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Erlassen durch	Prof. Guckenberger	ErstellerIn	P. Petric	Ersetzt	Keine Vorversion
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Postoperative Vulvar Cancer Radiotherapy

PATIENT GROUP

These guidelines cover treatment of patients with:

1. Primary surgery completed
2. Timely referral for radiotherapy (see overall treatment time section)
3. Histologically verified non-metastatic & oligometastatic cancer
4. Squamous-cell histology
5. Treatment decision reached at the Multidisciplinary tumour board.

These guidelines do not cover treatment of patients with:

1. Indications for definitive chemoradiation or palliative radiotherapy
2. Direct or metastatic spread of other primary tumour to the vulva.
3. Sarcoma, small cell carcinoma, melanoma and other non-epithelial histologies.
4. Patients with contraindications for pelvic radiotherapy.

PRE-TREATMENT WORKUP

1. History & general clinical examination
2. Consider geriatric assessment
3. Gynecological examination +/- colposcopy
    - Documentation on clinical drawing
    - Systematic written documentation of clinical findings
    - Photography
4. Pathological confirmation
5. Imaging:
    - Pelvic MRI & PET-CT or
    - Pelvic MRI & CT of thorax, abdomen or
    - PET-MRI
    - Endovaginal / transrectal / transabdominal US is optional.
2. Rectoscopy in case of clinical or imaging suspicion of rectal invasion.
3. Cystoscopy in case of clinical or imaging suspicion of bladder invasion.

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TNM stage, and FIGO$_{2021}$ stage Method of determination of the TNM stage should be recorded.	

INDICATIONS	
Indications for RT to the vulva	
• R1, if re-excision not possible. • Strongly consider if: close margins (<8 mm) plus one or more of the "minor" criteria: lymphovascular or perineural invasion or large tumour (>4 cm) or multifocality, or depth of invasion >5 mm. • Consider if: close margins (<8 mm) and no other factors • Consider if more than one "minor criteria" present • St. p. excision of a local recurrence, if previously non-irradiated. *Post-operative radiotherapy to the vulva is recommended for all women with a positive margin where re-excision is not possible. Radiotherapy may also be considered in the setting of risk factors for local recurrence: close margins, lymphovascular or perineural invasion, large tumor size, and/or depth of invasion >5 mm. ESGO Guidelines 2023* *Patients with vulvar squamous cell carcinoma and positive surgical mar gins derive an OS benefit from aRTwith a seemingly optimal dose in the range of 54.0 to 59.9 Gy. 2016 Chapman BV, et al. IJROBP 2017* *Adjuvant RT should be used for patients with positive/close surgical margins to improve their outcome. Ignatov T, et al. J Cancer Clin Res 2016*	ESGO Guidelines 2023 ESGO Guidelines 2023 Adjuvant RT for R1. Chapman BV, et al. IJROBP 2017 Adjuvant RT for close margins Ignatov T, et al. J Cancer Clin Res 2016
Indications for RT to the vulva, groins, +/-pelvis	
• pN+: 2 or more macrometastatic lymph nodes • Strongly consider if: pN+: 1 or more macrometastatic lymph nodes, with ECE or LVI • pN-, but high suspicion for residual nodal disease (non-removed metastatic GTV-N), when removal not possible. *<u>Indication for postoperative inguino/femoral/pelvic radiotherapy:</u>* *Database study of 2779 patients (1436 1N+, 1208 with ≥2 N+) showed better survival for adjuvant chemoradiotherapy compared with radiotherapy in patients with 1 and those with 2 or more positive nodes. 5-year overall survival was highest among patients with one positive node who received chemoradiotherapy (68.1%), compared with 55.9% for adjuvant external beam radiation therapy and 46.1% for no adjuvant treatment. Survival was likewise highest among patients with two or more positive nodes who received chemoradiotherapy (49.1%), compared with 29.4% for adjuvant external beam radiation therapy and 21.2% for no adjuvant treatment. However, in this analysis women with a*	Database Study on ChRT for N+ Vulvar Cancer Radiother Oncol 2018

single positive node derived a survival advantage from radiotherapy but no incremental advantage from the addition of chemotherapy to radiotherapy. Rydzewski NR, et al. Role of adjuvant external beam radiotherapy and chemotherapy in one versus two or more node-positive vulvar cancer: A National Cancer Database study. Radiother Oncol. 2018 Dec;129(3):534-539. *<u>Indication for including local irradiation of vulva to the inguino/femoral/pelvic radiotherapy:</u>* *Large retrospective AGO-CaRE −1 study on pN+ vulvar cancer showed that adjuvant radiation to the primary site in addition to the groins/pelvis lymph nodes results in less vulva-only recurrences (15.8%) as compared with 22.8% in patients with adjuvant radiotherapy to groins/pelvis and 25.5% with no adjuvant radiotherapy. The risk-reducing effect of local radiotherapy was independent of the resection margin status. There was greater impact of RT for HPV-related than -independent tumours with median disease-free survival of 20.7 versus 17.8 months, respectively. Woelber L, et al. Gynecol Oncol. 2022 Jan;164(1):68-75.*	AGO-CaRE −1 study
Indications for RT to the groins instead of lymphadenectomy	
• Consider in SLN+ (≤2 mm) instead of lymphadenectomy *Patients with SLN metastasis ≤2 mm can be treated with postoperative radiotherapy (2-year isolated groin recurrence rate of 1.6% in GROINSS-V II), as a safe alternative to inguinofemoral lymphadenectomy. Patients with early-stage vulvar cancer with SLN metastasis >2 mm following SLN biopsy should undergo inguinofemoral lymphadenectomy followed by post-operative radiotherapy in case of one or more additional lymph node metastasis and/or extracapsular tumor spread; the 2-year isolated groin recurrence rate was unacceptably high (22%) with radiotherapy alone using 50 Gy in the GROINSS-V II study (Oonk MHM, Slomovitz B, Baldwin PJW, et al. Radiotherapy versus inguinofemoral lymphadenectomy as treatment for vulvar cancer patients with micrometastases in the sentinel node: results of GROINSS-V II. J Clin Oncol 2021;39:3623–32. Lukovic J, Han K. Postoperative management of vulvar cancer. Int J Gynecol Cancer 2022;32:338–43.)*	GROINS V-II Review: postop. management
Indications for Concomitant Chemotherapy	

• Addition of concurrent chemotherapy to adjuvant radiotherapy should be considered in all patients on individual patient basis.
• Factors favouring chemotherapy:
  ○ pN+ with >1 lymph node
  ○ R2
  ○ ECE
  ○ LVI, …
• Standard choice of chemotherapy: Cisplatin 40 mg/m^2 weekly
 	
Retrospective studies suggest that the addition of concurrent chemotherapy to radiotherapy may improve survival. Toxicity of radiotherapy versus chemoradiotherapy
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in this situation needs to be carefully considered on an individual patient basis. Lukovic J, Han K. Postoperative management of vulvar cancer. Int J Gynecol Cancer. 2022.	Review: postop. management
Database study of 2779 patients (1436 1N+, 1208 with ≥2 N+) showed better survival for adjuvant chemoradiotherapy compared with radiotherapy in patients with 1 and those with 2 or more positive nodes. 5-year overall survival was highest among patients with one positive node who received chemoradiotherapy (68.1%), compared with 55.9% for adjuvant external beam radiation therapy and 46.1% for no adjuvant treatment. Survival was likewise highest among patients with two or more positive nodes who received chemoradiotherapy (49.1%), compared with 29.4% for adjuvant external beam radiation therapy and 21.2% for no adjuvant treatment. However, in this analysis women with a single positive node derived a survival advantage from radiotherapy but no incremental advantage from the addition of chemotherapy to radiotherapy. Rydzewski NR, et al. Role of adjuvant external beam radiotherapy and chemotherapy in one versus two or more node-positive vulvar cancer: A National Cancer Database study. Radiother Oncol. 2018 Dec;129(3):534-539.	Database Study on ChRT for N+ Vulvar Cancer Radiother Oncol 2018
In a large population-based analysis, adjuvant chemotherapy resulted in a significant reduction in mortality risk for node-positive vulvar cancer patients who received adjuvant radiotherapy. Gill BS, et al. Impact of adjuvant chemotherapy with radiation for node-positive vulvar cancer: A National Cancer Data Base (NCDB) analysis. Gynecol Oncol. 2015.	NCDB) analysis Gynecol Oncol. 2015

CT SIMULATOR

- Position:
  - Supine, not frog-leg
  - Arms up
  - Leg support.
- Bolus at discretion of radiation oncologist (with normal supine position/self-bolus of vulvar and thigh skin rarely indicated)
- I.v. contrast, if no contraindications.
- Bladder filling:
  - Bladder filling at simulation and treatment should be reproducible.
  - One CT scan - comfortably full bladder
- Rectal / sigmoid colon filling:
  - Patient is instructed to empty the rectum at simulation & each RT fraction.
  - If rectal diameter i>4 cm on one or more transverse slices at simulation the patient should be asked to empty the rectum and rescanned. If the problem persists, laxatives and CT re-appointment should be planned.
- Scanning:
  - 2 mm slice thickness
  - Region:

- Inguinal-pelvic RT: L 3 to mid femur; inguinal regions need to be scanned.

Pelvic + paraaortic RT: From T 8/9 to mid femur.

MRI SIMULATOR

1. Contraindications for MRI should be ruled out
2. Timing: optimally within 2 days of CT simulation.
3. Position:
   - Same as for CT
4. I.v. contrast: none.
5. Bladder filling: comfortably full.
6. Rectal / sigmoid colon filling: same as for CT simulator.
7. Sequences:
   - T2w TSE, axial (perpendicular to the couch)
   - T2w TSE, para-axial (perpendicular to vagina)
   - T2w TSE, para-coronal (parallel to vagina)
   - T2w TSA, para-sagittal (parallel to the vagina)
8. Scanned regions:
   - Axial, paraxial:
     i. From lower border of L5 to mid femur.
     ii. Include inguinofemoral regions
   - Para-sagittal:
     i. Region between lateral borders of obturator muscles.
   - Para-coronal:
     i. From ant. surface of sacrum to ant. border of symphysis.
9. Register MRI with CT simulator images.

If diagnostic MRI performed within 2 weeks of CT simulator, it can be used for registration with CT simulator and MRI simulator can be omitted.

PET CT

Register PET CT from diagnostic workup with CT simulator data set.

CONTOURING OF TARGET VOLUMES	
Naming of volumes: All below specified volumes should be named according to the departmental naming rules.	K:\RAO_QM\Handbuch\06. Patientenbezogener Behandlungsprozess\6.3. Bildgebung und Bestrahlungsplanung\6-3-10 Bestrahlungsplanung - Prozess\Pre-Planning
Adjuvant setting	
Gross Tumor Volume:	Consensus Contouring Recommendations Vulva Nodal regions:

Should be absent in adjuvant situation, both in tumor-bed as well as in nodal regions.
 	
Elective Clinical Target Volume – CTV - E:
 	
• When RT to vulva indicated:
  ○ Tumor bed + Vulva
• When RT to vulva and nodal regions indicated:
  ○ Tumor bed + Vulva
  ○ Inguinofemoral region on the side with pN+
  ○ Inguinofemoral region(s) on the side without affected lymph nodes +/- pelvic lymph nodes should be included (one level above the affected level) depending on:
  ▪ Size and number of affected pN+
  ▪ Extent and laterality of primary disease
  ▪ Lymphovascular space invasion
 	
Boost Clinical Target Volume – CTV-Boost:
 	
• When local R1 resection or close margin: Tumor bed
• When ECE of nodal metastases or regional R1 resection: Nodal metastasis bed.
 	
Planning Target Volume – PTV:
 	
• PTV-E = CTV-E + 5 mm
• PTV-Boost = CTV-Boost + 3-5 mm
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Postoperative R2 and/or cN+ (non-removed) setting	

• R2 local resection: follow SOP for primary definitive chemoradiation.
• Radiologically affected, but not removed or R2 removed metastatic lymph nodes in the groin or pelvis:
  ○ Contour GTV-N
  ○ CTV-N-Boost should be contoured according to the same principles as for cervical cancer radiotherapy (≈GTV-N + 0-3 mm asymmetrically).
  ○ In such cases, elective CTV should include bilateral inguinofemoral and pelvic nodes to
	Consensus Contouring Recommendations Vulva
	
	Nodal regions:
	
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at least one level above the most cranial involved lymph node. ○ PTV-E = CTV-E + 5 mm ○ PTV-N-Boost = CTV-N-Boost + 3 mm	

CONTOURING OF ORGANS AT RISK	
Organs at risk	
Depending on the clinical scenario, the following volumes need to be delineated:	
1. Anus	From marker caudally to approximately 3 cm in cranial direction.
2. Rectum	From ano-rectal border to recto-sigmoid junction
3. Anorectum	Anus + rectum
4. Sigmoid colon	From recto-sigmoid junction to the junction with descending colon.
5. Bladder	From urethro-vesical junction to bladder dome.
6. Urethra	From external orifice to urethro-vesical junction
7. Bowel bag	Potential space with bowel or where bowel is expected to move.
8. Bowel	Bowel loops
9. Femurs	Proximal femurs from the head to the level of ischial tuberosities.
10. Kidneys	When paraaortics included
11. Spinal cord	When paraaortics included

DOSE PRESCRIPTION	
Adjuvant Radiotherapy	
• PTV-E: 45 Gy in 25 fractions a 1.8 Gy • PTV-Boost for close margins: 9 Gy – 14.4 Gy a 1.8 Gy (Sequential) • PTV-Boost for R1: 14.4 Gy – 18 Gy a 1.8 Gy (Sequential) • PTV-Boost for N-ECE: 55 Gy - 57.5 Gy a 2.2 Gy - 2.3 Gy (SIB) • +/- Concomitant Chemotherapy	ESGO Guidelines 2023
Postoperative Radiotherapy in R2 and/or cN+ (non-removed) setting:	
• PTV-E: 45 Gy in 25 fractions a 1.8 Gy • PTV-Boost for R2 local resection: to total dose of 66 Gy-70 Gy a 1.8 Gy- 2 Gy; follow SOP for primary definitive chemoradiation. Brachytherapy boost can be considered. • PTV-N-Boost: 57.5 Gy a 2.3 Gy (SIB) +/- additional sequential boost to EQD2 of 66 Gy. • +/- Concomitant Chemotherapy	ESGO Guidelines 2023
Planning aims and dose constraints	
• Planning aims and dose constraints are aimed to be respected	

- If deviations are accepted, the justification should be documented

TREATMENT

External beam radiotherapy

1. Before treatment, education about dietary measures during and after radiotherapy.
2. Treatment at linear accelerator using VMAT technique.
3. Bolus at discretion of radiation oncologist (with normal supine position/self-bolus of vulvar and thigh skin rarely indicated)
4. Same daily position & bladder / rectum filling protocol is followed as at CT simulation.
5. Image guidance: daily cone beam CT (CBCT)
6. Clinical review at least once weekly
7. Complete blood count with differential count and biochemistry with electrolytes, urea, creatinine, creatinine clearance (if chemotherapy) weekly.
1. Analgesic, antidiarrhoeic, antiemetic and other supportive treatments including electrolyte replacement as needed to avoid/treat manageable acute toxicities.
2. Antiemetics and proton pump inhibitors considered in paraaortic EBRT.

Concomitant chemotherapy

EBRT can be combined with concomitant chemotherapy:

- Standard is weekly cisplatin, 40 mg/m2, max 80 mg (absolute).
- Alternative (renal dysfunction, elderly) is weekly carboplatin, 1.5 AUC.
- Other alternative regimens include 5-FU alone or in combination with cisplatin, carboplatin or mitomycin-C.

If ChT contraindicated, consider elective EBRT dose of 50.4 instead of 45 Gy (expert opinion).

OVERALL TREATMENT TIME	
Overall treatment time (OTT) should be kept within acceptable limits: • Surgery → Start of RT < 50 days • RT OTT < 50 days • Surgery → End of RT < 100 days *In a National Cancer Database series including 1500 patients treated with adjuvant radiotherapy, median overall survival with increased OTT was independently associated with poorer outcome. After propensity adjustment for factors predicting a shorter OTT, OTT continued to be associated with a significant increased risk of death per additional day. Ashmore S, et al. Optimal overall treatment time for adjuvant therapy for women with completely resected, node-positive vulvar cancer. Gynecol Oncol. 2021 Apr;161(1):63-69.*	Database Study on effects of OTT; Ashmore S, et al. Gyn Oncol 2021

FOLLOW UP

- For two months, the patient should avoid bathing, swimming, mechanical irritation of the vulva, local application of non-neutral cosmetic, hygienic and other preparations.
- Local skin care as advised by the radio-oncology nursing personnel.

- Analgesic / anti-inflammatory agents if indicated.
- Regular follow up in Gynaecology.
- Follow up in radio-oncology clinic for assessment of locoregional side effects in 6 weeks.
- Further follow up in radio-oncology clinic annually for 5 years.