Management of Advanced Stage-Vulvar Cancer

What is the Classical Treatment?

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Jinekolojik Onkoloji Bilimdalı
<table>
<thead>
<tr>
<th>FIGO stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Tumor confined to the vulva</td>
</tr>
<tr>
<td>IA</td>
<td>Lesions ≤2 cm in size, confined to the vulva or perineum and with stromal invasion ≤1.0 mm³, no nodal metastasis</td>
</tr>
<tr>
<td>IB</td>
<td>Lesions &gt;2 cm in size or with stromal invasion &gt;1.0 mm³, confined to the vulva or perineum, with negative nodes</td>
</tr>
<tr>
<td>II</td>
<td>Tumor of any size with extension to adjacent perineal structures (lower third of urethra, lower third of vagina, anus) with negative nodes</td>
</tr>
<tr>
<td>III</td>
<td>Tumor of any size with or without extension to adjacent perineal structures (lower third of urethra, lower third of vagina, anus) with positive inguinofemoral nodes</td>
</tr>
<tr>
<td>IIIA</td>
<td>1. With 1 lymph node metastasis (≥5 mm), or 2. With 1–2 lymph node metastasis(es) (&lt;5 mm)</td>
</tr>
<tr>
<td>IIIB</td>
<td>1. With 2 or more lymph node metastases (≥5 mm), or 2. With 3 or more lymph node metastases (&lt;5 mm)</td>
</tr>
<tr>
<td>IIIC</td>
<td>With positive nodes with extracapsular spread</td>
</tr>
<tr>
<td>IV</td>
<td>Tumor invades other regional (upper 2/3 urethra, upper 2/3 vagina), or distant structures</td>
</tr>
<tr>
<td>IVA</td>
<td>Tumor invades any of the following: 1. upper urethral and/or vaginal mucosa, bladder mucosa, rectal mucosa, or fixed to pelvic bone, or 2. fixed or ulcerated inguinofemoral lymph nodes</td>
</tr>
<tr>
<td>IVB</td>
<td>Any distant metastasis including pelvic lymph nodes</td>
</tr>
</tbody>
</table>

*The depth of invasion is defined as the measurement of the tumor from the epithelial–stromal junction of the adjacent most superficial dermal papilla to the deepest point of invasion.*
**Staging-Vulvar Cancer**

**Table 1. AJCC Tumor-Node-Metastases (TNM) and International Federation of Gynecology and Obstetrics (FIGO) Surgical Staging Systems for Carcinoma of the Vulva**

<table>
<thead>
<tr>
<th>T</th>
<th>FIGO Stage</th>
<th>Primary Tumor</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX</td>
<td>Primary tumor cannot be assessed</td>
<td></td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumor</td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>I</td>
<td>Tumor confined to the vulva and/or perineum. Multifocal lesions should be designated as such. The largest lesion or the lesion with the greatest depth of invasion will be the target lesion identified to address the highest pT stage. Depth of invasion is defined as the measurement of the tumor from the epithelial–stromal junction of the adjacent most superficial dermal papilla to the deepest point of invasion.</td>
</tr>
<tr>
<td>T1a</td>
<td>IA</td>
<td>Lesions 2 cm or less, confined to the vulva and/or perineum, and with stromal invasion of 1.0 mm or less</td>
</tr>
<tr>
<td>T1b</td>
<td>IB</td>
<td>Lesions more than 2 cm, or any size with stromal invasion of more than 1.0 mm, confined to the vulva and/or perineum</td>
</tr>
<tr>
<td>T2</td>
<td>II</td>
<td>Tumor of any size with extension to adjacent perineal structures (lower/distal third of the urethra, lower/distal third of the vagina, anal involvement)</td>
</tr>
<tr>
<td>T3</td>
<td>IVA</td>
<td>Tumor of any size with extension to any of the following—upper/proximal two thirds of the urethra, upper/proximal two thirds of the vagina, bladder mucosa, or rectal mucosa—or fixed to pelvic bone</td>
</tr>
</tbody>
</table>
### Staging Vulvar Cancer

**Table 1. (continued)**

<table>
<thead>
<tr>
<th>N</th>
<th>FIGO Stage</th>
<th>Regional Lymph Nodes</th>
</tr>
</thead>
<tbody>
<tr>
<td>NX</td>
<td></td>
<td>Regional lymph nodes cannot be assessed</td>
</tr>
<tr>
<td>N0</td>
<td></td>
<td>No regional lymph node metastasis</td>
</tr>
<tr>
<td>N0(i+)</td>
<td></td>
<td>Isolated tumor cells in regional lymph node(s) no greater than 0.2 mm</td>
</tr>
<tr>
<td>N1</td>
<td>III</td>
<td>Regional lymph node metastasis with one or two lymph node metastases each less than 5 mm, or one lymph node metastasis greater than or equal to 5 mm</td>
</tr>
<tr>
<td>N1a</td>
<td>IIIA</td>
<td>One or two lymph node metastases each less than 5 mm</td>
</tr>
<tr>
<td>N1b</td>
<td>IIIA</td>
<td>One lymph node metastasis greater than or equal to 5 mm</td>
</tr>
<tr>
<td>N2</td>
<td>IIIA</td>
<td>Regional lymph node metastasis with three or more lymph node metastases each less than 5 mm, or two or more lymph node metastases greater than or equal to 5 mm, or lymph node(s) with extranodal extension</td>
</tr>
<tr>
<td>N2a</td>
<td>IIIA</td>
<td>Three or more lymph node metastases each less than 5 mm</td>
</tr>
<tr>
<td>N2b</td>
<td>IIIB</td>
<td>Two or more lymph node metastases greater than or equal to 5 mm</td>
</tr>
<tr>
<td>N2c</td>
<td>IIIC</td>
<td>Lymph node(s) with extranodal extension</td>
</tr>
<tr>
<td>N3</td>
<td>IVA</td>
<td>Fixed or ulcerated regional lymph node metastasis</td>
</tr>
</tbody>
</table>

**M FIGO Stage**

- **M0**: No distant metastasis (no pathological M0; use clinical M to complete stage group)
- **M1 IVB**: Distant metastasis (including pelvic lymph node metastasis)

**G Histologic Grade**

- **GX**: Grade cannot be assessed
- **G1**: Well differentiated
- **G2**: Moderately differentiated
- **G3**: Poorly differentiated or undifferentiated
Advanced Stage Vulvar Cancer

- Vulvar cancer may be considered to be advanced on FIGO clinical stage III or IVA carcinoma of the vulva, tumor extension to the adjacent genitourinary system and anorectum, or fixation to bones.
- Approximately 30% of vulvar cancer patients present with stage III-IV disease or lymph node involvement.
- In the revised FIGO staging, stage II disease includes tumor of any size with extension to adjacent perineal structures (one third lower urethra, one third lower vagina, anus, with negative nodes). the basis of a T3, or a primary tumor or the presence of bulky groin lymph nodes.
- Management should be individualized, and a multidisciplinary team approach is desirable.
Radical changes in the treatment of vulvar cancer

- Treatment of the primary lesion
- Approach to groin lymph nodes
- Radiotherapy indications
Treatment of Vulvar Cancer

**Surgery**
- Radical vulvectomy
- Partial vulvectomy
- IFLND
- Pelvic Exenteration

**Surgery + adjuvant XRT**

**Surgery + adjuvant kemoterapi (KT)**

**Neoadjuvant XRT + Surgery**

**XRT**
Lymph nodes involvement is the most important prognostic factor

<table>
<thead>
<tr>
<th>FIGO Stage</th>
<th>5-year OS</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>78.5%</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>59%</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>43%</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>13%</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Lymph node status</th>
<th>5-year OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative</td>
<td>92%</td>
</tr>
<tr>
<td>Unilateral (+)</td>
<td>75%</td>
</tr>
<tr>
<td>Bilateral (+)</td>
<td>30%</td>
</tr>
<tr>
<td>Contralateral 2 nodes (+)</td>
<td>25%</td>
</tr>
<tr>
<td>Contralateral 6 nodes (+)</td>
<td>0%</td>
</tr>
</tbody>
</table>

Advanced vulvar cancer

• When confronted with advanced vulvar cancer, ideally the status of the groin nodes should be determined before treatment is planned.

• Patients with clinically suspicious nodes should have fine needle aspiration (FNA) or biopsy of their nodes, and pelvic CT, MRI, or PET-CT may be helpful in determining the extent of inguinal and pelvic lymphadenopathies and the presence of distant metastatic disease.

CT Scan of groins, pelvis and abdomen

- No suspicious nodes (N0, N1)
  - Complete Groin Dissection

- Operable suspicious nodes (N2, N3)
  - Resect Bulky Nodes RT Groin and Pelvis

- Inoperable groin nodes
  - Primary Chemoradiation Surgical Resection

Non-enlarged are left in-situ for treatment with post-op radiation, which will decrease the incidence of lymphedema
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Vulvar Cancer (Squamous Cell Carcinoma)

Locally advanced (larger T2,\textsuperscript{0} T3: non-visceral sparing primary surgery)
- Radiologic imaging workup if not previously done\textsuperscript{b}

Radiographically negative nodes → Inguinofemoral LN dissection\textsuperscript{b} → EBRT\textsuperscript{d} + concurrent chemotherapy\textsuperscript{a} to primary tumor/groin(s)/pelvis

Radiographically positive nodes (includes pelvic-confined M1, LN disease) → Inguinofemoral LN dissection not performed → Consider fine-needle aspiration (FNA) for enlarged LN

Positive LNs → EBRT\textsuperscript{d} + concurrent chemotherapy\textsuperscript{a} to primary tumor/groin/s/pelvis

Negative LNs → EBRT\textsuperscript{d} + concurrent chemotherapy\textsuperscript{a} to primary tumor (± selective groin LN coverage)
Management of Locally Advanced Vulvar Cancer

Management of the Primary Tumor

Tumor Resectable without requiring stoma
- Radical Tumor Resection with surgical margins of at least 1 cm of unstretched skin

Resection would require stoma
- Radiation ± Chemotherapy
  - Consider neoadjuvant chemotherapy + Resection of Tumor Bed

A recent cochrane review showed no survival advantage with the addition of chemotherapy
Pelvic Exenteration

• When the primary disease involves anus, rectum, rectovaginal septum or proximal uretra;
  – Adequate surgical clearance of the primary tumor is possible only by some type of infralevator exenteration, combined with radical vulvectomy and bilateral groin dissection
  – Postoperative morbidity are high
  – 5 year survival rate approximetly 50% can be expected
Radiotherapy

**Indications of RT in malignant diseases of the vulva:**

- Preoperative RT in stage III and IV:
  - The lesion shrunk and it limits the need for pelvic exenteration.
  - It also improves surgical respectability of tumors.
- Postoperative RT: can reduce regional recurrences and inguinal lymph node metastases. Node positive disease most important prognostic factor
  - Multiple positive groin nodes: It decreases the incidence of recurrence.
  - Positive surgical margins as seen on microscopic examination.
  - Multiple focal recurrences.
  - When the tumor size is > 4 cm
  - RT especially of benefit for clinically suspicious or fixed ulcerated groin nodes and two or more positive groin nodes
  - Role of RT for 1 single node metastasis remained unclear
Radiotherapy

• In relation to radiotherapy planning in advanced vulvar cancer,
• if the groin nodes are positive and meet the previously described indications for adjuvant radiation, the radiation treatment fields should include the pelvis, inguinal nodes, and vulva.
• These should be treated to a total dose of at least 50 Gy, with attention to adequate coverage of the inguinal nodes.

Radiotherapy

• Large vulvar tumors probably require 60–70 Gy to achieve local control, although the relationship between dose and local control remains the subject of ongoing investigation.

Adjuvant radio(chemo)therapy in lymph-node positive vulvar cancer: The AGO CaRe-1 Study

Adjuvant radiotherapy is standard of care for node-positive vulvar cancer

Neoadjuvant Chemotherapy

• Neoadjuvant treatment with cisplatin and 5-fluorouracil, or other chemotherapy combinations, has been reported to be effective for preservation of the anal sphincter and/or urethra in patients with advanced vulvar cancer. This is the subject of ongoing clinical research.

• FIGO cancer report 2018 Cancer of the vulva, Int J Gynecol Obstet 2018; 143 (Suppl. 2): 4–13
Neoadjuvant Chemotherapy for advanced vulvar cancer, prior to radical vulvectomy or RLE

- CT
  - cisplatin, FU:
    - cisplatin, 5FU, Paclitaxel;
    - cisplatin, Paclitaxel, Ifosfamid

- Complete response: 23-30%
- Partial response: 80-86%

• **Chemoradiation**

• Overall survival (OS) after primary chemoradiation was superior to OS following primary RT in a series of 54 patients with locally advanced disease.

• In the GOG 101 study, preoperative chemoradiation was examined in 73 patients with stage II/IV disease. The study investigated whether chemoradiation allowed for less radical surgery in patients with T3 tumors and avoidance of pelvic exenteration in patients with T3 tumors.

• Only 3 % of patients (2/71) had residual unresectable disease following chemoradiation, and preservation of urinary and/or gastrointestinal continence was possible in 96 % of patients.

Neoadjuvant Chemotherapy and Radiation

• In an attempt to further improve complete clinical/pathologic response rates, and ultimately improve local control, the GOG conducted a prospective phase II trial (GOG 205), using a combination of weekly cisplatin with daily fractionated RT to a total dose of 57.6 Gy. This dose was a 20% increase over that used in GOG 101.

• The authors concluded that this combination of radiation therapy plus weekly cisplatin successfully yielded high, complete clinical and pathologic response rates with acceptable toxicity.

Intensity-modulated Radiation Therapy (IMRT)

• Beriwal et al. evaluated using IMRT along with chemotherapy for preoperative treatment of 18 stage II-IVa vulvar cancer patients and found that the technique was well tolerated, with no patients experiencing grade 3 acute or late toxicity.

• Fourteen patients underwent surgery, 9 patients had a pathologic complete response, and 5 patients had partial responses.

• The next GOG phase II study (GOG 0279) is building on the success of GOG 0205 neoadjuvant chemoradiation therapy approach by improving the radiation technique approach using IMRT, increasing the radiation dose, and adding gemcitabine to cisplatin in achieving complete pathologic response in the treatment of LRAVC.

Conclusion

• Clear role for postoperatif radiotherapy in treatment of patients with vulvar cancer
  – For patients with involved nodes and/or involved margins
  – Reduces relapse and improves survival
  – Increasing role of chemoradiation

• Primary radio-chemotherapy for patients with advanced disease.
  – High complete response rates

• ESGO guideline presented October 2016 and available from ESGO website
vulvar cancer recurrences

• Most vulvar cancer recurrences occur on the vulva. It is thought that surgeons should aim for tumor-free pathological margins of 8 mm or more to minimize local disease recurrence.
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Vulvar Cancer (Squamous Cell Carcinoma)

- Interval H&P
every 3–6 mo for 2 y,
every 6–12 mo for 3–5 y,
then annually based on patient’s risk of
disease recurrence
- Cervical/vaginal cytology screening as
indicated for the detection of lower genital
tract neoplasia
- Imaging as indicated based on symptoms or
examination findings suspicious for
recurrence
- Laboratory assessment (CBC, blood urea
nitrogen [BUN], creatinine) as indicated
based on symptoms or examination findings
suspicious for recurrence
- Patient education regarding symptoms of
potential recurrence and vulvar dystrophy,
periodic self-examinations, lifestyle, obesity,
exercise, sexual health (including vaginal
dilator use and lubricants/moisturizers),
smoking cessation, nutrition counseling,
and potential long-term and late effects of
treatment (See NCCN Guidelines for
Survivorship and NCCN Guidelines for
Smoking Cessation)

Clinically suspected recurrence

- Imaging workup
  - Consider biopsy to confirm local and/or
distant recurrence

Therapy for recurrence clinically limited to the vulva
(See VULVA-9)

Therapy for clinical nodal or
distant recurrence
(See VULVA-10)
Recurrences

• Two types of local recurrences, those at the same site as the original (primary) tumor and those at a different vulvar site, were described by Rouzier et al.

• An analysis of vulvar cancer patients from the Royal Hospital for Women in Sydney showed that primary site recurrences occurred with a median disease-free interval of 21 months, and were associated with a histological margin of 8 mm or less, as reported in several other papers.

• “Recurrences” at remote vulvar sites occurred later, with a median disease-free interval of 69 months, and were more commonly associated with lichen sclerosus.


Recurrences

• Retrospective data suggest there is no difference in recurrence outcome between radical local excision compared with radical vulvectomy.

• For patients with stage IB-II disease, inguinal lymphadenectomy is recommended due to a risk of ≥ 8% of lymphatic metastases.

• A negative unilateral lymphadenectomy is associated with a ≤ 3% risk of contralateral metastases.
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**Vulvar Cancer (Squamous Cell Carcinoma)**

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### SITE OF RECURRENCE

**Vulva-confined recurrence (nodes clinically negative), not previously irradiated**

#### THERAPY FOR RECURRENCE

- **Margins negative; LN(s) surgically or clinically negative**
  - **Observe or EBRT**

- **Margins positive; LN(s) surgically or clinically negative**
  - **Re-excision**
  - **± brachytherapy ± concurrent chemotherapy**

- **Margins negative; LN(s) surgically positive**
  - **EBRT ± concurrent chemotherapy**

- **Margins positive; LN(s) surgically positive**
  - **EBRT ± brachytherapy ± concurrent chemotherapy ± re-excision**

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**Radical excision**

- **± unilateral or bilateral inguinofernal LN dissection**

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**Vulva-confined recurrence (nodes clinically negative), previously irradiated**

- **EBRT ± brachytherapy ± concurrent chemotherapy**

- **Complete response**
  - **Resection**

- **Gross residual vulvar tumor**
  - **Resection**
Metastatic disease beyond pelvis (any T, any N, M1 beyond pelvis) → EBRT for locoregional control/symptom palliation and/or systemic therapy or best supportive care (See NCCN Guidelines for Palliative Care)
Systemic Therapy for Recurrent/Metastatic Disease

No standard chemotherapy regimens exist for treating advanced or recurrent/metastatic disease.

Several reports provide anecdotal evidence for various regimens, at times extrapolating from regimens with known activity in advanced cervical and anal cancers, as well as other SCCs.

- Cisplatin (single or combination for metastatic disease).
- Cisplatin/vinorelbine was studied in a small series of patients with recurrent disease, producing a 40% response rate, 10-month PFS, and 19-month OS.
- Carboplatin or Carboplatin /paclitaxel
- Erlotinib
LRAVC can have a variety of presentations, but generally would have significant morbidity if managed with upfront exenterative surgery.

Whole-body FDG-PET/CT is a useful imaging modality for initial work-up and for assessing response to chemoradiotherapy.

Standard treatment for LRAVC includes neoadjuvant chemoradiotherapy with weekly concurrent cisplatin, as in GOG 205.
SUMMARY

• Radiation should involve CT planning, with treatment volumes including the vulva and the bilateral inguinal and pelvic lymph nodes, preferably with 3D or IMRT.

• In assessing response to neoadjuvant chemoradiotherapy, besides imaging, examination under anesthesia with directed biopsies can be helpful for determining if the patient requires surgery.

• Radiation can also be a useful palliative treatment option for patients with painful vulvar cancer and unable to tolerate more aggressive treatment.
CEHALET
Yenilmesi
gereken
en büyük
düşmandır.

K. Atatürk