice of MR sequence is
2397 essential for optimal visualisation of the applicator. Para-transverse imaging (oriented according to the applicator) with small slice
2398 thickness (< or =5 mm) is recommended or alternatively 3D MR sequences with isotropic voxel sizes. Preferably, contouring and
2399 reconstruction should be performed in the same image series in order to avoid fusion uncertainties. Clear and correct strategies for the
2400 applicator reconstruction will ensure that reconstruction uncertainties have limited impact on the delivered dose. Under well-
2401 controlled circumstances the reconstruction uncertainties are in general smaller than other brachytherapy uncertainties such as
2402 contouring and organ movement.

2403

2404 **Dimopoulos JC, Petrow P, Tanderup K, Petric P, Berger D, Kirisits C, Pedersen EM, van Limbergen E, Haie-Meder C, Pötter R.**
2405 **Recommendations from Gynaecological (GYN) GEC-ESTRO Working Group (IV): Basic principles and parameters for MR imaging**
2406 **within the frame of image based adaptive cervix cancer brachytherapy. Radiother Oncol. 2012 Apr;103(1):113-22.**

2407

2408 Abstract

2409 The GYN GEC-ESTRO working group issued three parts of recommendations and highlighted the pivotal role of MRI for the successful
2410 implementation of 3D image-based cervical cancer brachytherapy (BT). The main advantage of MRI as an imaging modality is its
2411 superior soft tissue depiction quality. To exploit the full potential of MRI for the better ability of the radiation oncologist to make the
2412 appropriate choice for the BT application technique and to accurately define the target volumes and the organs at risk, certain MR
2413 imaging criteria have to be fulfilled. Technical requirements, patient preparation, as well as image acquisition protocols have to be
2414 tailored to the needs of 3D image-based BT. The present recommendation is focused on the general principles of MR imaging for 3D
2415 image-based BT. Methods and parameters have been developed and progressively validated from clinical experience from different
2416 institutions (IGR, Universities of Vienna, Leuven, Aarhus and Ljubljana) and successfully applied during expert meetings, contouring
2417 workshops, as well as within clinical and interobserver studies. It is useful to perform pelvic MRI scanning prior to radiotherapy ("Pre-
2418 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
2419 both open and close magnet configurations conform to the requirements of 3D image-based cervical cancer BT. Multiplanar
2420 (transversal, sagittal, coronal and oblique image orientation) T2-weighted images obtained with pelvic surface coils are considered as
2421 the golden standard for visualisation of the tumour and the critical organs. The use of complementary MRI sequences (e.g. contrast-
2422 enhanced T1-weighted or 3D isotropic MRI sequences) is optional. Patient preparation has to be adapted to the needs of BT
2423 intervention and MR imaging. It is recommended to visualise and interpret the MR images on dedicated DICOM-viewer workstations,
2424 which should also assist the contouring procedure. Choice of imaging parameters and BT equipment is made after taking into account
2425 aspects of interaction between imaging and applicator reconstruction, as well as those between imaging, geometry and dose
2426 calculation. In a prospective clinical context, to implement 3D image-based cervical cancer brachytherapy and to take advantage of its
2427 full potential, it is essential to successfully meet the MR imaging criteria described in the present recommendations of the GYN GEC-
2428 ESTRO working group

2429

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

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

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

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

2432

2433 **22.4 APPENDIX 4. CLINICAL CASES FOR CONTOURING**

2434 22.4.1 CASES FROM VIENNA, UTRECHT AND AARHUS, CONTOURING TABLES

2435 Will be provided later.

2436

2437 22.5 APPENDIX 5: EBRT CONTOURING ATLAS (COMPLEMENT TO CHAPTER 9)

2438 22.5.1 INTRODUCTION

2439 This appendix document describes the process for radiotherapy treatment planning of cervix cancer and has been developed for the
2440 purpose of the EMBRACE II study. A precise target volume definition is crucial for radiotherapy planning and IMRT treatments. It
2441 requires detailed knowledge of CT and MRI-based anatomy. In developing the EMBRACE II study, considerable time was spent
2442 discussing target definition and OARs. There are differences in views among radiation oncologists regarding their preferred volume of
2443 elective nodal irradiation, their PTV margins and organs at risk delineation. To ensure homogenous contours and to provide an efficient
2444 workflow when contouring, a step-by-step pictorial guide is provided for the delineation of tumor related target volume, nodal target
2445 volume and OARs.

2446 It is well recognized that there is overlap with chapter 9 on EBRT. However, this appendix part is meant as practical guide to contouring
2447 which may contain some redundancies.

2448 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
2449 ICRU 88 for brachytherapy.

2450 22.5.2 CLINICAL TARGET VOLUMES RELATED TO THE PRIMARY TUMOR

2451 The following abbreviations are used in the appendix:

2452 GTV: Gross Tumor Volume (at diagnosis).

2453 CTV: Clinical Target Volume = GTV + suspected microscopic tumor extension.

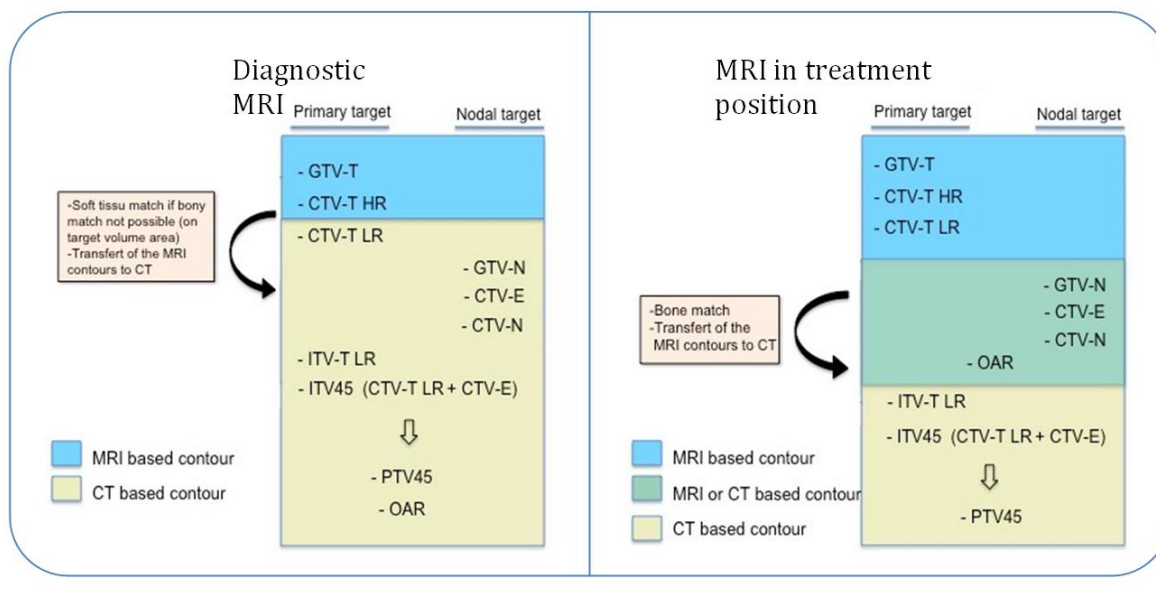
2454 ITV: Internal Target Volume = CTV + internal margins to compensate for internal motions.

2455 PTV: Planning Target Volume = CTV + set-up margin.

2456 Different imaging modalities are used for delineate of different volumes. To facilitate the comprehension of this stepwise contouring
2457 atlas, you can use the following schematic workflow (26.1 (App)) explaining which contours should be outlined on the MRI images and
2458 CT images respectively.

2459 Considering the difference in clinical practice of imaging in different centers, we propose two different ways of contouring. The choice
2460 of the strategies is at the discretion of the center/treating doctor. Each of these approaches needs at least a diagnostic MRI to contour
2461 the primary targets (GTV-T_{initial} and CTV-T_{initial} HR).

2462 As explained in the protocol, the planning CT should be done according to a bladder filling protocol allowing the patient to have a
2463 comfortably full bladder. In addition to their diagnostic MRI, some patients benefit from high quality MRI images in treatment position
2464 in which the range of motion of the cervix and uterus with different fillings of the bladder/bowel can be observed and expectations of
2465 most likely motion scenarios during radiotherapy can be defined and in which the image registration between the planning CT and the
2466 MRI is reliable. For these cases, we recommend an individualized approach in which the CTV-T LR_{initial} margin is adapted according to
2467 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
2468 CTV-T LR_{initial} will move in anterior direction and the ITV margin may be increased in anterior direction and reduced in posterior
2469 direction (see figure 26.1 (App)).



2470

2471 Figure 22.5.1 (App) Schematic workflow for contouring primary target and nodal target and OARs on diagnostic MRI, MRI in treatment
 2472 position and CT

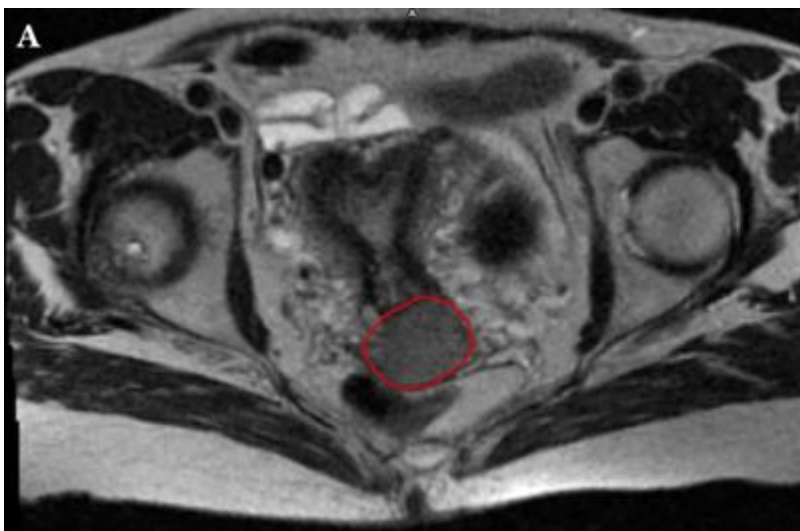
2473

2474 22.5.3 FIXED MARGIN APPROACH

2475 STEP 1

2476 Considering that every patient has a diagnostic MRI, contour the following structures on the MRI images:

2477 The GTV-T_{initial} (contour in red) is the extension of the cervical tumor defined by T2 weighted MRI supported by clinical investigation
 2478 and PET-CT (figure 22.5.2).



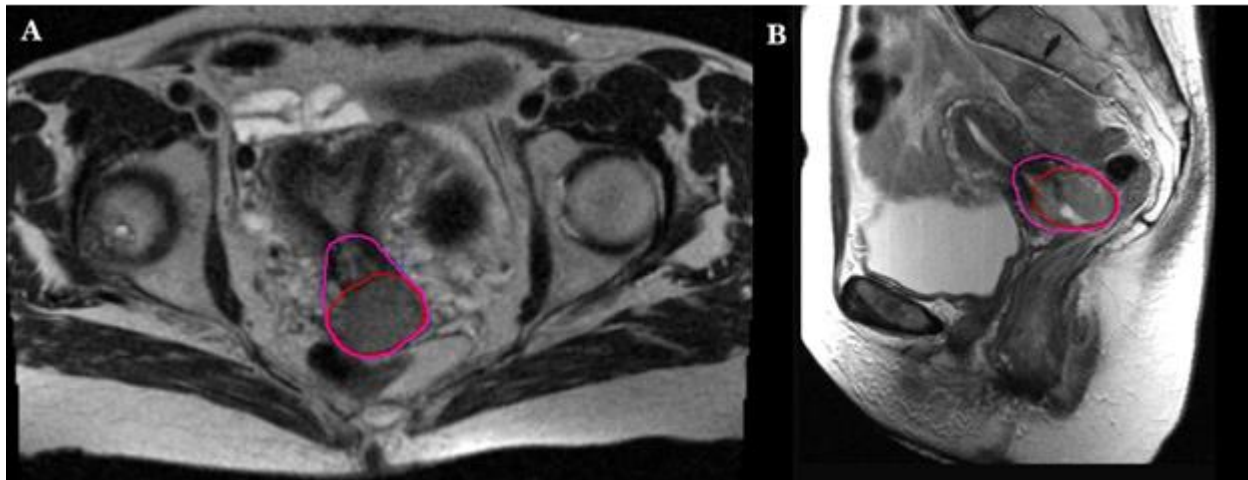
2479

2480 Figure 22.5.2 GTV-T_{initial} on MRI (T2), A : axial view, B : sagittal view

2481

2482 **STEP 2**

2483 Outline the CTV-T HR_{initial} (contour in magenta). It's the initial high risk CTV-T_{initial} including GTV-T_{initial} and any remaining cervix not
2484 infiltrated by the tumor (figure 3).



2485

2486 Figure 25.5.3 CTV-T HR_{initial} (magenta) and GTV-T_{initial} (red) on MRI (T2), A : axial view, sagittal view

2487 **STEP 3**

2488 Do the registration (fusion) of the MRI images with the planning CT images. The planning CT should have been done according to the
2489 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
2490 appropriately register the bony structures on the planning CT with the ones on MRI (due to positioning differences for example), try to
2491 match locally (the cervix region) on the soft tissue. Once fused, verify your MR-based contour on the planning CT.

2492 On the MRI, identify the CTV-T LR_{initial} (contour in dark green) which includes:

- 2493 • Initial CTV-T HR_{initial}
- 2494 • the complete parametria bilaterally
- 2495 • the whole uterus
- 2496 • uninvolved vagina with a 20 mm margin measured from the most inferior position of the HR CTV-T_{initial}, along the vaginal axis
2497 (not starting in the fornix)
- 2498 • CTV-T HR plus a margin of about 5 mm anterior and posterior towards bladder and rectum (excluding the non-involved walls)
- 2499 • In case of involvement of the pelvic wall, sacro-uterine ligaments, meso-rectum or other involved structures (e.g. bladder,
2500 rectum) a 20 mm margin around the initial HR CTV-T_{initial} will be extended into these structures as appropriate
- 2501 • In case of excessive uterine/ligamentum latum infiltration consider to include ovaries into CTV-T LR_{initial}
- 2502

2503 The CTV-T LR_{initial} volume is normally delineated as a single contiguous volume but for the purpose of these instructions we have
2504 separated the structures to aid description. The MRI information will help you to contour these volumes on the **planning CT**.

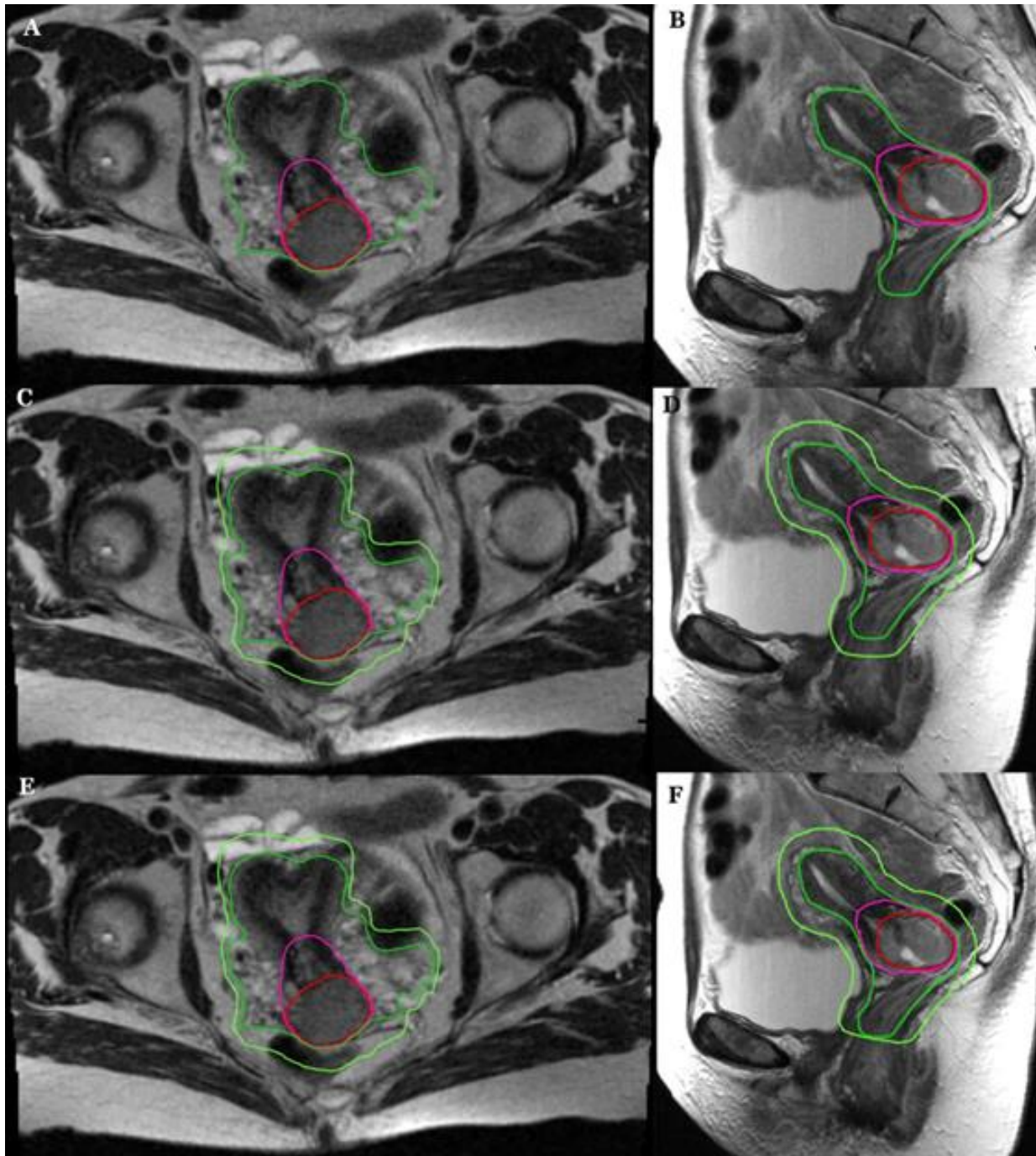
2505 Extend the outline of the CTV-T HR_{initial} to include the whole uterus and 20 mm in the vaginal direction. Subsequently, outline both
2506 parametria and paravaginal tissue (figure 22.5.4A and 22.5.4B) even if not involved with disease, the borders of the parametria are
2507 outlined in the figure 22.5.5 and defined on the table 22.5.1.

2508 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
2509 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.
2510 PIBS minus 2 cm).

2511 STEP 4

2512 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
2513 (figure 22.5.4C, figure 22.5.4D).

2514 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
2515 outline of the CTV-T LR_{initial} (figure 22.5.4E and 22.5.4F).



2516

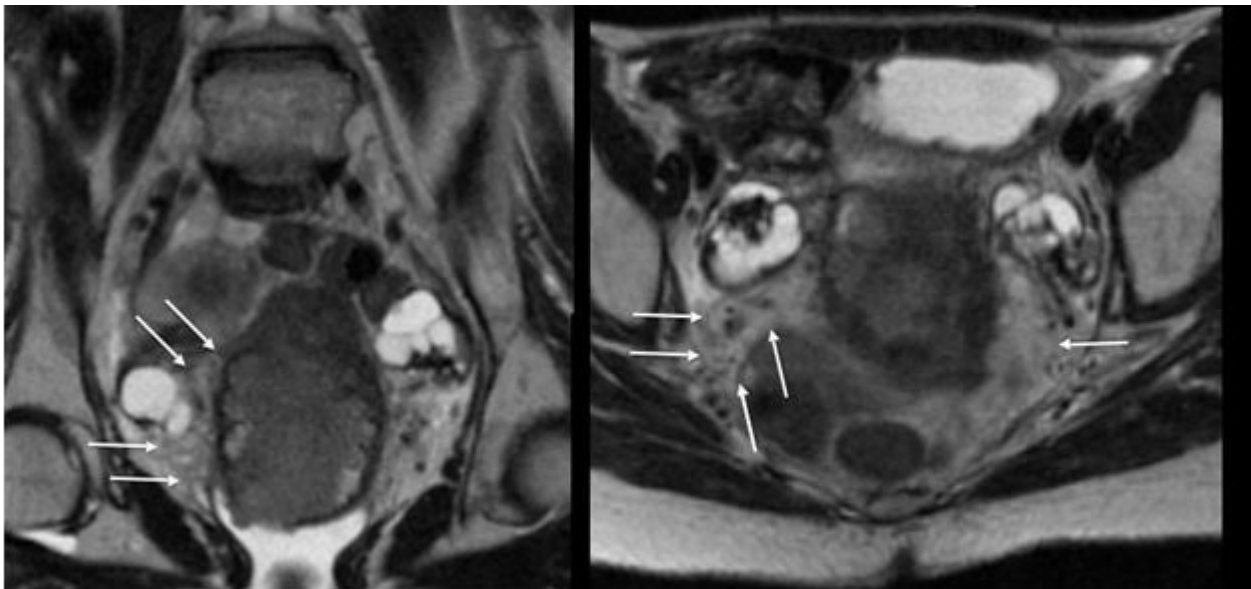
2517 Figure 22.5.4 ITV-T 45 (light green), CTV-T LR (dark green), CTV-T HR initial (magenta), GTV-T initial (red), MRI (T2) A, C, F : axial view, B,
2518 D, F : sagittal view

2519

2520

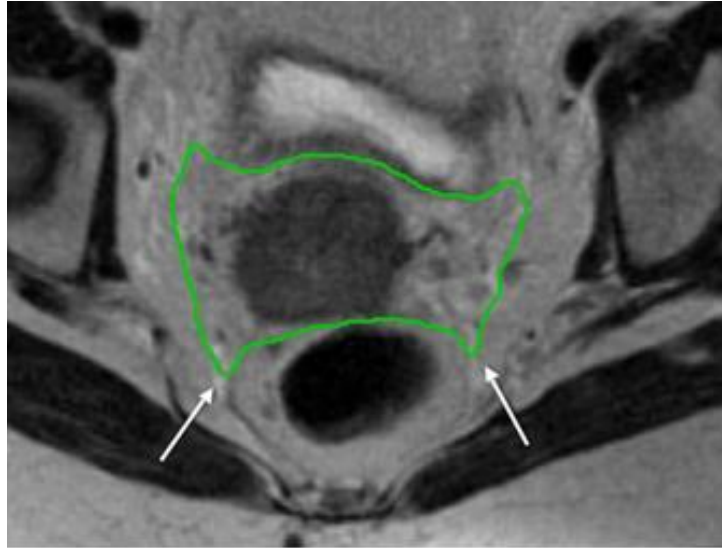
| Location | Anatomic structures |
|-------------|---|
| Anteriorly | Posterior wall of bladder or posterior border of external iliac vessel |
| Posteriorly | Uterosacral ligaments and mesorectal fascia (figure 6) |
| Laterally | Medial edge of internal iliac and obturator vessels |
| Superiorly | Top 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)



2525

2526 Figure 22.5.6 MRI (T2) axial, initial CTV-T LR_{initial} (dark green) Borders of the parametria

2527

2528 22.5.4 INDIVIDUALIZED APPROACH

2529 Follow the **step 1, step 2** as explained above.

2530 STEP 3

2531 On the MRI, identify **the CTV-T LR_{initial}** (contour in dark green) as defined for the standard approach.

2532 The CTV-T LR_{initial} volume is normally delineated as a single contiguous volume but for the purpose of these instructions we have
2533 separated the structures to aid description. The CTV-T LR is outlined on the **MRI** images.

2534 • Extend the outline of the CTV-T HR_{initial} to include the whole uterus and 20 mm in the vaginal direction. Subsequently, outline
2535 both parametria (figure 3A and 3B) even if not involved with disease, the borders of the parametria are outlined in the figure
2536 25.5.5 and defined on the table 25.5.1.

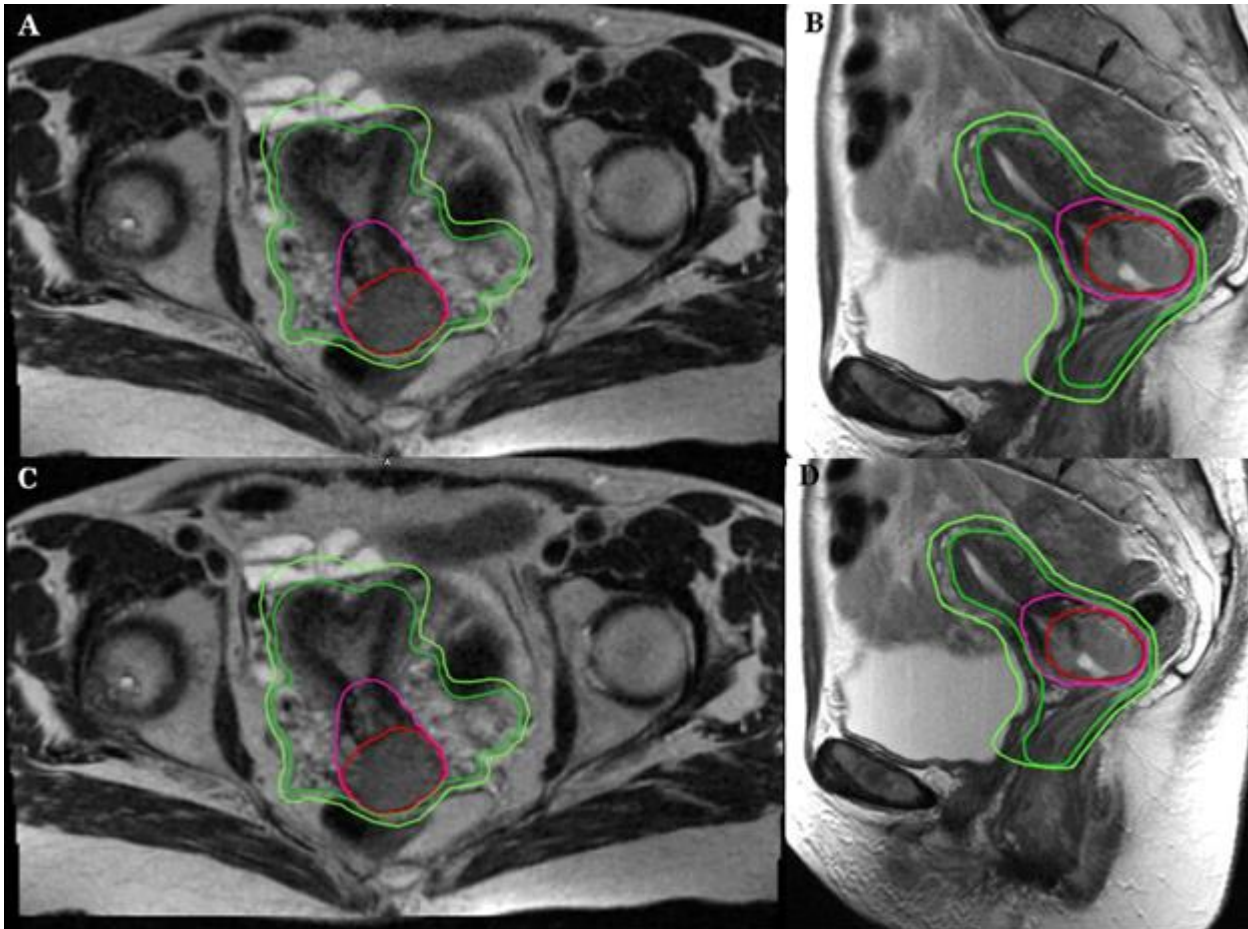
2537 • In the case of vaginal extension, the CTV-T LR_{initial} lower limit is 2cm below the caudal extension of the tumor. If the whole
2538 vagina had to be outlined, the CTV-T LR_{initial} should include the level of the introitus located below the level of the pelvic floor.
2539

2540 STEP 4

2541 Do the registration (fusion) of the MRI images with the planning CT images. The planning CT should have been done according to the
2542 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
2543 appropriately register the bony structures on the planning CT with the ones on MRI (due to positioning differences for example), try to
2544 match locally (the cervix region) on the soft tissue. Once fused, verify your MR-based contour on the planning CT.

2545 On the planning CT, generate the ITV-T LR by adding an individualized margin around the CTV-T LR_{initial} for the different directions
2546 (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
2547 bladder, rectum, uterus, and primary target motion from the different image set available (example figure 25.5.8).

2548

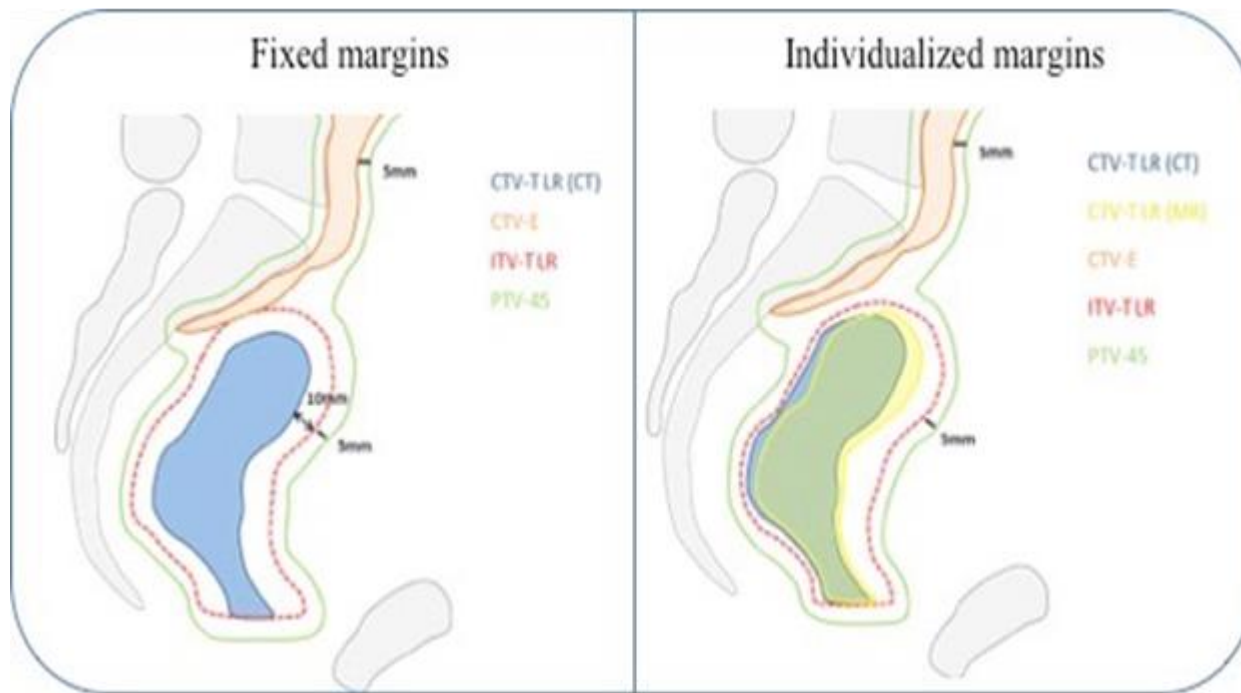


2549

2550 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,
2551 B,D: sagittal view

2552

2553 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
2554 outline of the CTV-T LR initial (figure 25.5.7C and 25.5.7D).



2555

2556 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)

2557 22.5.5 CLINICAL TARGET VOLUMES FOR NODAL METASTASES AND NODAL REGIONS

2558 *we recommend that the **step 1** and **step 2** are done on the MRI but they could be done on the CT as well.

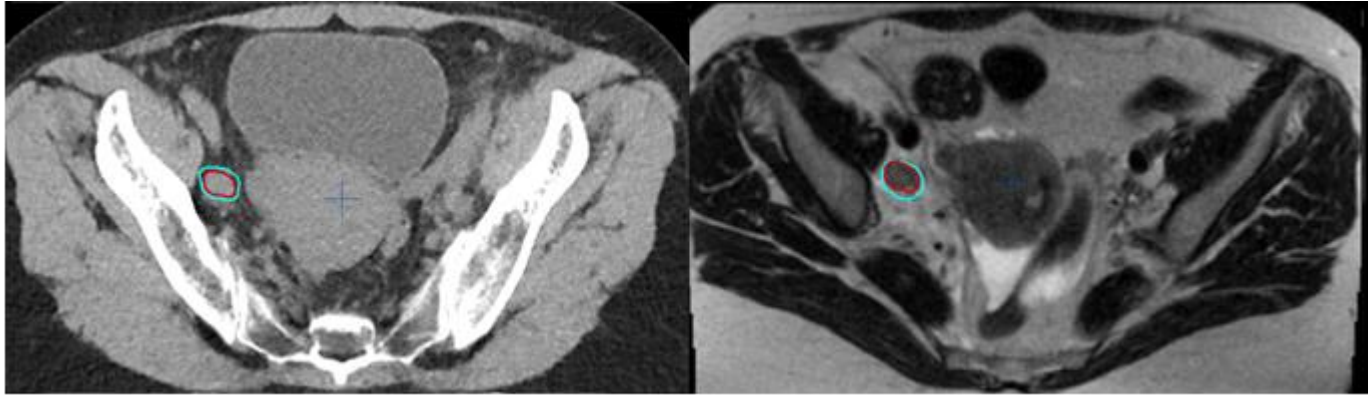
2559 **STEP 5**

2560 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
 2561 contoured and numbered, even if nodal boosting is not contemplated. PET-CT should primarily be used for overall guidance and not for
 2562 precise delineation of the pathological nodes. Include extracapsular extension if visible. In case of nodes beyond the extension of pelvic
 2563 MRI individual contours should be based on PET-CT appearance. Nodes are considered pathologic if they are:

- 2564
- FDG PET positive
 - 2565 • Short axis diameter of ≥ 10 mm on CT or MRI
 - 2566 • Diameter of 5-10 mm on MRI with pathological morphology: irregular border, high signal intensity and/or round shape.

2567 **STEP 6**

2568 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
 2569 taking possible progression during treatment planning interval and not visible extra-capsular extension into account, avoiding bones
 2570 and muscles. Furthermore, partial volume effect may lead to different appearance of the upper and lower boundary on CT and MRI.
 2571 The total CTV-N should ideally encompass the maximum extension of the pathologic node as visualized on both CT and MRI. For
 2572 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
 2573 allow for adequate inclusion into CTV-E and together with the PTV-N margin also if boosting is intended. Numbering of individual CTV-N
 2574 should be consistent with GTV-N.



2575

2576 Figure 25.5.9 A : CT scan, axial view B : MRI (T2) axial view, CTV-N1 (turquoise), GTV-N1 (red),

2577

2578 The **CTV-E** (contour in blue) encompasses all individual CTV-N **and** the bilateral lymph node regions for elective nodal irradiation.

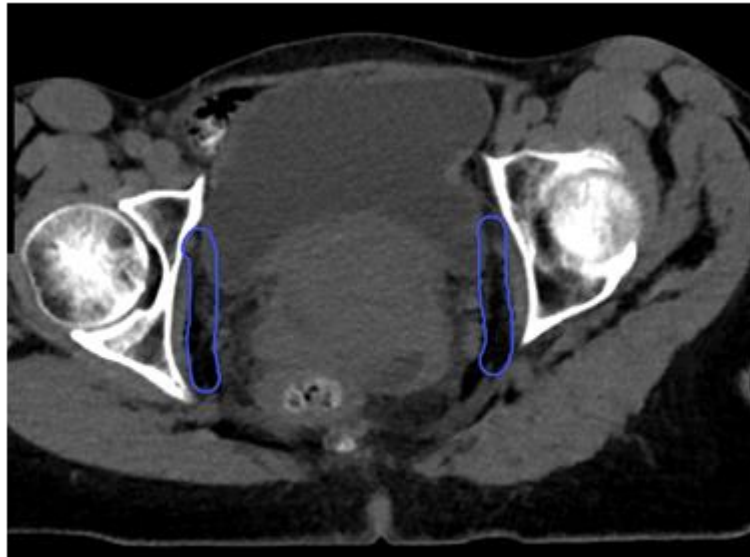
| Risk patients | Lymphatic nodal region to contour |
|--------------------------|--|
| Low risk | Internal iliac, external iliac, obturator and presacral regions |
| Intermediate risk | common iliac, internal iliac, external iliac, obturator, and presacral regions, (groins in case of distal vaginal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

2579 The extent of the nodal regions within CTV-E is determined according to the risk spread as defined in the introduction of chapter 9:

2580 **STEP 7**

2581 Transfer all previous MRI contours (GTV-N and CTV-N) to the planning CT if applicable

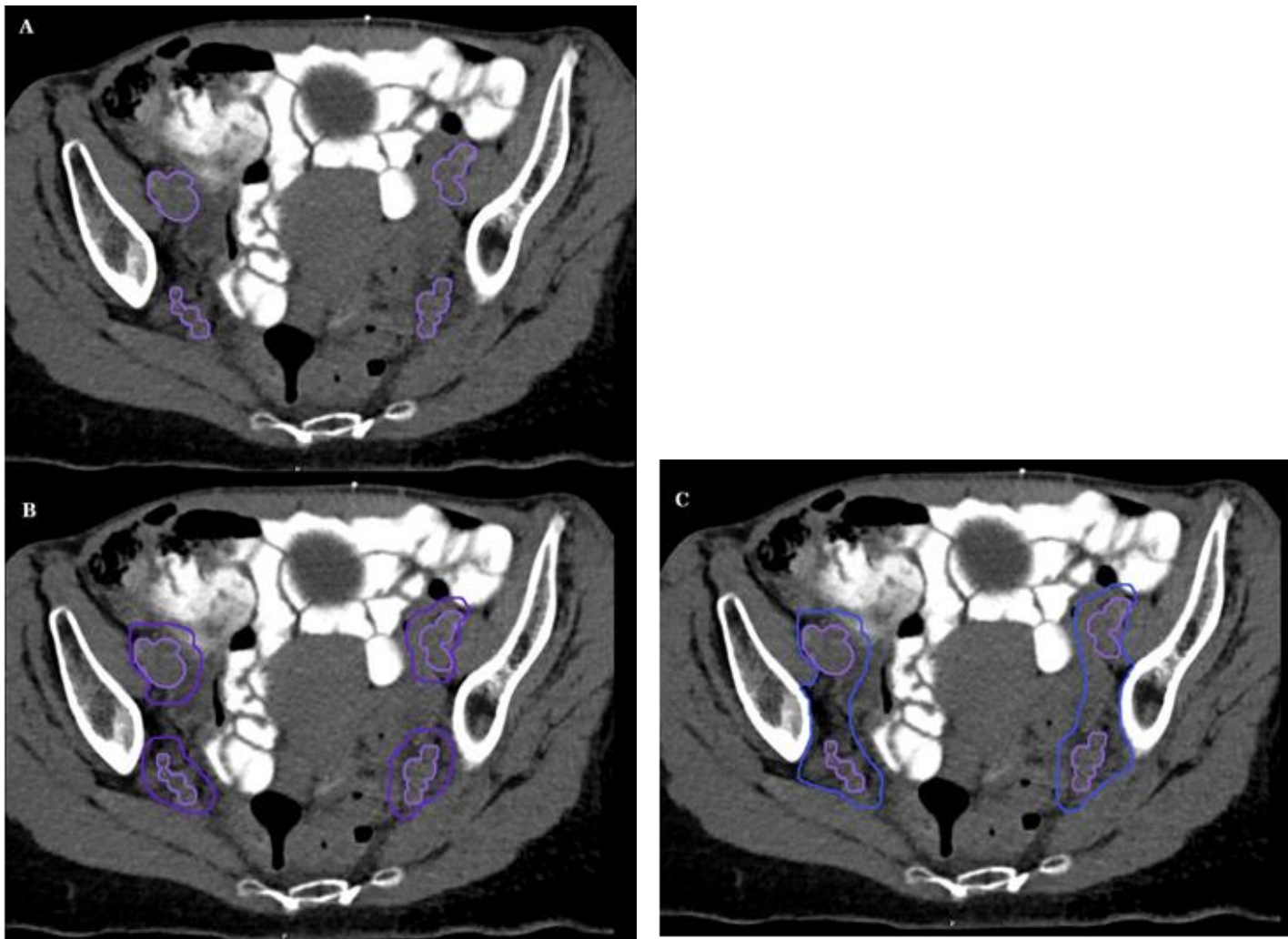
- 2582 • Identify the iliac blood vessels (figure 22.5.11A). The most superior axial outline should be at the aortic bifurcation. The most
2583 inferior border should be at the level of ischial spine and upper edge of obturator foramen were internal iliac vessels leave or
2584 enter the true pelvis) which represents the caudal margin of the external and internal iliac vessels.
- 2585 • Nodal regions should be contoured on the planning CT or pelvic MRI including the relevant vessels with at least 7 mm of
2586 perivascular tissue including pertinent clips or lymphocysts (figure 22.5.11B) (in case of prior nodal resection or
2587 lymphadenectomy). See the table 4 at the end of this annex for a more detail lymph nodes anatomical boundaries definition.
- 2588 • Using the drawing tools, join the outlines around the internal and external iliac vessels parallel/medial to the pelvic sidewall
2589 (figure 22.5.11C). This ensures the obturators and infra-iliac nodes to be included. Internal iliac border should be extend to the
2590 pelvic sidewall.
- 2591 • Continue to contour inferiorly to cover the obturator nodes (figure 22.5.10). The most inferior axial slice to include should be
2592 at the level of the pelvic floor (usually below the femoral heads). This outline should not include muscle or bone.



2593

2594 Figure 22.5.10 Contouring obturator nodal region on a CT scan, CTV-E (blue)

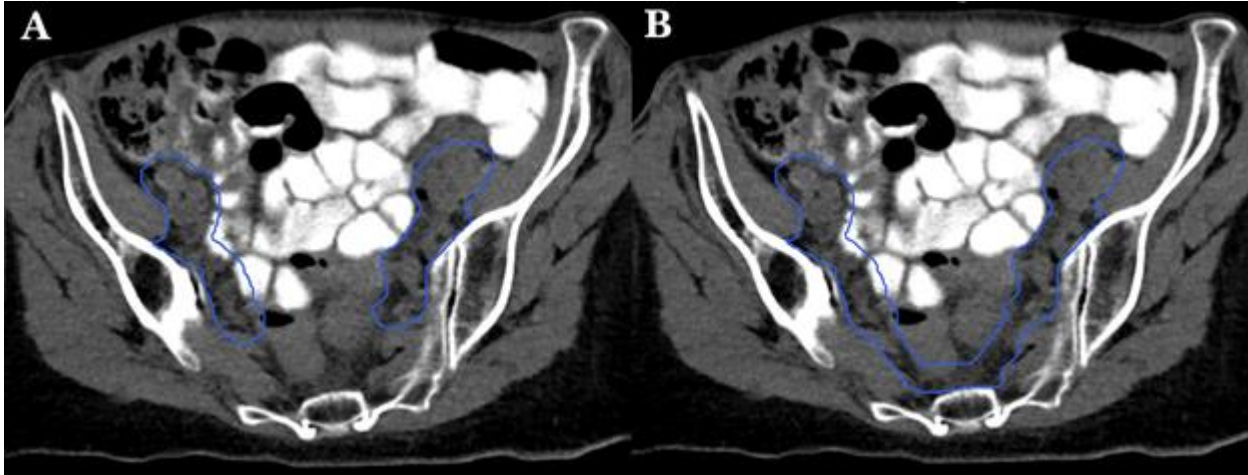
2595



2596

2597 Figure 25.5.11 Contouring steps for internal and external nodal region on a CT scan, A contour of iliac vessels, B :extension of vessel
2598 volume, C : CTV-E (blue)

- 2599
- 2600
- 2601
- 2602
- 2603
- 2604
- 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 22.5.12B) 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.



2605

2606 Figure 25.5.12 Contouring steps for sacral nodal region on a CT scan, B : CTV-E (internal, external and presacral nodal region (blue))



2607

2608 Figure 25.5.13 Contouring sacral nodal region on a CT scan , arrows : sacral foramina

2609

2610 • 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) |

2611 **Table 22.5.3** Superior irradiation field border

2612

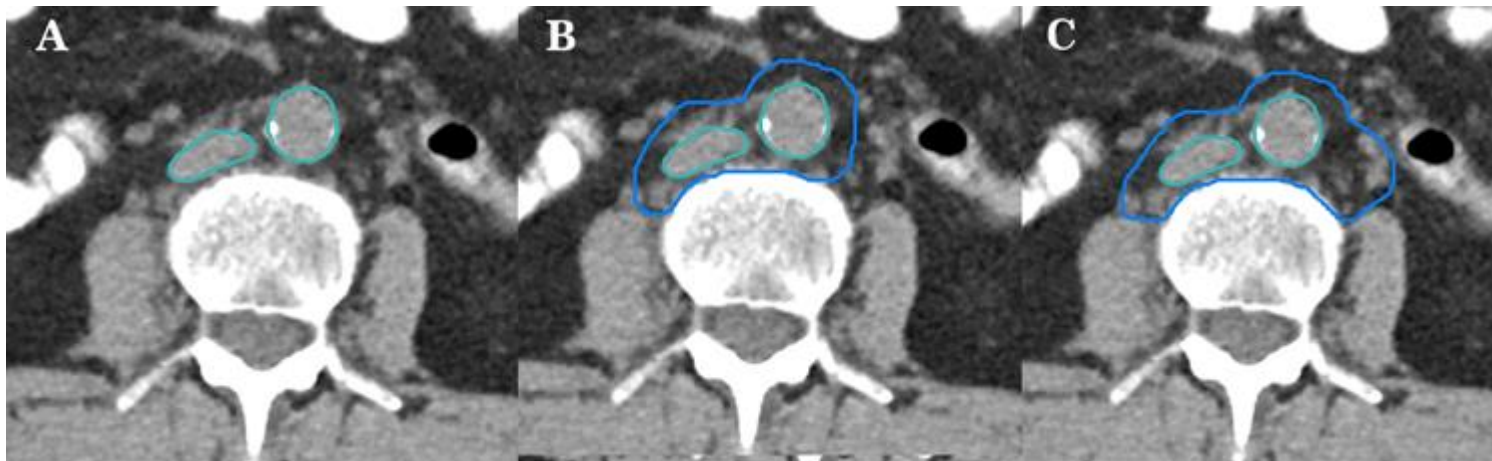
2613 22.5.6 PARA-AORTIC NODES

2614 STEP 8

2615 Nodal regions should be contoured on the planning CT including the relevant vessels (vena cava and aorta) (figure 22.5.14A) with at
2616 least 7 mm of perivascular tissue including pertinent clips or lymphocysts (figure 22.5.14B)

2617 STEP 9

2618 Edit to exclude any muscle or bone. Subsequently, extend the contour posterior-laterally along the vertebral body (figure 22.5.14C) to
2619 cover the left para-aortic area or any lymphocysts.



2620

2621 Figure 22.5.14 Contouring paraaortic region on a CT scan, axial view, A : Great vessels, B : 7mm extension, C : CTV-E (blue)

2622 22.5.7 INGUINAL NODES

2623 Inguinal lymph nodes irradiation should be added in case of positive inguinal lymph node or involvement of the lower third of the
2624 vagina.

2625 STEP 10

2626 The inguinal/femoral region should be contoured as a compartment with any identified nodes included (especially in the lateral inguinal
2627 region). The outline should have a minimum of 7-10 mm margin around vessels. The caudal extent of the inguinal region should be 2

2628 cm caudal to the saphenous/femoral junction. The posterior border is the ventral fascia of the pectineus muscle. The lateral border is
2629 the ventral fascia of the ileopsoas and sartorius muscles (figure 22.5.15).

2630
2631



2632
2633 Figure 22.5.15 Left inguinal lymphatic region, CT, a : sartorius, b : pectineus muscle, c : adductor longus, CTV-E (blue)

2634

2635 22.5.8 PLANNING TARGET VOLUMES (PTV)

2636 STEP11

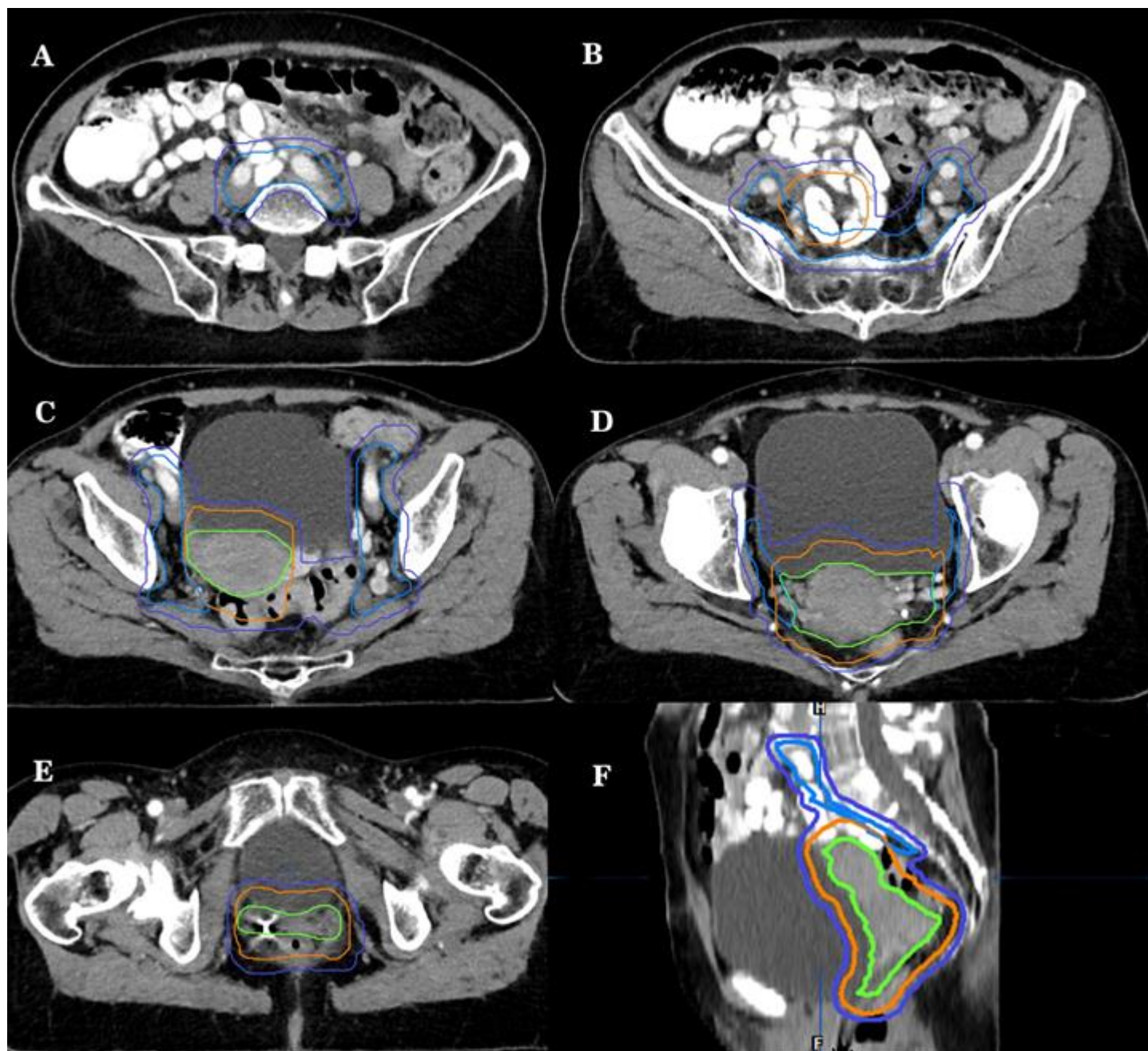
2637 Create one large volume (ITV 45) by fusing the following contours: ITV-T LR, and CTV-E.

2638 STEP12

2639 Add a margin of 5mm to the ITV 45 to create the PTV 45.

2640 Lymphocysts after lymphatic surgery should be included into PTV 45, In case lymphocysts shrink extensively during ERBT, re-contouring
2641 and re-planning should be considered (figure 22.5.16).

2642



2643

2644 Figure 25.5.16 CT,PTV 45 (purple), ITV-T 45 (orange), CTV-E (blue), CTV-T LRinitial (light green) ; A, B, C, D, E : axial view, F : sagittal view

2645 22.5.9 NODAL BOOST

2646 STEP13

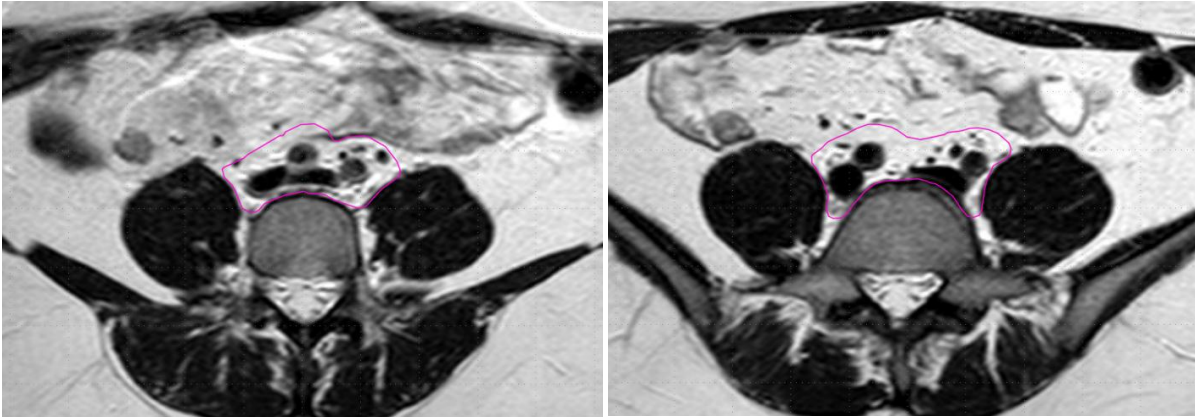
2647 Add a 5mm margin to each CTV-N1, CTV-N2, ... to create PTV-N1, PTV-N2, ...

2648

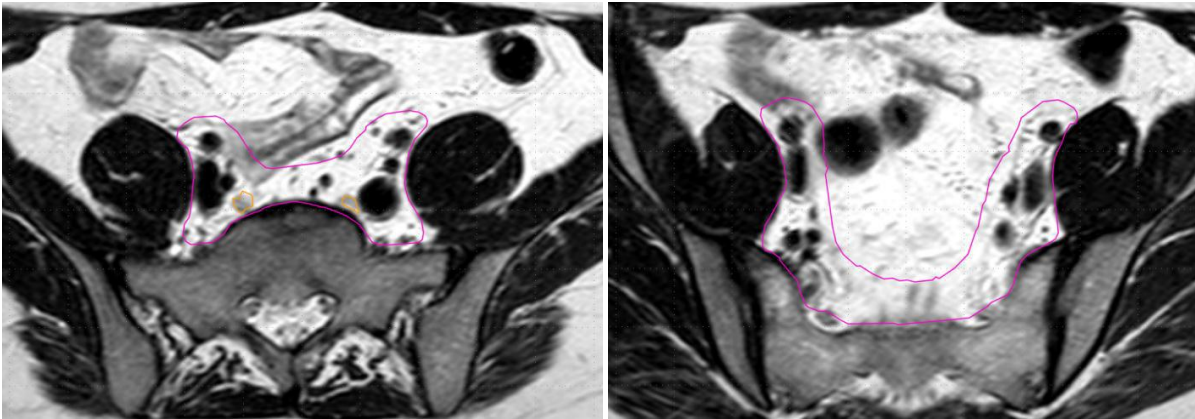
| | |
|---|---|
| On MRI | 1- Contour the GTV-T_{initial} . It's the extension of the primary tumor at the cervix |
| | 2- Outline the CTV-T HR_{initial} . It's the initial high risk CTV-T including GTV-T_{initial} and any remaining cervix not infiltrated by the tumor |
| <p>Surimposition/Registration/ fusion between the MRI and the planning CT*</p> <p>* 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</p> | |
| On CT | <p>3- Contour the CTV-T LR_{initial} in including the following structures:</p> <ul style="list-style-type: none"> -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) <p>4- Contour GTV-N and CTV-N (margin 0-3mm) and numerate them accordingly</p> <p>5- Delineate the CTV- E in contouring the nodal region corresponding to the patient risk category and including all the CTV-N</p> <p>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</p> |
| | 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 |

| | |
|---|--|
| 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 |

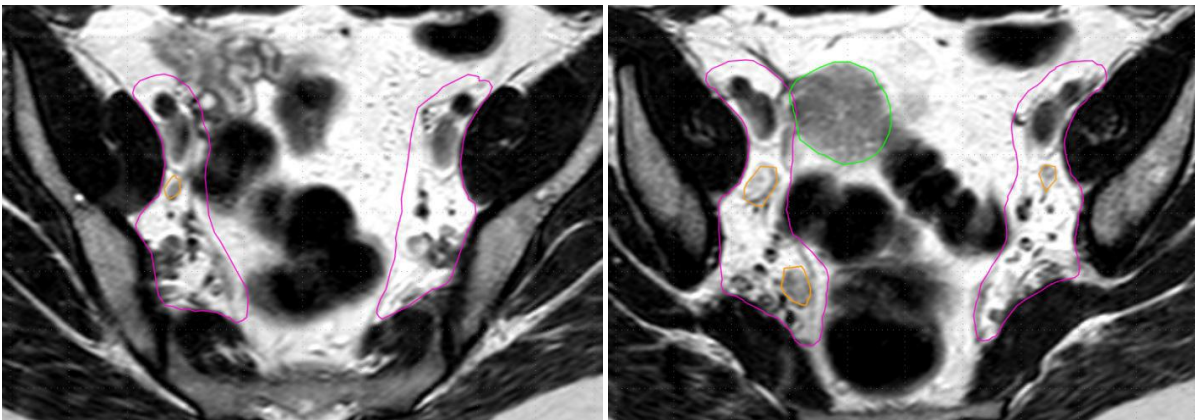
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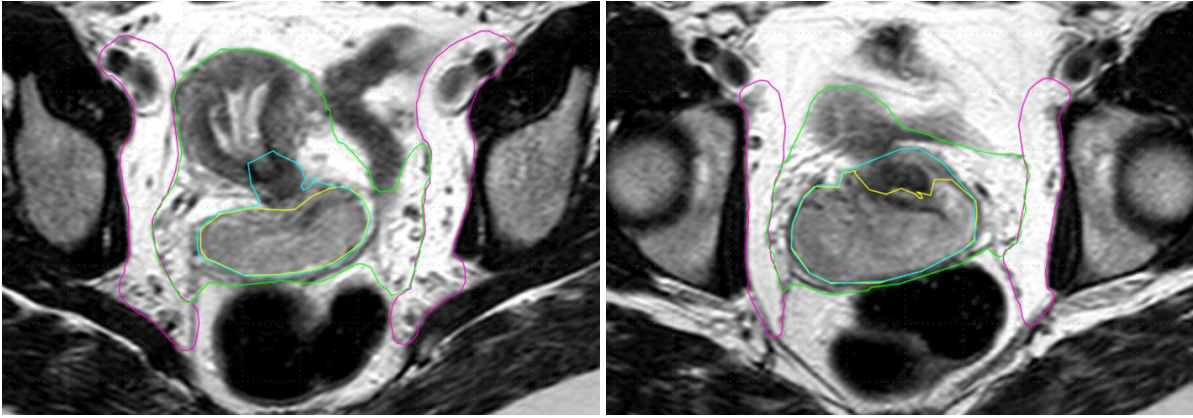
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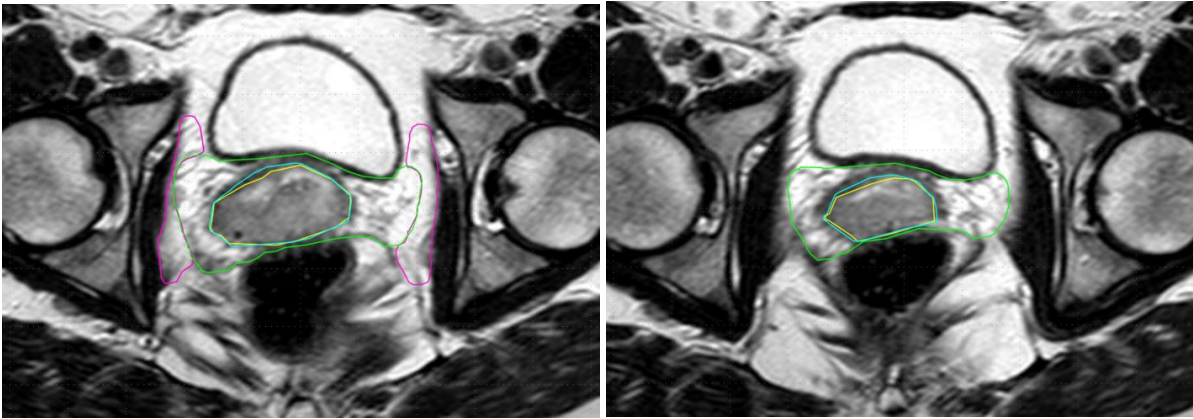
2658 Figure 22.5.1 Atlas example FIGO IB2 cervical cancer with pathological lymph nodes. MRI (T2) in treatment position, axial slices at
2659 regular interspaces from left to right and top to bottom, CTV-E (magenta), GTV-N (orange), CTV-T LR (green).

2660

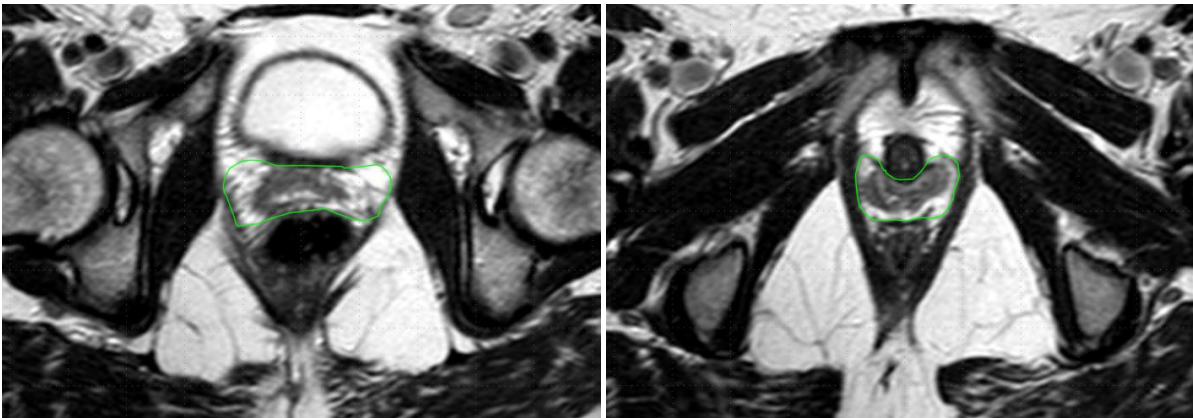
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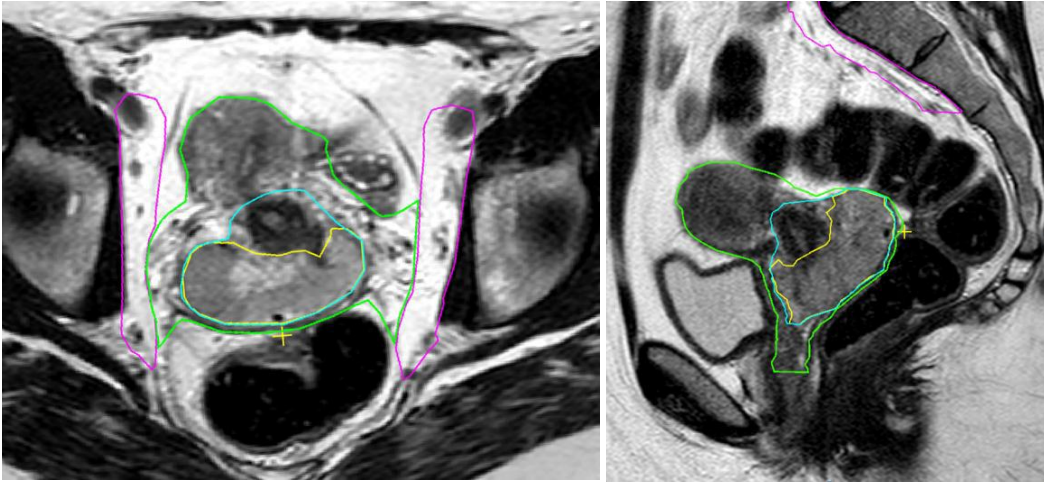
2663



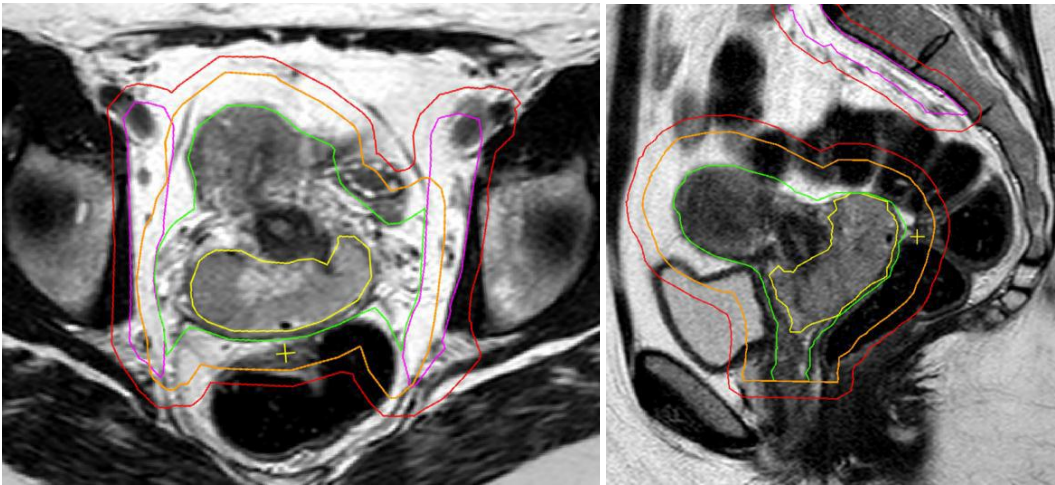
2664 Figure 22.5.2 Continued: MRI (T2) in treatment position, axial slices at regular interspaces from left to right and top to bottom, CTV-E
2665 (magenta), GTV-N (orange), CTV-T LR (green), GTV-T initial (yellow), CTV-T HR initial (light blue).

2666

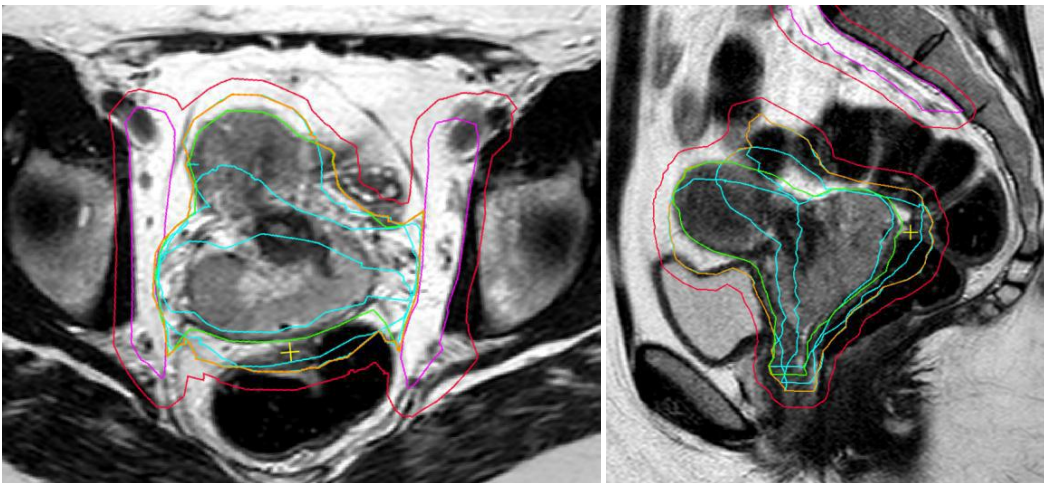
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2668



2669



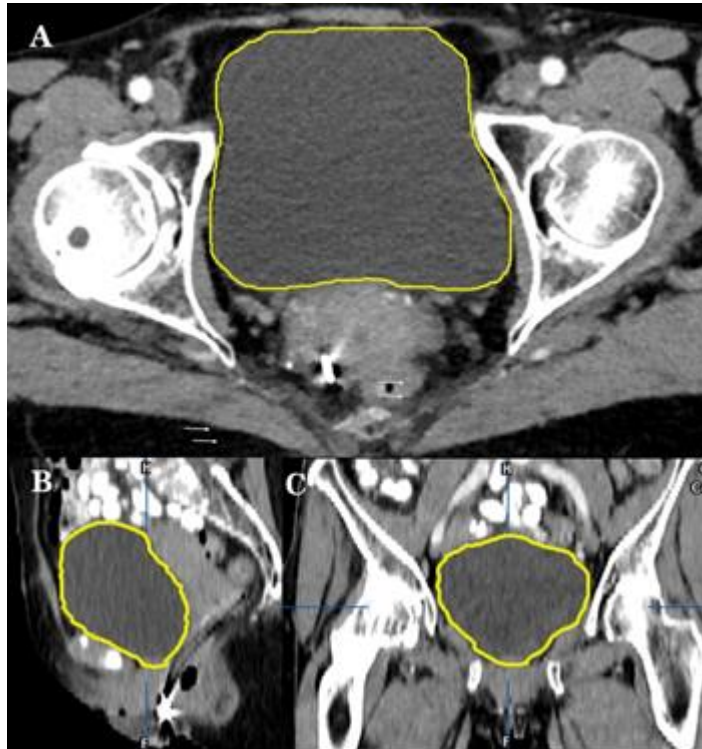
2670 Figure 22.5.3 Continued: MRI (T2) in treatment position; top left axial and top right sagittal CTV-E (magenta), CTV-T LR (green), GTV-T
2671 initial (yellow), CTV-T HR initial (light blue); middle left axial and middle right sagittal CTV-E (magenta), CTV-T LR (green), GTV-T initial
2672 (yellow), ITV-T LR using standard margins (orange) and PTV45 (red); bottom left axial bottom right sagittal CTV-E (magenta), CTV-T LR in
2673 treatment position (green) and three additional positions from different fused MRI and PET-CT scans (light blue), GTV-T initial (yellow),
2674 ITV-T LR using individual margins (orange) and PTV45 (red).

2675

2676 22.5.12 CONTOURING OF ORGANS AT RISK

2677 The outer contour of the following organs should be delineated separately:

2678 **Bladder:** Outline the whole organ including the bladder wall and the bladder neck (figure 17).

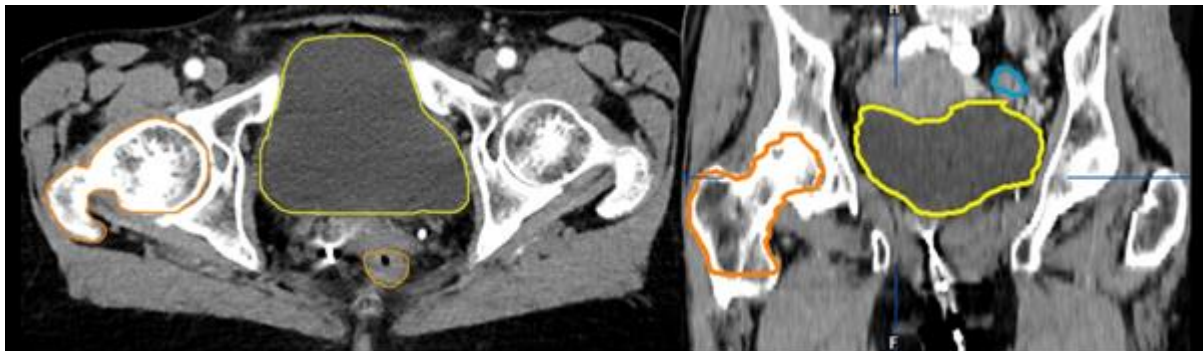


2679

2680 Figure 22.5.17 CT, Bladder contour (yellow) A :axial view, B : Sagittal view, C : Coronal view

2681 **Femoral heads:** Both femoral head and neck to the level of the trochanter minor. (figure 22.5.18)

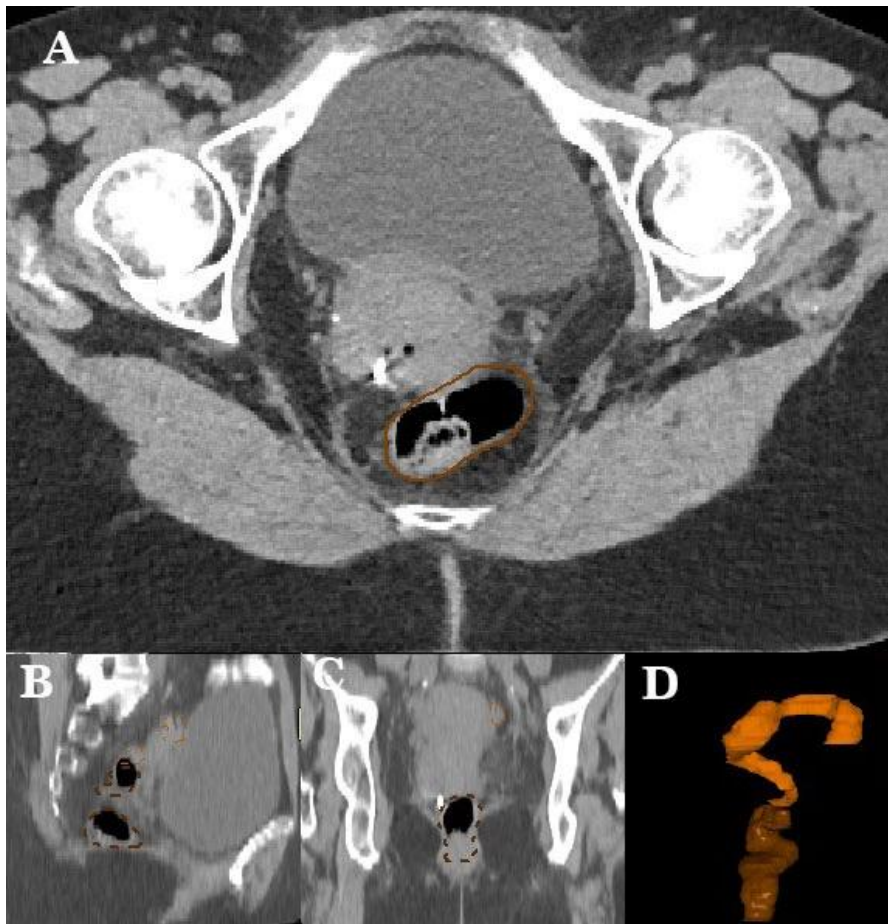
2682 **Rectum:** Outline the rectum from the ano-rectal sphincter (level of PIPS) to the recto-sigmoid junction (retroperitoneal deflection),
2683 including the rectal wall (figure 22.5.19).



2684

2685 Figure 22.5.18 Right femoral head contour (orange), A : axial view, B : coronal view

2686 **Sigmoid:** From the recto-sigmoid junction to the left iliac fossa (figure 22.5.18).



2687
2688 Figure 22.5.19 CT, rectum contour (brown) and sigmoid contour (orange), A :axial view, B : Sagittal view, C : Coronal view, D : 3-D
2689 reconstitution

2690

2691 **Bowel:** Outer contour of bowel loops including the mesenterium. Do not include abdominal cavity without bowel or sigmoid (figure
2692 22.5.20).



2693

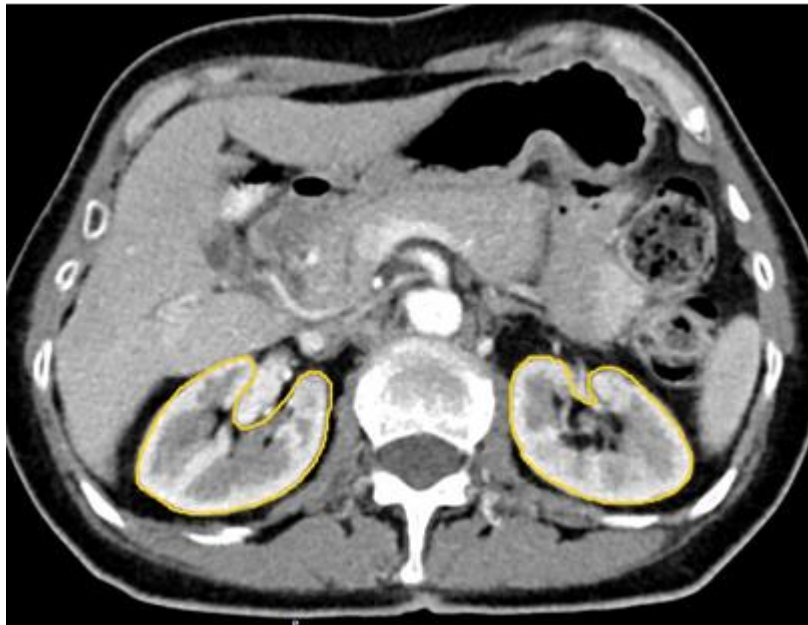
2694 Figure 22.5.20 CT. bowel contour (green)

2695

2696 22.5.13 FOR PARA-AORTIC IRRADIATION IN ADDITION

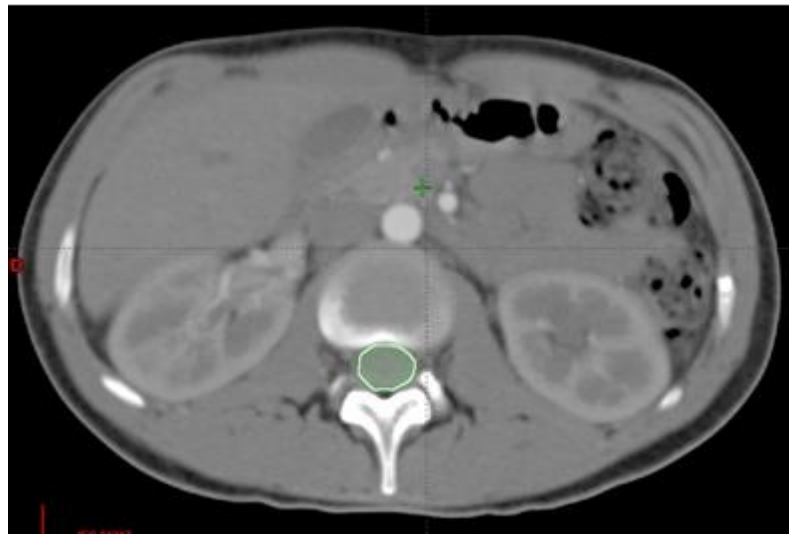
2697

2698 **Kidneys:** outer contour excluding pyelum (figure 22.5.21)



2699 Figure 22.5.21 Kidney contouring

2700 **Spinal cord: outer contour of spinal cord, contour down to L2** (figure 22.5.22)



2701

2702 Figure 22.5.22 CT. Spinal cord

2703

| 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 of 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 magna | 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

2706 22.6 APPENDIX 6: MEASUREMENT AND REPORTING OF SUV

2707 Measurement and reporting of SUV in primary tumour and lymph nodes is not mandatory in EMBRACE II, but when reported to the
2708 database, the following procedure should be used:

- 2709 • In general the FDG PET/CT: EANM procedure guidelines for tumour imaging: version 2.0 should be followed ([Boellaard R. et al.](#)
2710 [2015](#)).
- 2711 • CT can be performed as either a low-dose CT-scan for attenuation correction and anatomical correlation or as a diagnostic CT-
2712 scan.
- 2713 • Scans should be performed according to local guidelines with regard to fast and blood glucose levels.
- 2714 • Image reconstruction should be performed according to local guidelines.
- 2715 • Imaging should be evaluated using software that can display fused CT and PET data and use a SUV scale.
- 2716 • Time from injection to scan start should be between 60-90 minutes.
- 2717 • Reported to the database:
 - 2718 ○ SUV_{max} of the primary tumour
 - 2719 ○ SUV_{max} for each lymph node
 - 2720 ○ Necrosis (yes/no) for each lymph node

2721

2722 22.7 APPENDIX 8: CRFS (CH 16)

2723 This Appendix refers to a large excel file which is in principle based upon the CRF design of EMBRACE I with altogether 8 forms:

- 2724 1. Registration Form
- 2725 2. Status at Diagnosis Form
- 2726 3. Baseline Morbidity Form
- 2727 4. Status at Brachytherapy Form
- 2728 5. Treatment and DVH Form
- 2729 6. Follow-up Form
- 2730 7. Off Study and Vital Status Form
- 2731 8. Curative Salvage Treatment Form

2732 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
2733 80% already finished (estimate).

2734 This rework has been done based on our experience with EMBRACE I and the design of the CRFs and the evaluation of parameters. In
2735 addition the design of EMBRACE II was taken into account reflecting the major (new) endpoints. As EBRT has become an additional
2736 issue of major importance in EMBRACE II, this is reflected in the respective forms. The rework has tried to follow the EMBRACE I
2737 parametrization in order to provide the basis for comparison of data between EMBRACE I (RetroEMBRACE) and EMBRACE II.

2738

2739 22.8 APPENDIX 9: PRINCIPALS AND STRUCTURES OF EMBRACE RESEARCH GROUP

2740 Research work is organised based on written project proposals with a short and a long protocol version.

2741 Research protocols are organised according to classical research proposal structure for grant applications

2742 Research protocols have to result in minimum one major publication in a peer reviewed journal

- 2743 Research funding is not available directly through the EMBRACE study
- 2744 Research is organised within working groups focussing on a specific topic with a coordinator and co-workers
- 2745 Milestones to be defined with time lines in a research proposal: who, what, when
- 2746 Updates to be given in person on the occasion of meetings: Gyn GEC ESTRO network, midyear, annual EMBRACE end of the year
- 2747 Responsibility for project plan and research performance: Working group coordinator. Working group coordinator is assigned for 2
2748 years, can be renewed
- 2749 Bilateral Agreement on this outline with main mentor/mentor group before application
- 2750 Overall Agreement on all project outlines by EMBRACE Research mentor group continuously: start after 1st application round
- 2751 Publication authorship (for first major publication): Working group coordinator is first author, main mentor is senior author. In case of 2
2752 persons, co-equal authorship foreseen authors are persons with active participation in the publication project one authorship goes to
2753 one of the EMBRACE coordinators (co-mentor) provisional title of first major publication and authorship should be part of the short and
2754 long proposal version, may be adapted later
- 2755 EMBRACE Research Leader group are the Study coordinators plus senior advisors
- 2756 EMBRACE Research Mentor group: Richard Pötter, Kari Tanderup (coordinators)
- 2757 EMBRACE Research WG Coordinator group: all workgroup coordinators,
- 2758 Milestones and timelines for project progress and publication process have to be kept carefully in order to make this complex research
2759 structure feasible and to ensure our data to be handled in appropriate way .
- 2760 In case of somebody going repeatedly and significantly beyond timelines not fulfilling milestones in regard to project and publication
2761 process without upfront providing a rationale to the EMBRACE research leader group, the function of the coordinator and the
2762 authorship role will be re-considered and decided by the cooperative research leader group.
- 2763 Overall organisation structure: Research leader group regular 6 monthly telephone conferences. A work group coordinator or mentor
2764 may be invited, if appropriate organised by Vienna or Aarhus (RP, KT) decisions are taken by majority
- 2765 The overall EMBRACE Research group, working group coordinators together with mentors and co-workers meets on the occasion of
2766 annual EMBRACE meetings and Gyn GEC ESTRO network meetings, if feasible.
- 2767 Each working group and mentor group works according to its own specific working plan. Minimum actions to be taken by the working
2768 groups are telephone conference meetings in 3 months intervals (with the main mentor available) with a pre-meeting agenda and
2769 summarizing minutes (results). This is to be communicated in cc to the coordinators RP, KT.
- 2770 No extra funding is at present available for the performance of the research work. Specific funds are therefore encouraged to be
2771 applied for at the regional/national/ European/international level as appropriate after discussion and agreement on the proposal with
2772 the EMBRACE RESEARCH leader group.
- 2773
- 2774

2775 22.9 APPENDIX 10: PATIENT INFORMATION

2776 Patient information needs to be adapted to the needs, legislative and ethical requirements of each country and radiotherapy
2777 department. To facilitate this process and to maintain some uniformity, parts of the following paragraphs could be included in the
2778 written patient information but this information should be adjusted according to local institutional standard treatment policies and are
2779 subject to local ethical committee approval. In addition, a study specific consent form will need to accompany the patient information
2780 form that needs to be adapted to fulfill the regulations of the local ethical committee.

2781 **Summary**

2782 You have been asked to participate in a study for patients with cervical cancer who will be treated with a combination of external beam
2783 radiotherapy, chemotherapy and brachytherapy (internal radiation).

2784 The aim of this study is to collect exact details about:

- 2785 • Radiation dose to the tumor and surrounding normal organs
- 2786 • Effect of therapy on tumor control
- 2787 • Side effects of treatment
- 2788 • Quality of life during and after treatment

2789 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
2790 not participate in this study. The study is planned to include more than 1000 patients from approximately 25 different international
2791 radiotherapy departments. The radiotherapy departments who collaborate in this study all use advanced level technological methods
2792 to deliver radiation image guided, as precisely and optimally as possible, to the tumor while sparing the surrounding healthy organs. In
2793 this document you can read more information about the treatment, the possible side effects of treatment and this study.

2794 **Background**

2795 The combination of external beam radiotherapy, chemotherapy and brachytherapy is the current standard treatment for patients with
2796 locally advanced cervical cancer. The treatment starts with external beam radiotherapy together with chemotherapy. Brachytherapy
2797 (internal radiation) will be started during the last part of external beam treatment or starts when external beam treatment has ended.

2798 In the first EMBRACE study that was completed in 2015 more than 1000 patients participated. This study focused on implementing a
2799 brachytherapy treatment method in which the radiation dose was shaped to the individual patients anatomy or position of the tumor
2800 and the healthy normal surrounding organs using MRI imaging at time of brachytherapy. Results of this and other studies indicate that
2801 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.
2802 For these patients brachytherapy dose to normal surrounding organs can be lowered while maintaining the high chance of tumor
2803 control. On the other hand, in patients with larger tumors a higher dose of brachytherapy could be safely given with advanced
2804 brachytherapy techniques and this higher dose resulted in an improved chance of tumor control.

2805 The current EMBRACE-II study will collect and register details from patients who have been treated with advanced brachytherapy
2806 techniques including MRI at time of brachytherapy, and with advanced external beam radiotherapy image guided techniques. Based on
2807 the results described above in EMBRACE-II:

- 2808 • External beam radiotherapy will be done using intensity modulated radiotherapy, a technique that results in less radiation
2809 dose to surrounding healthy organs (bowel, bladder). Furthermore, each day patients will be positioned as accurate as possible
2810 on the treatment machine using imaging on the machine. This will increase the precision of treatment.
- 2811 • For brachytherapy it will be routinely possible to adjust the devices used to deliver internal radiation to the individual anatomy
2812 and position of the tumor and surrounding healthy organs. Together with MRI imaging at time of brachytherapy, this will
2813 increase the precision of treatment. For smaller tumors this will result in less dose to healthy surrounding organs, while for
2814 larger tumors this will allow to increase the radiation dose necessary to effectively treat the tumor.

2815 **External beam radiotherapy**

2816 External beam radiotherapy is an outpatient treatment that takes approximately 20-30 minutes per day and is usually given each day (5
2817 days a week). In total 25 external beam radiotherapy treatments are given over a period of 5-6 weeks.

2818 Side effects of external beam irradiation

2819 During the 5-6 week period that external beam radiotherapy is given, side effects will gradually develop, usually starting after 2-3
2820 weeks. The side effects are most pronounced during the last 2 weeks of external beam radiotherapy and the first 2 weeks after
2821 completion. During this period the tumor will decrease in size and sometimes patients will notice a change in discharge from the vagina.

2822 Side effects during and shortly after treatment include:

- 2823 • Irritation of bowel resulting in softening of stools or diarrhea, sometimes with bowel cramps and seldom with a little blood in
2824 the stool. This results in having to go to the toilet more often for bowel movements.
- 2825 • Irritation of the bladder, which leads to increased urgency or need to go to the toilet more often to pass urine, sometimes with
2826 a burning sensation.
- 2827 • Irritation of the vagina.
- 2828 • Loss of energy or feeling tired.

2829 **Brachytherapy**

2830 With brachytherapy radiation is given inside the tumor using an applicator. The placement of the applicator is done using a form of
2831 anesthetic (general or spinal). The applicator uses hollow tubes that are placed in the vagina and through the cervix into the cavity of
2832 the uterus (womb). It may be necessary to place additional hollow tubes or needles directly in the tumor area. Using an MRI scan with
2833 the brachytherapy applicator in position the radiation dose can be optimally shaped. During the treatment a radioactive source will be
2834 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
2835 how much treatments are given depends on the equipment used and your radiation oncologist will provide more detailed information
2836 on this procedure.

2837 Side effects of brachytherapy

2838 In period when brachytherapy is given there usually are already side effects from external beam radiotherapy. In addition to these,
2839 there may be some bleeding from the vagina, which should stop within two days after treatment. There may be some additional
2840 soreness of the vagina or with passing urine after the procedure.

2841 **Chemotherapy**

2842 Chemotherapy will be given using the drug cisplatin that will be given on one day each week during the first five weeks of external
2843 beam radiotherapy. Cisplatin is given intravenously, in the bloodstream.

2844 Side effects of chemotherapy

2845 Most common side effects of this weekly cisplatin treatment include:

- 2846 • Feeling sick (nausea) or having to vomit. To prevent this the treatment will be combined with medication to prevent this.
- 2847 • Cisplatin can damage the kidney. For this reason additional fluid will be given together with the drug intravenously. The
2848 function of the kidney will be tested each time before the treatment is given.
- 2849 • The chemotherapy temporary affects the normal blood cells. The number of blood cells will be tested each time before the
2850 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
2851 in tiredness and shortness of breath. A drop in blood platelets can result in bruising or bleeding more easily.
- 2852 • Seldom side effects include loss of taste, loss of appetite, some hearing loss, tingling or numbness in toes or fingers.

2853 **Long term side effects of treatment**

2854 Side effects that arise during or shortly after treatment usually pass away two weeks after treatment. However in the long run
2855 radiotherapy can directly damage some of the normal organ function or cause tissue to become less elastic (fibrosis). This can cause
2856 side effects that may become more apparent during the years following treatment. Your radiation oncologist will provide you with
2857 information on whom to contact in case of symptoms. These side effects may include:

- 2858 • Ovaries will stop functioning. This causes infertility and causes early menopause in women that have not had their menopause.
- 2859 • The vagina can become less elastic, narrower and dryer. Altogether these side effects may affect your sex life. The use of
2860 vaginal lubrication and vaginal dilators, to stretch the vagina, is recommended and you can receive more information on this
2861 subject separately.
- 2862 • Parts of the bowel in the pelvic area may become less elastic and function less well. This can result in more frequent, loose
2863 stools and bowel cramps. Seldom this results in constipation or a bloated feeling.
- 2864 • Due to reduced elasticity of the bladder it can not stretch as much which can give the sensation that its is full sooner.
- 2865 • Swelling of the legs may be a result of fibrosis along the draining lymphatic tissue in the pelvis.
- 2866 • Occasionally increased growth of small blood vessels in the mucosa of the bowel, bladder or vagina may cause bleeding.

2867 **After treatment**

2868 After treatment you will have regular outpatient visits with your radiation oncologist. These visits are used to check on the effect of
2869 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
2870 year every 6 months and then yearly up to five years after treatment. During these visits a gynecological examination will be done. In
2871 addition, both at 3 months and one year after treatment a MRI scan will be made.

2872 **Quality of life investigation**

2873 Quality of life investigation is done using a questionnaire. The questionnaire is handed out before treatment starts, during treatment
2874 and at regular intervals up to 5 years after treatment. The questionnaire consists of 54 questions and will take approximately 20-30
2875 minutes to fill in. These questions ask you about the most common symptoms (side effects) of treatment, but also ask about more
2876 general functioning such as physical activity and emotional functioning. Using these questionnaires you can provide direct information
2877 on what the consequences of treatment are for your wellbeing. The information from these questionnaires provides important results
2878 for the study. Strict privacy is enforced and the information from the questionnaires will be handled under coded.

2879 **Study participation**

2880 The treatment with expected outcome and side effects as described above is the standard treatment. You will receive the same
2881 treatment if you do not participate in this study. The aim of this study is collect and register details about the treatment, the outcomes
2882 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
2883 participate you will be asked to sign the written informed consent form. It is always possible to withdraw your study participation at any
2884 point in time. Your radiation oncologist may also propose to withdraw from the study if that may benefit your situation. If you decide
2885 not to participate you will receive the same standard treatment and this will not in any way affect the relationship with your radiation
2886 oncologist. You do not have to decide immediately if you want to participate, you can discuss the study with others and are provided
2887 with enough time to consider the possible benefits and disadvantages.

2888 In summary the main benefits and disadvantages of study participation are:

- 2889 • The benefits of participating to this study are that external review and quality assurance of treatment planning and execution
2890 is part of the study and that you're outcomes (tumor control and side effects of treatment) will be used to better understand
2891 how to improve this treatment further in the future.
- 2892 • Having to fill in quality of life questionnaires may be seen as a disadvantage of participating to the study.

2893 **Confidentiality**

2894 You can be assured that all information that will be registered for this study will be handled confidential. Information that will be
2895 registered includes that of details of the treatment, details of the outcome on tumor control and side effects of treatment during the
2896 first five years after treatment. Before your data is sent to a central database anonymously, it will be coded using a unique study code.
2897 Only you're treating radiation oncologist and any personnel that is directly authorized through you're radiation oncologist will be able
2898 to see your information.

2899 **Tumor tissue**

2900 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
2901 this. This research will focus on finding alterations in the tissue that can help to better understand the outcomes of this study (effect of
2902 treatment on tumor control and side effects). The piece of tumor will be stored anonymously using you're unique study code. You will
2903 be asked separately to provide signed written informed consent for the use of the tumor tissue.

2904 **Financial support**

2905 This study receives limited financial support from Varian and Electa, both are companies that produce radiation therapy equipment.
2906 This financial support is limited and is used for administration and database management and data analysis. None of the individual
2907 persons involved in the study receive financial support from these companies.

2908 **Insurance**

2909 Since the standard treatment is used in this study, there is no separate insurance policy for this study. In case of complaints or liability
2910 issues, the standard procedure as is used for any other medical treatment or condition in your hospital will apply.

2911 **Further information**

2912 If you have any other questions about this study you can ask your treating radiation oncologist, medical oncologist or gynecologist
2913 about these. [provide contact details and phone numbers, including an independent physician].

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23 REFERENCES

- 2919
- 2920
- 2921 Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, Filiberti A, Flechtner H, Fleishman SB, de Haes JC, et al. The
- 2922 European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials
- 2923 in oncology. *J Natl Cancer Inst.* 1993 Mar 3;85(5):365-76.
- 2924
- 2925 Assenholt M. Application of coverage probability treatment planning for lymph node boosting in locally advanced cervical cancer.
- 2926 Abstract BigART, 13th Acta Oncologica Symposium 2015.
- 2927
- 2928 Beadle BM, Jhingran A, Yom SS, Ramirez PT, Eifel PJ. Patterns of regional recurrence after definitive radiotherapy for cervical cancer. *Int*
- 2929 *J Radiat Oncol Biol Phys.* 2010 Apr;76(5):1396-403.
- 2930
- 2931 Bentzen SM, Parliament M, Deasy JO, Dicker A, Curran WJ, Williams JP, Rosenstein BS. Biomarkers and surrogate endpoints for normal-
- 2932 tissue effects of radiation therapy: the importance of dose-volume effects. *Int J Radiat Oncol Biol Phys.* 2010 Mar 1;76(3 Suppl):S145-50.
- 2933
- 2934 Boellaard R. The engagement of FDG PET/CT image quality and harmonized quantification: from competitive to complementary. *Eur J*
- 2935 *Nucl Med Mol Imaging.* 2015 Oct 1.
- 2936
- 2937 Chai Y, Wang J, Gao Y, Wang T, Shi F, Su J, Yang Y, Zhou X, Song L, Liu Z. Identification of biomarkers for radiation-induced acute
- 2938 intestinal symptoms (RIAISs) in cervical cancer patients by serum protein profiling. *J Radiat Res.* 2015 Jan;56(1):134-40.
- 2939
- 2940 Charra-Brunaud C, Harter V, Delannes M, Haie-Meder C, Quetin P, Kerr C, Castelain B, Thomas L, Peiffert D. Impact of 3D image-based
- 2941 PDR brachytherapy on outcome of patients treated for cervix carcinoma in France: results of the French STIC prospective study.
- 2942 *Radiother Oncol.* 2012 Jun;103(3):305-13.
- 2943
- 2944 Cancer Therapy Evaluation Program, Common Terminology Criteria for Adverse Events, Version 3.0, DCTD, NCI, NIH, DHHS March 31,
- 2945 2003 (<http://ctep.cancer.gov>), Publish Date: August 9, 2006.
- 2946
- 2947 Dimopoulos JC, Kirisits C, Petric P, Georg P, Lang S, Berger D, Pötter R. The Vienna applicator for combined intracavitary and interstitial
- 2948 brachytherapy of cervical cancer: clinical feasibility and preliminary results. *Int J Radiat Oncol Biol Phys.* 2006 Sep 1;66(1):83-90.
- 2949
- 2950 Dimopoulos JC, Petrow P, Tanderup K, Petric P, Berger D, Kirisits C, Pedersen EM, van Limbergen E, Haie-Meder C, Pötter R.
- 2951 Recommendations from Gynaecological (GYN) GEC-ESTRO Working Group (IV): Basic principles and parameters for MR imaging within
- 2952 the frame of image based adaptive cervix cancer brachytherapy. *Radiother Oncol.* 2012 Apr;103(1):113-22.
- 2953
- 2954 EMBRACE study. www.embracestudy.dk. (retrieved 28.09.2015).
- 2955
- 2956 European Organisation for Research and Treatment of Cancer (EORTC). www.eortc.be. (retrieved 28.09.2015).
- 2957
- 2958 Fayers PM, Aaronson NK, Bjordal K et al., on behalf of the EORTC Quality of Life Group. The EORTC QLQ-C30 Scoring Manual (3rd
- 2959 Edition). Published by: European Organisation for Research and Treatment of Cancer, Brussels 2001.
- 2960
- 2961 Ferrandina G, Gambacorta A, Gallotta V, Smaniotto D, Fagotti A, Tagliaferri L, Foti E, Fanfani F, Autorino R, Scambia G, Valentini V.
- 2962 Chemoradiation with concomitant boosts followed by radical surgery in locally advanced cervical cancer: long-term results of the
- 2963 ROMA-2 prospective phase 2 study. *Int J Radiat Oncol Biol Phys.* 2014 Nov 15;90(4):778-85.
- 2964
- 2965 Fokdal L, Tanderup K, Hokland SB, Røhl L, Pedersen EM, Nielsen SK, Paludan M, Lindegaard JC. Clinical feasibility of combined
- 2966 intracavitary/interstitial brachytherapy in locally advanced cervical cancer employing MRI with a tandem/ring applicator in situ and
- 2967 virtual replanning of the interstitial component. *Radiother Oncol.* 2013 Apr;107(1):63-8.
- 2968
- 2969 Forrest J, Presutti J, Davidson M, Hamilton P, Kiss A, Thomas G. A dosimetric planning study comparing intensity-modulated
- 2970 radiotherapy with four-field conformal pelvic radiotherapy for the definitive treatment of cervical carcinoma. *Clin Oncol (R Coll Radiol).*
- 2971 2012 May;24(4):e63-70.
- 2972

2973 Fortin I. Distant Metastases in Locally Advanced Cervical Cancer Pattern of Relapse and Prognostic Factors: Early Results From the
2974 EMBRACE Study. Abstract ASTRO 2015.
2975

2976 Georg P, Pötter R, Georg D, Lang S, Dimopoulos JC, Sturdza AE, Berger D, Kirisits C, Dörr W. Dose effect relationship for late side effects
2977 of the rectum and urinary bladder in magnetic resonance image-guided adaptive cervix cancer brachytherapy. *Int J Radiat Oncol Biol*
2978 *Phys.* 2012 Feb 1;82(2):653-7.
2979

2980 Gibson RJ, Bowen JM. Biomarkers of regimen-related mucosal injury. *Cancer Treat Rev.* 2011 Oct;37(6):487-93.
2981

2982 Greimel ER, Kuljanic Vlasic K, Waldenstrom AC, Duric VM, Jensen PT, Singer S, Chie W, Nordin A, Bjelic Radisic V, Wydra D; European
2983 Organization for Research and Treatment of Cancer Quality-of-Life Group. The European Organization for Research and Treatment of
2984 Cancer (EORTC) Quality-of-Life questionnaire cervical cancer module: EORTC QLQ-CX24. *Cancer.* 2006 Oct 15;107(8):1812-22.
2985

2986 Greimel E, Nordin A, Lanceley A, Creutzberg CL, van de Poll-Franse LV, Radisic VB, Galalae R, Schmalz C, Barlow E, Jensen PT,
2987 Waldenström AC, Bergmark K, Chie WC, Kuljanic K, Costantini A, Singer S, Koensgen D, Menon U, Daghofer F; EORTC Quality of Life
2988 Group. Psychometric validation of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-
2989 Endometrial Cancer Module (EORTC QLQ-EN24). *Eur J Cancer.* 2011 Jan;47(2):183-90.
2990

2991 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,
2992 Nevinson J, Nulens A, Petrow P, Wachter-Gerstner N; Gynaecological (GYN) GEC-ESTRO Working Group. Recommendations from
2993 Gynaecological (GYN) GEC-ESTRO Working Group (I): concepts and terms in 3D image based 3D treatment planning in cervix cancer
2994 brachytherapy with emphasis on MRI assessment of GTV and CTV. *Radiother Oncol.* 2005 Mar;74(3):235-45. Review.
2995

2996 Heijkoop ST, Langerak TR, Quint S, Bondar L, Mens JW, Heijmen BJ, Hoogeman MS. Clinical implementation of an online adaptive plan-
2997 of-the-day protocol for nonrigid motion management in locally advanced cervical cancer IMRT. *Int J Radiat Oncol Biol Phys.* 2014 Nov
2998 1;90(3):673-9.
2999

3000 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;
3001 Gynaecological (GYN) GEC-ESTRO Working Group. Recommendations from Gynaecological (GYN) GEC-ESTRO Working Group:
3002 considerations and pitfalls in commissioning and applicator reconstruction in 3D image-based treatment planning of cervix cancer
3003 brachytherapy. *Radiother Oncol.* 2010 Aug;96(2):153-60.
3004

3005 Henson CC, Ang YS. Biomarkers of normal tissue toxicity after pelvic radiotherapy. *Curr Opin Support Palliat Care.* 2012 Mar;6(1):33-40.
3006

3007 Hille A, Rave-Fränk M, Christiansen H, Herrmann MK, Kertesz T, Hermann RM, Wolff HA, Schirmer M, Hess CF, Ramadori G. Faecal
3008 calprotectin and lactoferrin values during irradiation of prostate cancer correlate with chronic radiation proctitis: results of a
3009 prospective study. *Scand J Gastroenterol.* 2009;44(8):939-46.
3010

3011 ICRU. Prescribing, Recording and Reporting Brachytherapy for Cancer of the Cervix. ICRU Report 88. 2015, in press.
3012

3013 Jadon R, Pembroke CA, Hanna CL, Palaniappan N, Evans M, Cleves AE, Staffurth J. A systematic review of organ motion and image-
3014 guided strategies in external beam radiotherapy for cervical cancer. *Clin Oncol (R Coll Radiol).* 2014 Apr;26(4):185-96.
3015

3016 Jensen NBK, Nyvang L, Assenholt MS, Vestergaard A, Ramlov A, Lindegaard JC, Fokdal L, Tanderup K. EP-1515: Evaluation of organ
3017 motion and uterine dose summation for IMRT in locally advanced cervical cancer. *Radiother Oncol.* 2015 April;115(1): 826-827.
3018

3019 Johnson CH, Patterson AD, Krausz KW, Kalinich JF, Tyburski JB, Kang DW, Luecke H, Gonzalez FJ, Blakely WF, Idle JR. Radiation
3020 metabolomics. 5. Identification of urinary biomarkers of ionizing radiation exposure in nonhuman primates by mass spectrometry-
3021 based metabolomics. *Radiat Res.* 2012 Oct;178(4):328-40.
3022

3023 Jürgenliemk-Schulz IM, Tersteeg RJ, Roesink JM, Bijmolt S, Nomden CN, Moerland MA, de Leeuw AA. MRI-guided treatment-planning
3024 optimisation in intracavitary or combined intracavitary/interstitial PDR brachytherapy using tandem ovoid applicators in locally
3025 advanced cervical cancer. *Radiother Oncol.* 2009 Nov;93(2):322-30.
3026
3027

3028 Keys HM, Bundy BN, Stehman FB, Muderspach LI, Chafe WE, Suggs CL 3rd, Walker JL, Gersell D. Cisplatin, radiation, and adjuvant
3029 hysterectomy compared with radiation and adjuvant hysterectomy for bulky stage IB cervical carcinoma. *N Engl J Med.* 1999 Apr
3030 15;340(15):1154-61.
3031
3032 Kidd EA, Siegel BA, Dehdashti F, Grigsby PW. Pelvic lymph node F-18 fluorodeoxyglucose uptake as a prognostic biomarker in newly
3033 diagnosed patients with locally advanced cervical cancer. *Cancer.* 2010 Mar 15;116(6):1469-75.
3034
3035 Kirchheiner K, Nout RA, Tanderup K, Lindegaard JC, Westerveld H, Haie-Meder C, Petrič P, Mahantshetty U, Dörr W, Pötter R.
3036 Manifestation pattern of early-late vaginal morbidity after definitive radiation (chemo)therapy and image-guided adaptive
3037 brachytherapy for locally advanced cervical cancer: an analysis from the EMBRACE study. *Int J Radiat Oncol Biol Phys.* 2014 May
3038 1;89(1):88-95.
3039
3040 Kirchheiner K, Nout RA, Lindegaard JC, Haie-Meder C, Mahantshetty U, Petrič P, Jürgenliemk-Schulz IM, Hoskin PJ, Rai B, Dörr W, Kirisits
3041 C, Bentzen SM, Pötter R, Tanderup K. Dose effect relationship and risk factors for vaginal stenosis after definitive radio(chemo)therapy
3042 with image-guided brachytherapy for locally advanced cervical cancer in the EMBRACE study. In submission *Radioth Oncol* 2015.
3043
3044 Kirisits C, Lang S, Dimopoulos J, Berger D, Georg D, Pötter R. The Vienna applicator for combined intracavitary and interstitial
3045 brachytherapy of cervical cancer: design, application, treatment planning, and dosimetric results. *Int J Radiat Oncol Biol Phys.* 2006 Jun
3046 1;65(2):624-30.
3047
3048 Kirisits C, Lang S, Dimopoulos J, Oechs K, Georg D, Pötter R. Uncertainties when using only one MRI-based treatment plan for
3049 subsequent high-dose-rate tandem and ring applications in brachytherapy of cervix cancer. *Radiother Oncol.* 2006 Dec;81(3):269-75.
3050
3051 Kirisits C, Rivard MJ, Baltas D, Ballester F, De Brabandere M, van der Laarse R, Niatsetski Y, Papagiannis P, Hellebust TP, Perez-Calatayud
3052 J, Tanderup K, Venselaar JL, Siebert FA. Review of clinical brachytherapy uncertainties: analysis guidelines of GEC-ESTRO and the AAPM.
3053 *Radiother Oncol.* 2014 Jan;110(1):199-212.
3054
3055 Koom WS, Sohn DK, Kim JY, Kim JW, Shin KH, Yoon SM, Kim DY, Yoon M, Shin D, Park SY, Cho KH. Computed tomography-based high-
3056 dose-rate intracavitary brachytherapy for uterine cervical cancer: preliminary demonstration of correlation between dose-volume
3057 parameters and rectal mucosal changes observed by flexible sigmoidoscopy. *Int J Radiat Oncol Biol Phys.* 2007 Aug 1;68(5):1446-54.
3058
3059 Lacombe J, Solassol J, Coelho M, Ozsahin M, Azria D. [Interest of blood markers in predicting radiation-induced toxicity]. *Cancer*
3060 *Radiother.* 2011 Aug;15(5):390-3.
3061
3062 Laursen LV, Elstrøm UV, Vestergaard A, Muren LP, Petersen JB, Lindegaard JC, Grau C, Tanderup K. Residual rotational set-up errors
3063 after daily cone-beam CT image guided radiotherapy of locally advanced cervical cancer. *Radiother Oncol.* 2012 Nov;105(2):220-5.
3064
3065 Lim K, Kelly V, Stewart J, Xie J, Cho YB, Moseley J, Brock K, Fyles A, Lundin A, Rehbinder H, Milosevic M. Pelvic radiotherapy for cancer of
3066 the cervix: is what you plan actually what you deliver? *Int J Radiat Oncol Biol Phys.* 2009 May 1;74(1):304-12.
3067
3068 Lindegaard JC, Fokdal LU, Nielsen SK, Juul-Christensen J, Tanderup K. MRI-guided adaptive radiotherapy in locally advanced cervical
3069 cancer from a Nordic perspective. *Acta Oncol.* 2013 Oct;52(7):1510-9.
3070
3071 Lutgens LC, Deutz NE, Gueulette J, Cleutjens JP, Berger MP, Wouters BG, von Meyenfeldt MF, Lambin P. Citrulline: a physiologic marker
3072 enabling quantitation and monitoring of epithelial radiation-induced small bowel damage. *Int J Radiat Oncol Biol Phys.* 2003 Nov
3073 15;57(4):1067-74.
3074
3075 Mazon R, Dumas I, Rivin E, Martin V, Benhabib-Boukhelif W, Tailleur A, Guemnie-Tafo A, Martinetti F, Chargari C, Lefkopoulos D, Haie-
3076 Meder C. D2cm³/DICRU ratio as a surrogate of bladder hotspots localizations during image-guided adaptive brachytherapy for cervical
3077 cancer: assessment and implications in late urinary morbidity analysis. *Brachytherapy.* 2015 Mar-Apr;14(2):300-7.
3078
3079 Mohamed S, Lindegaard JC, de Leeuw A, Jürgenliemk-Schulz IM, Pötter R, Kirisits C, Tanderup K. Brachytherapy vaginal dose de-
3080 escalation in locally advanced cervical cancer. In submission *Radioth Oncol* 2015.
3081

3082 Mohamed SM, Aagaard T, Fokdal LU, Pedersen EM, Lindegaard JC, Tanderup K. Assessment of radiation doses to the para-aortic, pelvic,
3083 and inguinal lymph nodes delivered by image-guided adaptive brachytherapy in locally advanced cervical cancer. *Brachytherapy*. 2015
3084 Jan-Feb;14(1):56-61.

3085

3086 Mundt AJ, Mell LK, Roeske JC. Preliminary analysis of chronic gastrointestinal toxicity in gynecology patients treated with intensity-
3087 modulated whole pelvic radiation therapy. *Int J Radiat Oncol Biol Phys*. 2003 Aug 1;56(5):1354-60.

3088

3089 National Cancer Institute. Common Terminology Criteria for Adverse Events v3.0. NCI, NIH, DHHS. March 31, 2003

3090

3091 National Cancer Institute. Common Terminology Criteria for Adverse Events v4.0. NCI, NIH, DHHS. May 29, 2009

3092

3093 Nkiwane KS, Pötter R, Tanderup K, Federico M, Lindegaard JC, Kirisits C. Single line source with and without vaginal loading and the
3094 impact on target coverage and organ at risk doses for cervix cancer Stages IB, II, and IIIB: treatment planning simulation in patients
3095 treated with MRI-guided adaptive brachytherapy in a multicentre study (EMBRACE). *Brachytherapy*. 2013 Jul-Aug;12(4):317-23

3096

3097 Nkiwane KS, Pötter R, Fokdal LU, Hoskin P, Pearcey R, Segedin B, Mahantshetty U, Kirisits C. Use of bladder dose points for assessment
3098 of the spatial dose distribution in the posterior bladder wall in cervical cancer brachytherapy and the impact of applicator position.
3099 *Brachytherapy*. 2015 Mar-Apr;14(2):252-9.

3100

3101 Onal C, Kotek A, Unal B, Arslan G, Yavuz A, Topkan E, Yavuz M. Plasma citrulline levels predict intestinal toxicity in patients treated with
3102 pelvic radiotherapy. *Acta Oncol*. 2011 Nov;50(8):1167-74.

3103

3104 Onal C, Guler OC, Reyhan M, Yapar AF. Prognostic value of 18F-fluorodeoxyglucose uptake in pelvic lymph nodes in patients with
3105 cervical cancer treated with definitive chemoradiotherapy. *Gynecol Oncol*. 2015 Apr;137(1):40-6.

3106

3107 Pearcey R, Brundage M, Drouin P, Jeffrey J, Johnston D, Lukka H, MacLean G, Souhami L, Stuart G, Tu D. Phase III trial comparing radical
3108 radiotherapy with and without cisplatin chemotherapy in patients with advanced squamous cell cancer of the cervix. *J Clin Oncol*. 2002
3109 Feb 15;20(4):966-72.

3110

3111 Petric P, Hudej R, Marolt-Mušič M. MRI assisted cervix cancer brachytherapy pre-planning, based on insertion of the applicator in para-
3112 cervical anaesthesia: preliminary results of a prospective study. *J Contemp Brachyther*. 2009;1(3):163-169.

3113

3114 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,
3115 Rownd J, Kirisits C; GEC ESTRO Working Group. Recommendations from gynaecological (GYN) GEC ESTRO working group (II): concepts
3116 and terms in 3D image-based treatment planning in cervix cancer brachytherapy-3D dose volume parameters and aspects of 3D image-
3117 based anatomy, radiation physics, radiobiology. *Radiother Oncol*. 2006 Jan;78(1):67-77.

3118

3119 Pötter R, Dimopoulos J, Georg P, Lang S, Waldhäusl C, Wachter-Gerstner N, Weitmann H, Reinthaller A, Knocke TH, Wachter S, Kirisits C.
3120 Clinical impact of MRI assisted dose volume adaptation and dose escalation in brachytherapy of locally advanced cervix cancer.
3121 *Radiother Oncol*. 2007 May;83(2):148-55.

3122

3123 Pötter R, Georg P, Dimopoulos JC, Grimm M, Berger D, Nesvacil N, Georg D, Schmid MP, Reinthaller A, Sturdza A, Kirisits C. Clinical
3124 outcome of protocol based image (MRI) guided adaptive brachytherapy combined with 3D conformal radiotherapy with or without
3125 chemotherapy in patients with locally advanced cervical cancer. *Radiother Oncol*. 2011 Jul;100(1):116-23.

3126

3127 Ramlov A, Kroon PS, Jürgenliemk-Schulz IM, De Leeuw AA, Gormsen LC, Fokdal LU, Tanderup K, Lindegaard JC. Impact of radiation dose
3128 and standardized uptake value of (18)FDG PET on nodal control in locally advanced cervical cancer. *Acta Oncol*. 2015 Aug 14:1-7.
3129 RetroEMBRACE study. www.retroembrace.com (retrieved 28.09.2015)

3130

3131 Rose PG, Ali S, Whitney CW, Lanciano R, Stehman FB. Outcome of stage IVA cervical cancer patients with disease limited to the pelvis in
3132 the era of chemoradiation: a Gynecologic Oncology Group study. *Gynecol Oncol*. 2011 Jun 1;121(3):542-5.

3133

3134 Schmid MP, Franckena M, Kirchheiner K, Sturdza A, Georg P, Dörr W, Pötter R. Distant metastasis in patients with cervical cancer after
3135 primary radiotherapy with or without chemotherapy and image guided adaptive brachytherapy. *Gynecol Oncol*. 2014 May;133(2):256-
3136 62.

3137

3138 Shield PW. Chronic radiation effects: a correlative study of smears and biopsies from the cervix and vagina. *Diagn Cytopathol.* 1995
3139 Aug;13(2):107-19.
3140

3141 Tanderup K, Nielsen SK, Nyvang GB, Pedersen EM, Røhl L, Aagaard T, Fokdal L, Lindegaard JC. From point A to the sculpted pear: MR
3142 image guidance significantly improves tumour dose and sparing of organs at risk in brachytherapy of cervical cancer. *Radiother Oncol.*
3143 2010 Feb;94(2):173-80.
3144

3145 Tanderup K, Pötter R, Lindegaard JC, Berger D, Wambersie A, Kirisits C. PTV margins should not be used to compensate for uncertainties
3146 in 3D image guided intracavitary brachytherapy. *Radiother Oncol.* 2010 Dec;97(3):495-500.
3147

3148 The INTERLACE trial. [http://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-trial-of-chemotherapy-before-](http://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-trial-of-chemotherapy-before-chemoradiation-for-cervical-cancer-interlace)
3149 [chemoradiation-for-cervical-cancer-interlace](http://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-trial-of-chemotherapy-before-chemoradiation-for-cervical-cancer-interlace)
3150 (retrieved 28.09.2015)
3151

3152 The OUTBACK trial. <https://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?study=1174>
3153 (retrieved 28.09.2015)
3154

3155 Trnková P, Pötter R, Baltas D, Karabis A, Fidarova E, Dimopoulos J, Georg D, Kirisits C. New inverse planning technology for image-
3156 guided cervical cancer brachytherapy: description and evaluation within a clinical frame. *Radiother Oncol.* 2009 Nov;93(2):331-40.
3157 Varela E, Antolín M, Guarner F, Verges R, Giralt J, Malagelada JR. Faecal DNA and calprotectin as biomarkers of acute intestinal toxicity
3158 in patients undergoing pelvic radiotherapy. *Aliment Pharmacol Ther.* 2009 Jul 1;30(2):175-85.
3159

3160 Vargo JA, Kim H, Choi S, Sukumvanich P, Olawaiye AB, Kelley JL, Edwards RP, Comerci JT, Beriwal S. Extended field intensity modulated
3161 radiation therapy with concomitant boost for lymph node-positive cervical cancer: analysis of regional control and recurrence patterns
3162 in the positron emission tomography/computed tomography era. *Int J Radiat Oncol Biol Phys.* 2014 Dec 1;90(5):1091-8.
3163

3164 Verma J, Sulman EP, Jhingran A, Tucker SL, Rauch GM, Eifel PJ, Klopp AH. Dosimetric predictors of duodenal toxicity after intensity
3165 modulated radiation therapy for treatment of the para-aortic nodes in gynecologic cancer. *Int J Radiat Oncol Biol Phys.* 2014 Feb
3166 1;88(2):357-62.
3167

3168 Viswanathan AN, Kirisits C, Erickson BE, Pötter R. (Eds.). *Gynecologic Radiation Therapy. Novel Approaches to Image-Guidance and*
3169 *Management.* Springer-Verlag Berlin Heidelberg 2011.
3170

3171 Westerveld H, Pötter R, Berger D, Dankulchai P, Dörr W, Sora MC, Pötter-Lang S, Kirisits C. Vaginal dose point reporting in cervical
3172 cancer patients treated with combined 2D/3D external beam radiotherapy and 2D/3D brachytherapy. *Radiother Oncol.* 2013
3173 Apr;107(1):99-105.
3174

3175 Xu KM, Rajagopalan MS, Kim H, Beriwal S. Extended field intensity modulated radiation therapy for gynecologic cancers: Is the risk of
3176 duodenal toxicity high? *Pract Radiat Oncol.* 2015 Jul-Aug;5(4):e291-7.
3177