East of England Radiotherapy Network:

# Cervix Protocol V1.0

## Contents




UNCONTROLLED IF PRINTED
EofE RTN Cervix Protocol V1
Date Agreed: March 2024
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# 1.0 Indications and patient population

**This protocol covers treatment in the following situations:**

a. **Curative Radiotherapy** of biopsy proven Squamous carcinoma, adenocarcinoma or adeno-squamous carcinoma of the uterine cervix, FIGO Stage 1B, 2A, 2B ,3A, 3B, 3C, 4A [FIGO2018]

   This includes patients who are treated with chemo irradiation or radiotherapy as a single modality.

b. **Post –Operative Radiotherapy** of those patients who have had either:

   i. Previous radical surgical procedure-Hysterectomy or Trachelectomy
   ii. Incidental cervical cancer found in a hysterectomy for presumed benign disease
   iii. Cervical cancer in previous subtotal hysterectomy

   This includes patients treated with chemo irradiation or radiotherapy alone.

c. **Palliative Radiotherapy**

## 1.1 Curative treatment eligibility

### 1.1.1 Inclusion criteria

Biopsy proven squamous carcinoma, adenocarcinoma, adeno-squamous carcinoma of the uterine cervix, **FIGO [2018]** stage IA [If surgery is considered inappropriate] to Stage IV A

### 1.1.2 Exclusion criteria

Contra-indications to pelvic radiotherapy, e.g., prior radiotherapy treatment, significant inflammatory bowel disease

### 1.1.3 Essential Pre-Radiotherapy investigations for curative patients

**Bloods:** FBC U&E LFT eGFR

**Examination**: Outpatient or Examination Under Anaesthesia [EUA] Biopsy and pathological confirmation

**Imaging:** MRI pelvis. Whole body imaging: PET CT or CT of chest abdomen and pelvis

**It is assumed that each centre will have imaging protocols developed for initial staging and post treatment imaging protocols.**

## 2.0 Localisation

| Localisation | | Notes |
|---|---|---|
| Position | Supine | |
| Arm position | Hands on chest<br>Arms above head if PA nodes to be treated. | |
| Immobilisation and supports | Knee wedge and ankle stocks | |
| Organ pre-requisites | Comfortably full bladder<br><br>Empty bladder scan if using for ITV generation | Suggested drinking protocol if full: Void 1 hour before imaging and drink 300ml water/ clear fluid before CT/ treatment delivery |
| | Empty bowels | Bowels should be emptied before CT and treatment. Deflation or rescan should be considered if rectum diameter greater than 4cm.<br>Bowel preparation may be given prior to radiotherapy planning scan and treatment to ensure empty rectum, individual department protocols may vary. |
| Contrast | IV Contrast | Unless contra-indicated |
| CT acquisition | Slice thickness: 2-2.5mm<br>Sup scanning limits: Top of L3<br>Inf scanning limits: 2cm below ischium | Will need to increase superior scan limit to T8/T9 if para aortics are involved |
| Examination | Gynaecological examination preferably with diagrammatic documentation. | |

| | | |
|---|---|---|
| MRI | Planning MRI or use diagnostic MRI for planning (with or without co-registration) | |

## 3.0 Dose prescription & chemotherapy

| Intent | Dose (Gy)/# | #/week | Chemo/ comments |
|---|---|---|---|
| a. Curative Radiotherapy | 45Gy/25# | 5 | EBRT + concomitant cisplatin + HDR brachytherapy boost (as per EMBRACE II)<br>Or EBRT 45Gy/25# + Vault HDR brachytherapy boost<br>Use of brachytherapy will be defined in HDR Gynae Brachytherapy ODN protocol) |
| | 45Gy/25# with integrated boost of 57.5Gy to involved nodes outside true pelvis) | 5 | |
| | 45Gy/25# with integrated boost of 55Gy to involved nodes inside true pelvis) | 5 | |
| b. Post-operative Radiotherapy | 45Gy/25# | | If unable/unsuitable to receive brachytherapy<br>EBRT + concomitant cisplatin |
| | 45Gy/25# with integrated boost of 60Gy to involved nodes | 5 | |
| | 45Gy/25# + PH2 20Gy/10# | 5 | EBRT + concomitant cisplatin<br>Sequential EBRT boost to primary target following 45Gy/25# e.g. when brachytherapy fails. Boost may be reduced within the range 10-20Gy/5-10# to spare OARs |
| | 50.4Gy/28# | 5 | If unable/unsuitable to receive brachytherapy<br>EBRT + concomitant cisplatin |
| | 50.4Gy/28# with integrated boost of 60Gy to involved nodes | 5 | |
| | 45Gy/25# + PH2 5.3Gy/3# | 5 | |
| | 64Gy/32# to high dose primary disease, 60Gy to involved nodes, 50Gy to low dose primary and elective nodes | 5 | If unable to receive brachytherapy or chemotherapy |
| c. Palliative Radiotherapy | 8Gy/1# | 1 | |
| | 20Gy/5# | 5 | |
| | 30Gy/10# | 5 | |

**N.B For recurrence: dose should be considered as appropriate on a patient-by-patient basis, taking into consideration previous treatment delivered. This should be discussed at MDT.**

## 4.0 Target volumes

XXXX is prescription in cGy

### 4.1 Primary target volumes

GTVp_XXXX - Gross Tumour Volume of the primary tumour e.g. GTV inside and outside the cervix and as a minimum the whole cervix
GTVn_XXXX - Gross Tumour Volume of individual pathological involved lymph node

CTVp_XXXX - GTV (if present) + paracervical and parametrial tissues.

CTVn_XXXX - GTVn + 0-3 mm - Clinical Target Volume of individual pathologic lymph nodes;

### 4.2 Elective Nodal target volumes

CTVe_XXXX = Clinical Target Volume of the elective nodal region, including pathological lymph nodes if present. Contour according to the assumed risk of microscopic nodal involvement as per the Table below. If there are meso-rectal lymph nodes present then whole of the meso-rectum should be included as part of the CTV_E.
if lower 1/3 of vagina is involved include the inguinal nodes, these may be contoured separately.

| Risk Group IN | Definition | EBRT Lymph node regions |
|---|---|---|
| Low Risk (LR LN) | Tumour size <4cm<br>AND Stage 1A/1B1/11A2<br>AND N0<br>AND Squamous cell carcinoma<br>AND no uterine invasion | **"Small Pelvis"**<br>Internal Iliac<br>External Iliac<br>Obturator<br>Pre-sacral |
| Intermediate Risk (IR LN) | Not low risk<br>No high-risk features | **"Large Pelvis"**<br>Nodes included in "Small Pelvis" and common iliac region (including the aortic bifurcation).<br>In addition:<br>• inguinal in case of distal vaginal involvement. |

| Risk Group IN | Definition | EBRT Lymph node regions |
|---|---|---|
| | | • Mesorectal space in case of mesorectal nodes and advanced local disease |
| High Risk (HR LN) | Based on nodal pathology<br>• >1 pathologic node at common iliac or above<br>• OR ≥3 pathologic nodes | "**Large Pelvis + Para-aortic"**<br>Nodes included in "Large Pelvis" and para-aortic region with the upper border of CTV minimum at the level of renal veins (Usually INC 12) and at least 3cm cranial of the highest pathological node in case of para-aortic nodes) |

*As per EMBRACE II

## 4.3 ITV

Use of an ITV is highly recommended for curative/adjuvant radiotherapy. There are several options for creation of ITV, "Basic ITV" using geometric expansion, "Intermediate ITV" using variable bladder filling planning CT/MR scans and diagnostic images or "Advanced ITV" using Plan of the Day. The strategy to derive ITV will be according to local protocols.

The "Basic ITV" method is detailed here.

- ITVp_XXXX= CTVp with following margins
  - 10 mm Ant-post
  - 10 mm Sup-Inf
  - 5 mm lateral
  - No additional margin, distal vagina [along vaginal axis] i.e., delete inferior slices of ITV up to CTV
  - Manual adaptation at muscle and bone
  - *An extra 5mm in all directions in area of uterine body involvement*
- **ITVpe_XXXX** = ITVp_XXXX + CTVe_XXXX

## 4.3 Curative / adjuvant radiotherapy PTV

ITV method

- PTVpe_XXXX = ITV_XXXX + 5 mm
- PTVn_XXXX = CTVn_XXXX + 5 mm

If no ITV generated

- PTVp_XXXX = CTVp_ XXXX + 10-15 mm
- PTVe_XXXX = CTVe_XXXX + 5-7 mm
- PTVn_XXXX = CTVn_XXXX + 5 mm

### 4.4 Palliative radiotherapy

VOI defined for Simple planning e.g. virtual simulation parallel opposed.

For 3D conformal/IMRT/VMAT contouring margins will depend on disease and technique used by treating centre. Suggested palliative margins are below or use as per local department protocol. Consider using radical contouring if appropriate.

GTVp_XXXX = All gross disease

PTVp_XXXX = GTVp_XXXX + 5-20 mm.

## 5.0 Organs at risk

- Aim for the use of standard nomenclature as per Global Harmonization Group consensus guidelines: https://www.thegreenjournal.com/action/showPdf?pii=S0167-8140%2820%2930294-2

| Structure name | Description |
|---|---|
| Bladder | Whole organ including the bladder neck |
| Rectum | From the ano-rectal sphincter to recto-sigmoid junction |
| Colon_Sigmoid | From recto-sigmoid junction to the left iliac fossa |
| Bowel | Outer contour of bowel loops including the peritoneum. Colon_Sigmoid may be included in Bowel if not reported separately |
| FemurHeadNeck_L and FemurHeadNeck_R | Both femoral head and neck to the level of the trochanter min |
| For para-aortic irradiation also include: | |
| Kidney_L and Kidney_R Kidneys | Outer contour excluding renal pelvis |
| SpinalCord | Outer contour |
| Optional (if para-aortic RT above L1 is applied): | |
| Duodenum | Whole organ |
| Ovary_L and Ovary_R (in cases of ovarian transposition) | Outer contour |

## 5.1 Planning structures

For patients being planned for external beam with a brachytherapy boost, extra planning structures are required.

CTV_HR - High Risk Clinical Target Volume of the primary tumour which will be boosted with HDR brachytherapy

CTV_HR_Eval – CTV_HR + 10mm cropped back 10-15mm from PTVn

OAR_Eval – OARs cropped back 10-15mm from PTVn

PTV_4500_Eval - PTV_4500 cropped back 10mm from PTVn

## 5.2 Constraints

### 45Gy/ 25# without LN boost

| | Structure Name | Mandatory | Optimal |
|---|---|---|---|
| **Targets** | PTV_4500 | V42.75Gy >95%<br>D0.1cc <107% | V42.75Gy = 95% |
| | ITV_4500 | D99.9% >95% | |
| **Help contour** | CTV_HR_10mm_Eval | | D0.1cc <103% |
| **OARs** | Bowel | D0.1cc <105% | When no lymph node boosts:<br>• V40Gy<250cm$^3$<br>• V30Gy<500cm$^3$ |
| | Colon_Sigmoid | D0.1cc <105% | |
| | Bladder | D0.1cc <105% | V40Gy <60%<br>V30Gy <85% |
| | Rectum | D0.1cc <105% | V40Gy <75%<br>V30Gy <95% |
| | SpinalCord | D0.1cc <48Gy | |
| | FemurHeadNeck_L and FemurHeadNeck_R | D0.1cc <50Gy | |
| | Kidney | Dmean <15Gy | Dmean <10Gy |
| | Body | D0.1cc <107% | |
| **Optional** | Ovary_L or Ovary_R (in cases of ovarian transposition) | <5-8 Gy | |
| | Duodenum | V55<15cm$^3$ | |

Dmin = D99.9%, Dmax=D0.1cc

*Optimal constraints which can be used in the treatment plan optimisation. Values are based on the clinical data of EMBRACEII patients entered in the study before June 2017. The constraints are not supposed to be fulfilled by all patients, but rather by ~70-80% of the patients.

### 45Gy/ 25# with LN boost

| | Structure Name | Mandatory | Optimal |
|---|---|---|---|
| **Targets** | PTV_4500_Eval | V42.75Gy>95% | V42.75Gy = 95%<br>Dmax >107% |
| | ITV_4500 | D99.9% >42.75Gy | |
| | PTVn_XXXX | D98% >90% of prescribed LN dose<br>D0.1cc <107% of prescribed LN dose | D98%=90% of prescribed LN dose |
| | CTVn_XXXX | D98% >100%<br>Of prescribed LN dose | D50% >102% |
| **Help contour** | CTV_HR_Eval | | Dmax <103% |
| **OARs** | Bowel_Eval | D0.1cc <105% (47.3Gy)* | When lymph node boost or para-aortic irradiation:<br>• V40Gy<300cm$^3$<br>• V30Gy<650cm$^3$<br>D0.1cc <57.5Gy |
| | Colon_Sigmoid_Eval | D0.1cc <105% (47.3Gy)* | D0.1cc <57.5Gy |
| | Bladder_Eval | D0.1cc <105% (47.3Gy)* | V40Gy <60%<br>V30Gy <85%<br>D0.1cc <57.5Gy |
| | Rectum_Eval | D0.1cc <105% (47.3Gy)* | V40Gy <75%<br>V30Gy <95%<br>D0.1cc <57.5Gy |
| | SpinalCord | D0.1cc <48Gy | |
| | FemurHeadNeck_L and FemurHeadNeck_R | D0.1cc <50Gy | |
| | Kidney_L and Kidney_R | Dmean <15Gy | Dmean <10Gy |
| | Body_Eval | D0.1cc <107%* | |
| **Optional** | Ovary_L or Ovary_R (in cases of ovarian transposition) | <5-8 Gy | |
| | Duodenum | V55<15cm$^3$ | |

Dmin = D99.9%, Dmax=D0.1cc
* Percentages of 45Gy unless otherwise stated for nodes.

Optimal constraints can be used in the treatment plan optimisation. Values are based on the clinical data of EMBRACEII patients entered in the study before June 2017. The constraints are not supposed to be fulfilled by all patients, but rather by ~70-80% of the patients.

### 64Gy/32#

No available OAR tolerances for 64Gy/32# gynaecological cancers.

In lieu of tolerances – recommendation to keep OARs as low as reasonable practicable while achieving PTV V95%>=95% coverage.

Use of IMPART bladder cancer trial for 64Gy/32# Rectum and Bowel doses, POPs prostate bed trial for 66Gy/33# Bladder doses and INTERLACE trial for Kidney doses can be used as sensible start point for planning aims.

| Organ | Lower priority Planning Aim | Higher priority Planning Aim |
|---|---|---|
| **PTV** | V0.1cc<105% | V95%>=95%<br>V0.1cc<107% |
| **PTVn** | | V98%>=90%<br>V0.1cc<107% |
| **Rectum** | V65Gy <0.1cc | V30Gy <80%<br>V50Gy <60%<br>V60Gy <50%<br>V65Gy <30% |
| **Bowel (including Sigmoid)** | V45Gy <139cc<br>V50Gy <122cc<br>V65Gy <0.1cc | V45Gy <209cc<br>V50Gy <183cc<br>V55Gy <105cc<br>V60Gy <84cc<br>V65Gy <26cc |
| **Bladder** | V50Gy <50%<br>V60Gy <25%<br>V65Gy <0.1cc | V65Gy<50% |
| **Kidney_R and Kidney_L** | V15Gy ≤ 25% | Mean <18Gy |

## 6.0 Planning process/ technique

- All EBRT treatment is IMRT/ VMAT/ Tomotherapy with inverse plan optimisation.
- Plan of the day may be used.
- Conformal or simple field arrangements can be used for palliative treatments.
- For brachytherapy see ODN Cervix Brachytherapy protocol

For Patients who were intending to have brachytherapy but brachytherapy was subsequently not been possible e.g. due to failed/unsuitable insertion or due to limited capacity of brachytherapy service.

- A 'replanning' CT scan must be performed expeditiously (after any applicators have been removed, if inserted) to minimise any gap from conclusion of delivered EBRT.
- It is expected that the planning CT will be done with intravenous contrast and follow all protocols defined in the initial PH1 planning scan

## 7.0 Peer Review/ Contour QA

- All curative volumes should aim to be prospectively peer reviewed.
- A description of the contouring (planning note) and of the peer review process including changes made should be saved in the patient record.
- The peer review process and outcomes should be audited.

## 8.0 Target verification

Daily 3D CBCT and action for adaptive measures.

3D Soft tissue verification (daily if 3D CBCT) **

| Modality | Frequency | Match point | Additional information |
|---|---|---|---|
| CBCT | Daily CBCT | Bony match using ROI/clipbox placed around the pelvis. Radiographers should perform a visual match of the structures within the PTVs and OAR check. Manual adjustments or subsequent soft tissue match to be made if required, but ensuring nodal targets still sufficiently covered. The match should be verified on all planes. | Check external contour and report to physics if changes greater than 1cm.<br><br>If all CTVs cannot be achieved within PTVs then plan must be referred for CBCT review and adaptive action may be taken if persists. |

# 9 Side effects

| 9.1 Possible early or short-term side-effects | |
|---|---|
| **Expected (50-100%)** | **Initial Management (if appropriate)** |
| Tiredness | Rest when required<br>Light exercise |
| Mild Pelvic Pain | Appropriate pain medication (paracetamol/ibuprofen) |
| Urinary Frequency | Decrease caffeine |
| Bowel Frequency | Low Fibre diet |
| Vaginal Itching, discharge or light bleeding (spotting) | Emollient |
| Discomfort from prolonged bed rest | |
| | |
| **Common (10-50%)** | **Management (if appropriate)** |
| Cystitis/pain when you urinate | Drink plenty of fluids<br>Paracetamol<br>MSU |
| Urinary incontinence | Incontinence pads |
| Rectal Pain/discomfort | Instilagel<br>Paracetamol |
| **Less common (Less than 10%)** | **Management (if appropriate)** |
| Looser Stools | Low fibre diet<br>Loperamide<br>Codeine phosphate |
| Skin Soreness, itching and redness | Moisturising<br>Emollient |
| Bleeding from your Bladder or bowel | |
| Moderate pelvic pain | Appropriate pain medication (paracetamol/ibuprofen) |
| **Rare (Less than 1%)** | **Management (if appropriate)** |
| Heavy Bleeding | Tranexamic acid |
| Infection | Antibiotics |
| Risk of developing symptomatic blood clot | Completion of TRA |
| Risk of pressure sore | Appropriate dressings |

| 9.2 Possible late or long-term side-effects | |
|---|---|
| **Definite 100%** | **Initial Management (if appropriate)** |
| Early menopause | |
| Infertility | |
| **Expected 50%-100%** | **Initial Management (if appropriate)** |
| Vaginal narrowing, shortening or dryness | Use of vaginal dilators |
| **Common (10-50%)** | **Initial Management (if appropriate)** |
| Urinary frequency | Pelvic floor exercises |
| Urinary incontinence | Incontinence pad<br>Pelvic floor exercises |
| Bowel frequency | Low fibre diet |
| Looser Stools | Low fibre diet<br>Loperamide<br>Codeine phosphate |
| **Less common (Less than 10%)** | **Management (if appropriate)** |
| Cystitis/pain when you urinate | Drink plenty of fluids<br>Paracetamol<br>MSU |
| Rectal pain/discomfort | Instilagel<br>Paracetamol |
| Bleeding from your bladder, bowel or vagina | |
| Bowel/bladder damage which may require surgery | |
| **Rare (Less than 1%)** | **Management (if appropriate)** |
| A different cancer in the treatment area | |

## 10.0 References

Embrace II dose prescription protocol v1.0 - https://www.embracestudy.dk

Tan et al. The Intensity-Modulated Pelvic Node and Bladder Radiotherapy (IMPART) Trial: A Phase II Single-Centre Prospective Study. Clin Onc 32 (2020) 93-100.

POPS trial Protocol V7.1 - A randomised phase II trial assessing Post-Operative use of ProSpare™, a rectal obturator in prostate cancer radiotherapy

INTERLACE: A phase III multicenter trial of weekly induction chemotherapy followed by standard chemoradiation versus standard chemoradiation alone in patients with locally advanced cervical cancer

## 11.0 Members of the protocol drafting committee

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## 12.0 Amendment History

A record of changes in this document

| Date | Updated version number | Previous version number | Page Number/ Section (updated version) | Details |
|---|---|---|---|---|
| | V1.0 | | | New Document |
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