Dokument	AA	Gültig ab	15. 12. 2024	Version	2.0
Erlassen durch	Prof. Guckenberger	ErstellerIn	P. Petric	Ersetzt	1.0
Geltungsbereich	Klinik für Radioonkologie	Dateiname	06_02_04_EBRT_Cervixkarzinom_2024.09.12		

Cervixkarzinom - definitive EBRT

ABBREVIATIONS	
EBRT	External Beam RadioTherapy
ChT	Chemotherapy
OS, DFS, LR-DFS, LC	Survival rates (overall, disease-free, locoregional, local control)
IGABT	Image guided adaptive brachytherapy
LVSI	Lymphovascular space invasion
ChRT	Chemoradiation
M	Metastases
SIB	Simultaneous integrated boost
D	Dose
VMAT	Volumetric modulated arc therapy
CBCT	Cone beam computed tomography
OTT	Overall treatment time
AUC	Area under curve
EQD2	Equivalent Dose in 2 Gy per fraction

PATIENT GROUP

<u>This covers treatment of patients with:</u>

1. Histologically verified non-metastatic & oligometastatic cancer.
2. Squamous cell-, adeno-squamous- or adeno-carcinoma histology.
3. Treatment decision by multidisciplinary tumor board.
4. Signed informed consent to treatment.

<u>This doesn`t cover treatment of patients with:</u>

1. Direct or metastatic spread of other tumor to the cervix.
2. Sarcoma, small cell carcinoma and other non-epithelial histologies.
3. Contraindications for pelvic RT.

PRE-TREATMENT WORKUP	Reference

1. General examination 2. Gynecological examination +/- colposcopy o Documentation & clinical drawing 3. Pathological confirmation of 1° tumor. 4. Imaging: o Pelvic MRI & PET-CT or o Pelvic MRI & CT of thorax, abdomen or o PET-MRI. o US optional. 2. Rectoscopy if clinical or imaging suspicion of rectal invasion. 3. Cystoscopy if clinical or imaging suspicion of bladder invasion. 4. Para-aortic nodal dissection (considered) in imaging-negative para-aortic lymph nodes. 5. Debulking of suspicious pelvic lymph nodes not recommended. 6. *Recording*: TNM, FIGO stage, T-score, drawings, staging methods.	The European Society of Gynaecological Oncology/European Society for Radiotherapy and Oncology/European Society of Pathology Guidelines for the Management of Patients With Cervical Cancer | International Journal of Gynecologic Cancer (bmj.com) cervical.pdf (nccn.org) Revised FIGO staging for carcinoma of the cervix uteri - Bhatla - 2019 - International Journal of Gynecology & Obstetrics - Wiley Online Library https://www.leitlinienprogramm-onkologie.de/fileadmin/user_upload/Downloads/Leitlinien/Zervixkarzinom/LL_Zervixkarzinom_Langversion_1.0.pdf

TREATMENT ACCORDING TO STAGE	
STAGES IA1, IA2, IB1, IB2, IIA1	
Evidence	Reference
• Surgery vs. EBRT + conventional BT: Randomized phase 3 trial: no significant difference in OS, DFS & morbidity between EBRT without chemotherapy + conventional BT versus surgery for stage IB-IIA. Trend for inferiority of RT in adenocarcinoma. Morbidity worst after surgery and postoperative radiotherapy.	Randomized study between radical surgery and radiotherapy for the treatment of stage IB–IIA cervical cancer: 20-year update (nih.gov)
• Concomitant ChT: Meta-analysis of individual patient data, 18 randomized trials: Addition of ChT to EBRT + conventional BT offers a modest, but significant benefit on OS, DFS, LR-DFS, M, and time to locoregional recurrence/progression. Effect in all stages with a trend for a higher benefit in 1A-IIA. Positive impact on time to metastases was smaller.	Reducing Uncertainties About the Effects of Chemoradiotherapy for Cervical Cancer: A Systematic Review and Meta-Analysis of Individual Patient Data From 18 Randomized Trials | Journal of Clinical Oncology (ascopubs.org)

• ChRT + IGABT: retroEMBRACE stage I study: ChRT + IGABT in T1b1, T1b2 leads to excellent 5-year LC (98%), PC (96%), CSS (90%) & OS (83%) with limited morbidity and can be regarded equivalent to modern surgical techniques in terms of oncologic outcome.	Results of image guided brachytherapy for stage IB cervical cancer in the RetroEMBRACE study - ScienceDirect
• Consensus statement on surgery vs. RT: National Institute of Health: "stages IB-IIA are appropriately treated with equal effectiveness by either surgery or RT, but not both, to avoid increased cost and morbidity."	National Institutes of Health Consensus Development Conference Statement on Cervical Cancer - ScienceDirect
Standard procedure: IA1 & IA2	
• LVSI negative: consider BT if not a surgical candidate. • LVSI positive: consider EBRT + BT if not a surgical candidate.	The European Society of Gynaecological Oncology/European Society for Radiotherapy and Oncology/European Society of Pathology Guidelines for the Management of Patients With Cervical Cancer | International Journal of Gynecologic Cancer (bmj.com) cervical.pdf (nccn.org)
Standard procedure: IB1, IB2 & IIA1	
• ChRT + IGABT should be discussed as a treatment option. Consider menopausal status, comorbidities, histological type, tumour size & patient preference during decision-making. • ChRT + IGABT should be the 1. choice if unfavorable pre-treatment attributes, to avoid postop. therapy. Avoid surgery & RT (increased morbidity and cost & no survival benefit).	The European Society of Gynaecological Oncology/European Society for Radiotherapy and Oncology/European Society of Pathology Guidelines for the Management of Patients With Cervical Cancer | International Journal of Gynecologic Cancer (bmj.com) cervical.pdf (nccn.org) Randomized study between radical surgery and radiotherapy for the treatment of stage IB–IIA cervical cancer: 20-year update (nih.gov) Results of image guided brachytherapy for stage IB cervical cancer in the RetroEMBRACE study - ScienceDirect
STAGES IB3 – IVA	
Evidence	Reference

• ChRT + IGABT: EMBRACE 1 study of ChRT + IGABT: excellent 5-y LC (92%), PC (87%), DFS (68%) & OS (74%), limited morbidity (all stages). Stage IVA/B: LC 91%/89%, PC 81%/81%, OS 52%/61%.	MRI-guided adaptive brachytherapy in locally advanced cervical cancer (EMBRACE-I): a multicentre prospective cohort study - ScienceDirect
• ChRT + IGABT: retroEMBRACE study of ChRT + IGABT: excellent 3-y LC (91%), PC (87%) and OS (74%), limited morbidity (all stages).	Image guided brachytherapy in locally advanced cervical cancer: Improved pelvic control and survival in RetroEMBRACE, a multicenter cohort study - ScienceDirect
• Concomitant ChT: Meta-analysis; individual patient data from 18 randomized trials. Adding ChT to EBRT + conventional BT → a modest, but significant, benefit on OS, DFS, LR-DFS, MFS & time to locoregional recurrence/progression. Effect in all stages with a trend for a decrease with increasing stage. Positive impact on time to metastases smaller.	Reducing Uncertainties About the Effects of Chemoradiotherapy for Cervical Cancer: A Systematic Review and Meta-Analysis of Individual Patient Data From 18 Randomized Trials | Journal of Clinical Oncology (ascopubs.org)
• Adjuvant ChT: Meta-analysis; individual patient data from 18 randomized trials: no benefit of adding adjuvant ChT to EBRT + conventional BT. OUTBACK trial: negative.	
• Neoadjuvant ChT + surgery versus ChRT + IGABT: Randomized phase 3 trial: ChRT + conventional BT superior to neoadjuvant ChT + surgery (stage IB3-IIB) in terms of higher DFS. OS not significantly different. INTERLACE Study protocol should not be considered standard in unselected patients. Selection criteria for eventual NACT not established.	Neoadjuvant Chemotherapy Followed by Radical Surgery Versus Concomitant Chemotherapy and Radiotherapy in Patients With Stage IB2, IIA, or IIB Squamous Cervical Cancer: A Randomized Controlled Trial | Journal of Clinical Oncology (ascopubs.org)
Standard procedure: IB3 & IIA2	
• ChRT + IGABT preferred to avoid surgery + adjuvant therapy. Neoadjuvant ChT + surgery not recommended. NACT plus radiotherapy not recommended for unselected patients; can be considered on individualized-concept basis by tumour-board.	The European Society of Gynaecological Oncology/European Society for Radiotherapy and Oncology/European Society of Pathology Guidelines for the Management of Patients With Cervical Cancer | International Journal of Gynecologic Cancer (bmj.com) cervical.pdf (nccn.org) Lindegaard JC, Petric P, Tan LT, Hoskin P, Schmid MP, et al. Are we making progress in curing advanced cervical cancer-again? Int J Gynecol
Standard procedure: IIB-IVA • ChRT + IGABT recommended. Neoadjuvant chemotherapy + surgery not recommended. NACT plus radiotherapy not recommended for unselected patients; can be considered on individualized-concept basis by tumour-board. N+: SIB_{EBRT} to involved N.	

• Stages III-IV (T3-4 or node positive T1-2): KEYNOTE A18 experimental regimen can be considered, on individual basis, after tumour-board discussion. At the time of preparing this SOP, this regimen is not an internationally accepted standard	Cancer. 2024 Dec 2;34(12):1940-1945. doi: 10.1136/ijgc-2024-00 Schmid MP, Petric P, Mahantshetty U, Kirisits C, Tanderup K, Jürgenliemk-Schulz I, Lindegaard J, Pötter R. Pembrolizumab for locally advanced cervical cancer. Lancet. 2024 Nov 23;404(10467):2050-2051. doi: 10.1016/S0140-6736(24)02231-1. PMID: 39580199. Lorusso D, Xiang Y, Hasegawa K, et al. Pembrolizumab or placebo with chemoradiotherapy followed by pembrolizumab or placebo for newly diagnosed, high-risk, locally advanced cervical cancer (ENGOT-cx11/GOG-3047/KEYNOTE-A18): overall survival results from a
STAGE IVB, OLIGOMETASTATIC	
Evidence:	Reference
• Systemic therapy: main treatment. There is increasing use of high dose EBRT & BT, but no consensus. Consider high-dose RT for oligo-M.	Management of oligo-metastatic and oligo-recurrent cervical cancer: A pattern of care survey within the EMBRACE research network - ScienceDirect
Standard procedure- Oligometastatic disease	
• Consider definitive ChRT + IGABT. • N+: SIB_{EBRT} to involved nodes recommended. • Oligo-M sites: treat according to respective SOP. • Systemic therapy.	

SIMULATION	
CT SIMULATOR	Reference

1. Position: ○ Supine, bra removed, arms up. ○ Leg support. 2. Tattoos & markers ○ Lateral tattoos. ○ Additional tattoos when para-aortic nodes treated. 3. I.v. contrast. 4. Bladder filling: ○ Reproducible at simulation and treatment. ○ 2 CT scans (full & empty bladder) for ITV generation. 5. Rectal / sigmoid colon filling: ○ Patient should empty rectum at simulation & each RT. ○ If rectal diameter >4 cm on ≥1 axial slices (~mid-volume): empty rectum & rescan. Persistence: laxatives & CT re-appointment. 6. Scanning: ○ Volumetric scan, 2 mm slices. ○ Region: • Pelvic RT: L 1/2 to upper 1/3 of femur. • Pelvic + paraaortic RT: T 8/9 to upper 1/3 of femur. • Inguinal RT: lower border mid-femur.	Image guided intensity modulated External beam radiochemotherapy and MRI based BRAchytherapy in locally advanced CErvical cancer (embracestudy.dk)
PLANNING MRI	Reference
7. Contraindications should be ruled out. 8. Timing: optimally within 2 days of CT simulation. 9. Position: ○ As for CT. 10. I.v. contrast: no. 11. Bladder: comfortably full. 12. Rectal / sigmoid colon filling: as for CT. 13. Sequences - all T2w FSE: ○ axial (perpendicular to couch) ○ para-axial (perpendicular to cervical canal)	Recommendations from Gynaecological (GYN) GEC-ESTRO Working Group (IV): Basic principles and parameters for MR imaging within the frame of image based adaptive cervix cancer brachytherapy - PubMed (nih.gov)

○ para-coronal (parallel to cervical canal) ○ para-sagittal (parallel to cervical canal) 14. <u>Scanned regions:</u> ○ Axial, paraxial: i. Upper border L3 to lower border ischial tuberosities. ii. Always entire uterus. iii. Entire vagina when invaded. ○ Para-sagittal: i. Between lateral borders of obturator muscles. ii. Include uterine corpus, cervix, vagina, tumor. ○ Para-coronal: i. Ant. surface of sacrum to post. border of symphysis. ii. Include uterine corpus, cervix, vagina, tumor. 15. MRI registered with CT. 16. If diagnostic MRI was done within 2 weeks of CT simulator, they can be registered & planning MRI can be omitted.	
PET CT	
Co-register images from diagnostic workup with planning CT.	

SELECTION & CONTOURING: TARGET VOLUMES	
Selection and Contouring guidelines are detailed in “Cervix TV Contouring” SOP: K:\RAO_QM\Handbuch\06. Patientenbezogener Behandlungsprozess\6.2. Therapieindikation-Durchführung-Nachsorge\06_02_04_Gynäkologie	
1. GTV T init	Initial Gross Tumor Volume - primary tumor
2. CTV T HR init	Initial High-Risk Clinical Target Volume of primary tumor
3. CTV T match	CTV T HR init, transferred to CT & matched to the CT anatomy.
4. V homogen	CTV T match with a margin – V of homogeneous dose.
5. CTV T LR init	Initial Low-Risk Clinical Target Volume of the primary tumor
6. ITV T LR	Internal Target Volume - primary tumor
7. GTV-N	Initial Gross Tumor Volume - lymph node(s)
8. CTV N	Clinical Target Volume - involved lymph node(s)
9. CTV E	Elective Clinical Target Volume - nodal regions

10. ITV 45/25	Internal target volume to be treated to 45 Gy in 25 fractions
11. ITV 55/25	Internal target volume to be treated to 55 in 25 fractions (refers to CTV N in the small pelvis with BT dose contribution)
12. ITV 57.5/25	Internal target volume to be treated to 57.5 Gy in 25 fractions (refers to CTV N outside the small pelvis / with minimal BT dose contribution)
13. ITV1_V1_1a	Internal target volume to be treated to 57.5 Gy in 25 fractions*
14. ITV2_V1_1a	Internal target volume to be treated to 55 in 25 fractions*
15. ITV3_V1_1a	Internal target volume to be treated to 45 in 25 fractions*
16. PTV1_V1_1a	Planning target volume to be treated to 57.5 Gy in 25 fractions*
17. PTV2_V1_1a	Planning target volume to be treated to 55 in 25 fractions*
18. PTV3_V1_1a	Planning target volume to be treated to 45 in 25 fractions*
SELECTION & CONTOURING: ORGANS AT RISK	
Image guided intensity modulated External beam radiochemotherapy and MRI based BRAchytherapy in locally advanced CErvical cancer (embracestudy.dk)	
1. Anus	Anal verge to ano-rectal junction ≈3 cm cranially.
2. Rectum	Ano-rectal to recto-sigmoid junction.
3. Anorectum	Anus + rectum.
4. Sigmoid colon	Recto-sigmoid junction to junction with descending colon.
5. Bladder	Urethro-vesical junction to bladder dome.
6. Bowel bag	Outer bowel contour (not peritoneal space).
7. Femurs	Femoral heads to ischial tuberosities.
8. Kidney	Parenchima
9. Myelon	Myelon / Cauda Equina

Radiotherapy Fractionation	
• EBRT to PTV3: 45 Gy / 25 daily fractions / 5 weeks • SIB to PTV2: 55 Gy /25 daily fractions / 5 weeks • SIB to PTV1: 57.5 Gy /25 daily fractions / 5 weeks	
• IGABT: 28 Gy / 4 fractions (CTV HR D90 aim): weeks 6 & 7.	K:\RAO_QM\Handbuch\06. Patientenbezogener Behandlungsprozess\6.2. Therapieindikation-Durchführung-Nachsorge\06_02_04_Gynäkologie

TREATMENT PLANNING, PLANNING AIMS & D CONSTRAINTS, PLAN PRESENTATION, EVALUATION	
• Aim: respect planning aims & D constraints.	K:\RAO_QM\Handbuch\06. Patientenbezogener Behandlungsprozess\6.2.

• Deviations: may be accepted if justified & documented.	Therapieindikation-Durchführung-Nachsorge\06_02_04_Gynäkologie

TREATMENT	
External beam radiotherapy	
1. Pre-RT dietary education. 2. Linear accelerator, VMAT. 3. Daily position & bladder / rectum filling as at CT simulation. 4. Image guidance: daily CBCT, offline reviews by radiation oncologist. 5. Patients reviewed min. once weekly. 6. Laboratory min. weekly. 1. Supportive treatments for acute toxicities. 2. Antiemetics & proton pump inhibitors if paraaortic EBRT. 3. OTT (including BT) aimed at ≤50 days.	Image guided intensity modulated External beam radiochemotherapy and MRI based BRAchytherapy in locally advanced CErvical cancer (embracestudy.dk) file:////fs-group/RAO_Daten/RAO_QM/Handbuch/06. Patientenbezogener Behandlungsprozess/6.4. Durchführung Bestrahlung/6-4-10 Linac/IGRT
Concomitant chemotherapy	
• Standard: weekly cisplatin, 40 mg/m2, max 80 mg. • Alternative: weekly carboplatin, 1.5-2 AUC.	Reducing Uncertainties About the Effects of Chemoradiotherapy for Cervical Cancer: A Systematic Review and Meta-Analysis of Individual Patient Data From 18 Randomized Trials | Journal of Clinical Oncology (ascopubs.org)
Brachytherapy	
Detailed elsewhere.	K:\RAO_QM\Handbuch\06. Patientenbezogener Behandlungsprozess\6.2. Therapieindikation-Durchführung-Nachsorge\06_02_04_Gynäkologie

TREATMENT RECORDING & REPORTING	
• According to the ICRU Report 89. • Departmental EQD2 spreadsheets.	Prescribing, Recording, and Reporting Brachytherapy for Cancer of the Cervix - PubMed (nih.gov) K:\RAO_Aerzte\Anforderung_Planungsauftrag\HDR_Planungsauftrag\1. TOOLS\Cervix Tools

INSTRUCTIONS AND FOLLOW UP
• Vaginalstab zur Prophylaxe vaginaler Fibrosen und Anwendungsbeschreibung • Nach 6 Wochen: Telefonische oder Klinische Nachsorge • Regelmässige Radio-Onkologische Kontrolle mit Gyn Untersuchungen: ○ Monat: 3, 6, 9, 12, 18, 24, 30, 36, 48, 60

- Bildgebung:
    - Monat: 3, 12: MRI
    - Monat 3, 12: +/- PET CT (bei N+ paraaortal, Oligometastasen oder Symptome)
- Regelmässige Gynäkologische Nachsorge alle 3-6 Monate sicherstellen.
- Regelmässige hormonelle Kontrolle durch Gynäkologen.
- Brief an Zuweiser, Hausarzt und alle involvierten Aerzte.