



# **Guidelines for irradiation of vulvar cancer**

**Radiotherapy Group**

**Nordic Society for Gynecological Oncology**

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### 1. Writing Committee:

Mansoor Raza Mirza (Odense), Inger-Lena Lamm (Lund), Ann-Charlotte Waldenström (Göteborg), Jacob Ch. Lindegaard (Aarhus), Kolbein Sundfør (Oslo)

The board of NSGO has approved these guidelines.

The guidelines should be perceived as minimal standards in the curative treatment and should not replace independent medical judgment or the use of more advanced technique where this is possible or needed based on the clinical situation.

### 2. Introduction

These guidelines for curative radiotherapy of vulvar cancer are intended for use in the clinical routine, and as a basis for development of cancer care programmes and for participation in clinical trials. These guidelines are in general written for external beam radiotherapy, EBRT. It is to be noted, though, that interstitial brachytherapy could also be used to deliver higher doses to small volumes.

### 3. Indications for radiotherapy:

Clinical characteristics of the primary tumour, presence or absence of regional node involvement, anatomic level and extent of node metastases and context of therapy (preoperative, postoperative, definitive, salvage) influence the selection of radiotherapeutic treatment parameters.

There is no indication of radiotherapy in stage Ia patients.

In patients with stage  $\geq$  Ib disease indications vary depending upon the clinical scenario.

#### 3.1: Indications for radiotherapy at the primary tumour site, vulva

Vulva should be irradiated in the following situations:

##### 3.1.1 Pre-operative or radical radiotherapy at the primary tumour site:

- Pre-operative or radical RT should be considered only if the vulvar disease is either unresectable or complete resection will endanger function of urethra, anal sphincter or clitoris.

##### 3.1.2 Post-operative radiotherapy at the primary tumour site:

- Gross tumour, which cannot be removed surgically without endangering function of anal sphincter or urethra.
- Insufficient surgical margins<sup>1</sup>: the margins of resection either not free of tumour or close ( $\leq$  8mm on fixed specimen).
- Irradiation of the whole vulva to the sub-clinical dose may be considered for patients with positive lymph nodes, even if the surgical margins are sufficient.

#### 3.2: Indications for radiotherapy at the nodal site:

##### *Central vs. lateral primary tumour:*

*Lateral primary tumour:* Risk of metastatic spread to the contralateral inguinal nodes is minimal if the primary tumour is situated laterally ( $>1$  cm lateral to midline)<sup>2</sup>. This means, in principle, that for a laterally situated tumour the nodal target volume can be restricted to the involved side, the ipsilateral side. However, the evidence supporting this strategy is not yet strong enough in the literature. It is thus advisable to investigate the nodal status also of the contralateral side.

- Ipsilateral side: Radiotherapy is indicated.
- Contralateral side: 'Prophylactic' radiotherapy is recommended, if the nodal status is unknown.

*Central primary tumour:* Radiotherapy is indicated bilaterally at the nodal site.

##### *Principle of "plus one level":*

When radiotherapy is indicated at the nodal site, it is advisable to treat an additional level of lymph nodes; For example, if gross tumour is present in the inguinal region (level 1+2), the target volume must include the nodes present at the lower half of the external iliac artery level (level 3).

##### 3.2.1 Pre-operative or radical radiotherapy at the nodal site:

- Pre-operative or radical RT should be considered only in case of primary clinically enlarged regional lymph nodes, or if complete resection of vulvar tumour will endanger function of urethra, anal sphincter or clitoris.
- Target volumes are adapted to the situation:
  - Cyto-/histological verification are advisable.
  - Side with enlarged nodes: principle of "plus one level".
  - Side with no enlarged nodes: "prophylactic" radiation therapy.
  - Bilateral nodes: principle of "plus one level" on both sides.

### 3.2.2 Post-operative radiotherapy at the nodal site:

- Node negative on lymphadenectomy: no indications for radiotherapy on the negative site.
- Lymphadenectomy performed:  $\geq 2$  positive nodes or at least one macroscopic nodal involvement or one or more nodes with growth through the capsule at level (1+2):
  - Regional radiotherapy is indicated at the site of positive nodes.
  - Ipsilateral nodal target: Gross tumour at nodal site if any + superficial inguinal nodes + deep inguinofemoral nodes + lower half of the external iliac nodes; principle of “plus one level”.
  - Contralateral nodal target: “prophylactic” radiotherapy is recommended to level 1+2 only in case if lymphadenectomy is not performed.

## 4. Pre-treatment work-up

Gynecologic examination in general or spinal anesthesia.

Histological verification.

Marking of gross tumor & pathologically enlarged nodes. In case of postoperative radiotherapy it is suggested to mark the tumor bed during operation.

CT/MR scans of abdomen, pelvis and inguinofemoral region with intravenous contrast.

Ultrasound guided FNA of suspicious regional nodes.

## 5. Treatment planning -EBRT

An essential step prior to the treatment planning is written and photographic recordings of the anatomic extent of initial disease involvement.

Treatment planning must be based on a three dimensional volume acquired by computed tomography (a 3D CT data set), preferably with a slice thickness 0.5 cm, and the treatment planning must be performed on a 3D treatment planning system.

Stability and reproducibility in the patient set-up is of utmost importance during the whole radiotherapy procedure to reach the treatment goal. The same immobilization devices should be used during the whole radiotherapy procedure.

Immobilisation of the patient is optional, but in order to ensure a relaxed and reproducible patient position during the whole external beam radiotherapy procedure, at least some type of knee cushions should be used.

It is recommended that markers be used to indicate tumour extension when the treatment planning CT is performed.

## 6. Target definition

Target definition should be based on integrated information obtained by CT (MRI) and gynecological examination in general or spinal anesthesia. For post-operative radiotherapy, the information gained at surgery should also be included.

The volumes of interest (VOI) should be defined according to ICRU 62:

GTV: Gross Tumor Volume (*if present*).

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

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

PTV: Planning target Volume = ITV + set-up margin.

To evaluate competing dose plans it is recommended to define volumes of organs at risk, (primarily hip joints, bladder and rectum) and to add internal and set-up margins using the same principles as for PTV to obtain the Planning Organ at Risk Volume.

**IMPORTANT: It is mandatory to delineate GTV(s) and PTV(s) in order to obtain a full 3D definition of the target volumes. The standard margins used for defining VOI should be modified when more precise knowledge is available.**

If there is **no gross tumour** present in the vulvar and nodal areas, there will only be target volumes for subclinical disease at both these sites. The subclinical target volumes for irradiation are the whole vulva (CTV-V) and the elective regional nodes at the appropriate levels, CTV-RN-1+2 and CTV-RN-3.

If **gross tumour** is present in the vulvar and/or the nodal area, target volumes must be defined both for gross tumour and subclinical disease:

1. **Gross tumour:** Target volumes should be defined for the gross tumour at the vulva (GTV-T) and/or at the site/s of regional nodes (GTV-N). A 5 mm margin is added to these volumes to define the clinical target volumes CTV-T and the CTV-N.
2. **Subclinical disease:** Target volumes should be defined for the subclinical disease sites, the whole vulva (CTV-V) and the elective regional nodes at the appropriate levels, CTV-RN-1+2 and CTV-RN-3.

**Note** that in case of presence of gross tumour *within* the above-mentioned volumes, these subclinical volumes should include a margin of 0.5 cm around the CTV-T & CTV-N respectively. *This should ensure a subclinical target volume with a minimum of 10 mm tissue around the gross tumour volume.*

### **Vulvar target**

#### ***Gross tumour (if present):***

**GTV-T:** Gross Tumour Volume defined by gynaecologic and radiological examinations. In post-operative situation, Gross Tumour Volume also defined at surgery.

**CTV-T:** GTV-T + 0.5 cm

#### ***Subclinical disease:***

**CTV-V:** The whole vulva + (if present) a 0.5 cm margin around CTV-T

### **Nodal target**

#### ***Gross tumour at nodal site (if present):***

**GTV-N:** Gross Tumour Volume at nodal site defined by gynaecologic and radiological examinations. In post-operative situation, Gross Tumour Volume also defined at surgery.

**CTV-N:** GTV-N + 0.5 cm

**Subclinical disease at nodal site:**

Level 1+2 (superficial inguinal nodes + deep inguinofemoral nodes)

**CTV-RN-1+2:** Superficial inguinal nodes + deep inguinofemoral nodes + (if present) a 0.5cm margin around CTV-N.

*Note: The depth of deep inguinofemoral nodes is measured by the depth of femoral artery.*

Level 3 (Lower half of external iliac nodes)

**CTV-RN-3:** Lower half of external iliac nodes + (if present) a 0.5 cm margins around CTV-N.

Note! If there is gross tumour present at level 3, one should consider other treatment options, e.g. palliative radiation therapy.

**ITV:**

For all above mentioned target volumes:

ITV=CTV, as there are no internal organ movements.

**PTV:**

For all above mentioned target volumes:

PTV = ITV + set-up margin.

Set-up margin may vary at different radiotherapy centers; therefore each centre should define its own set-up margins.

**Planning organs at risk volume (PRV):**

PRV, the planning organ at risk volume, includes internal margins and set-up margins as described for PTV. The contours of the organs at risk and their PRVs should be drawn if the total treatment dose exceeds 50 Gy. The percent of PRV, which may not exceed a certain dose level, should be predefined.

Dose is measured in a volume of 2cm<sup>3</sup> of risk organ. Volume of risk organ should be chosen around the point of maximum dose - hotspot

The organs at risk, OR, are hip joints, bladder, and rectum.

Femoral Head: BED<sub>α/β3; 2Gy/frak</sub> 56Gy (cumulative for EBRT & brachytherapy)

Bladder: BED<sub>α/β3; 2Gy/frak</sub> 90Gy (cumulative for EBRT & brachytherapy)

Rectum: BED<sub>α/β3; 2Gy/frak</sub> 75Gy (cumulative for EBRT & brachytherapy)

**7. Fractionation, dose and overall treatment time, EBRT**

EBRT is normally given as five fractions per week and a dose per fraction of ~ 1.8 – 2.0 Gy to the respective ICRU reference points.

Prescription of doses should be made according to local practice. However, the prescribed dose and the ICRU reference point dose should deviate  $\leq \pm 2\%$  from the mean dose for the target volume considered. Split course is not recommended.

The actual total treatment time should be kept within 110% of the prescribed time. Two daily external beam radiotherapy (EBRT) fractions at least 6 hours apart should be used to compensate for unplanned treatment breaks. The dose accumulation of EBRT should not exceed 12 Gy per week to avoid consequential late damage. For biological equivalence calculations, it is assumed that the  $\alpha/\beta$  is 10 Gy for tumor effects and 3 Gy for late normal tissue damage.

### **Vulvar target**

- PTV-T: minimum 64 Gy to the macroscopic disease volume in 2.0 Gy/fraction.
- PTV-V: 50 Gy to the subclinical disease volume in 1.7-1.8 Gy/fraction, though dose should be increased to 56 Gy in the areas of prior major surgery in order to overcome hypoxia in the field.

### **Nodal target**

- PTV-N: minimum 64 Gy to the macroscopic disease volume in 2.0 Gy/fraction.
- PTV-RN: 50 Gy to the subclinical disease volume in 1.7-1.8 Gy/fraction, though dose should be increased to 56 Gy in the areas of prior major surgery in order to overcome hypoxia in the field.

### **Dose variation**

- 98% of the PTV should receive at least 95% of the prescribed dose.

It is feasible to treat subclinical volume and gross tumour volume simultaneously. This can be achieved by delivering concomitant boost (additional daily fields of 0.2 - 0.3 Gy/fraction to the gross tumour volume within the big fields of 1.7-1.8 Gy/fraction to the subclinical disease).

## **8. Technique for EBRT**

- Stability and reproducibility in the patient set-up is of utmost importance during the whole radiotherapy procedure to reach the treatment goal. The same immobilization devices should be used during the whole radiotherapy procedure.
- When more than one beam is used, the technique should be isocentric.
- IMRT techniques are allowed though these guidelines do not take account of altered dose per fraction in the case of IMRT.
- The use of bolus material should be considered for the superficial parts of the target volumes, both for photon and electron beams.
- Beam shaping should be individualized according to target definitions; the use of a multileaf collimator (MLC) is recommended.

## **9. Minimal standards for quality assurance**

- Verification image of EBRT at start and mid time through treatment.
- In vivo dosimetry for EBRT.

## **10. Minimal standards for documentation**

- Dose plans and simulator and verification images must be stored for inspection.
- Total dose and dose per fraction, according to local specification practice, and total treatment time.
- ICRU point doses for each target volume.
- Maximum dose in the patient, mean dose with one standard deviation and dose volume histograms (DVH) for the PTV(s) (according to ICRU 50 and 62).
- Maximum doses at organs at risk and DVH.
- Treated Volumes for gross tumour and subclinical disease (as applicable).

## **11. References**

1. Hullu et al., Cancer 2002;95:2331-8.
2. Homesley HD et al., Gynecol Oncol 1993; 49:279.

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4. Curry SI et al., Gynecol Oncol 1980; 9:63.
5. Ericksson E et al., Gynecol Oncol 1984; 17:291

Other suggested literature:

- Chao et al., IJRPB 2002;54: 1147-52
- Russel, Chapter 14: Radiation therapy for vulvar cancer. In Eifel PJ & Levenback C: Cancer of the female lower genital tract; 2001, BC Decker Inc.
- Van Doorn, Neoadjuvant chemoradiation for advanced primary vulvar cancer. In: The Cochrane Library, issue 4, 2002, Oxford

## 12. Appendix

### Appendix 12.1: Staging and spread pattern

#### 12.1.1: FIGO Classification

**Table 1** Carcinoma of the vulva: FIGO nomenclature

<b>Stage 0</b>	Carcinoma <i>in situ</i> , intraepithelial neoplasia Grade III
<b>Stage I</b>	Lesions $\leq 2$ cm in size, confined to the vulva or perineum, no nodal metastasis
Ia	Lesions $\leq 2$ cm confined to the vulva or perineum and with stromal invasion $\leq 1.0$ mm*, no nodal metastasis
Ib	Lesions $\leq 2$ cm confined to the vulva or perineum and with stromal invasion $> 1.0$ mm*, no nodal metastasis
<b>Stage II</b>	Tumor confined to the vulva and/or perineum; $> 2$ cm in greatest dimension; no nodal metastasis
<b>Stage III</b>	Tumour of any size with adjacent spread to the lower urethra and/or the vagina, or the anus, and/or unilateral regional lymph node metastasis
<b>Stage IV</b>	
IVa	Tumour invades any of the following; upper urethra, bladder mucosa, rectal mucosa, pelvic bone, and/or bilateral regional node metastasis
IVb	Any distant metastasis including pelvic lymph nodes

\* The depth of invasion is defined as the measurement of the tumour from the epithelial-stromal junction of the adjacent most superficial dermal papilla, to the deepest point of invasion.

**Table 2** Carcinoma of the vulva: stage grouping for vulvar cancer

FIGO stage	T	UICC N	M
0	Tis	N0	M0
Ia	T1a	N0	M0
Ib	T1b	N0	M0
II	T2	N0	M0
III	T1	N1	M0
	T2	N1	M0
	T3	N0	M0
	T3	N1	M0
IVa	T1	N2	M0
	T2	N2	M0
	T3	N2	M0
	T4	Any N	M0
IVb	Any T	Any N	M1

**12.1.2: Spread Patterns:**

- Risk of lymph node metastases is dependant on both the size of primary tumour and its depth of invasion<sup>2</sup>.
- As a rule, metastatic spread follows the following pathway<sup>3</sup> (see Appendix II for anatomical illustration):
  - Superficial inguinal lymph nodes (*level 1*) →
  - Deep inguinofemoral nodes (*level 2*) →
  - Pelvic nodes along the external iliac artery – lower half only (*level 3*)
- The deep femoral nodes are always situated within the openings in the fascia at the fossa ovalis. No nodes are situated deeper than the level of femoral artery<sup>3</sup>.
- Primary tumours arising from clitoris or mons pubis have a risk of metastasising directly to the pelvic nodes situated along the external iliac artery and in the obturator<sup>4,5</sup>.
- There is about 20-25% risk of involvement of pelvic nodes (external iliac) if two or more inguinal nodes are positive<sup>4</sup>.
- Risk of metastatic spread to the contralateral inguinal nodes is minimal if the primary tumour is situated laterally (>1 cm lateral to midline)<sup>2</sup>.

## Appendix 12.2: Recommended dosages to target volumes for different clinical scenarios

### 12.2.1: Preoperative radiotherapy:

*Clinically & radiologically node negative patients:*

- Primary tumour in vulva, PTV-T: 50 Gy
- Subclinical disease in vulva, PTV-V: 50 Gy
- Subclinical nodal disease, Principle of “plus one level” and prophylactic RT: PTV-RN-1+2: 50 Gy

*Clinically & radiologically node positive patients:*

- Primary tumour in vulva, PTV-T: 50 Gy
- Subclinical disease in vulva, PTV-V: 50 Gy
- Gross tumour at nodal site, PTV-N: 50 Gy
- Subclinical nodal disease, Principle of “plus one level” and prophylactic RT: PTV-RN-1+2 and PTV-RN-3, as appropriate: 50 Gy

### 12.2.2: Radical radiotherapy:

*Clinically & radiologically node negative patients:*

- Primary tumour in vulva, PTV-T: minimum 64 Gy
- Subclinical disease in vulva, PTV-V: 50 Gy
- Subclinical nodal disease, Principle of “plus one level” and prophylactic RT: PTV-RN-1+2: 50 Gy

*Clinically & radiologically node positive patients:*

- Primary tumour in vulva, PTV-T: minimum 64 Gy
- Subclinical disease in vulva, PTV-V: 50 Gy 1.7-1.8 Gy/fraction, though dose should be increased to 56 Gy in the areas of prior major surgery.
- Gross tumour at nodal site, PTV-N: minimum 64 Gy
- Subclinical nodal disease, Principle of “plus one level” and prophylactic RT: PTV-RN-1+2 and PTV-RN-3, as appropriate: 50 Gy in 1.7-1.8 Gy/fraction, though dose should be increased to 56 Gy in the areas of prior major surgery.

### 12.2.3: Postoperative radiotherapy:

*Patients node negative on lymphadenectomy:*

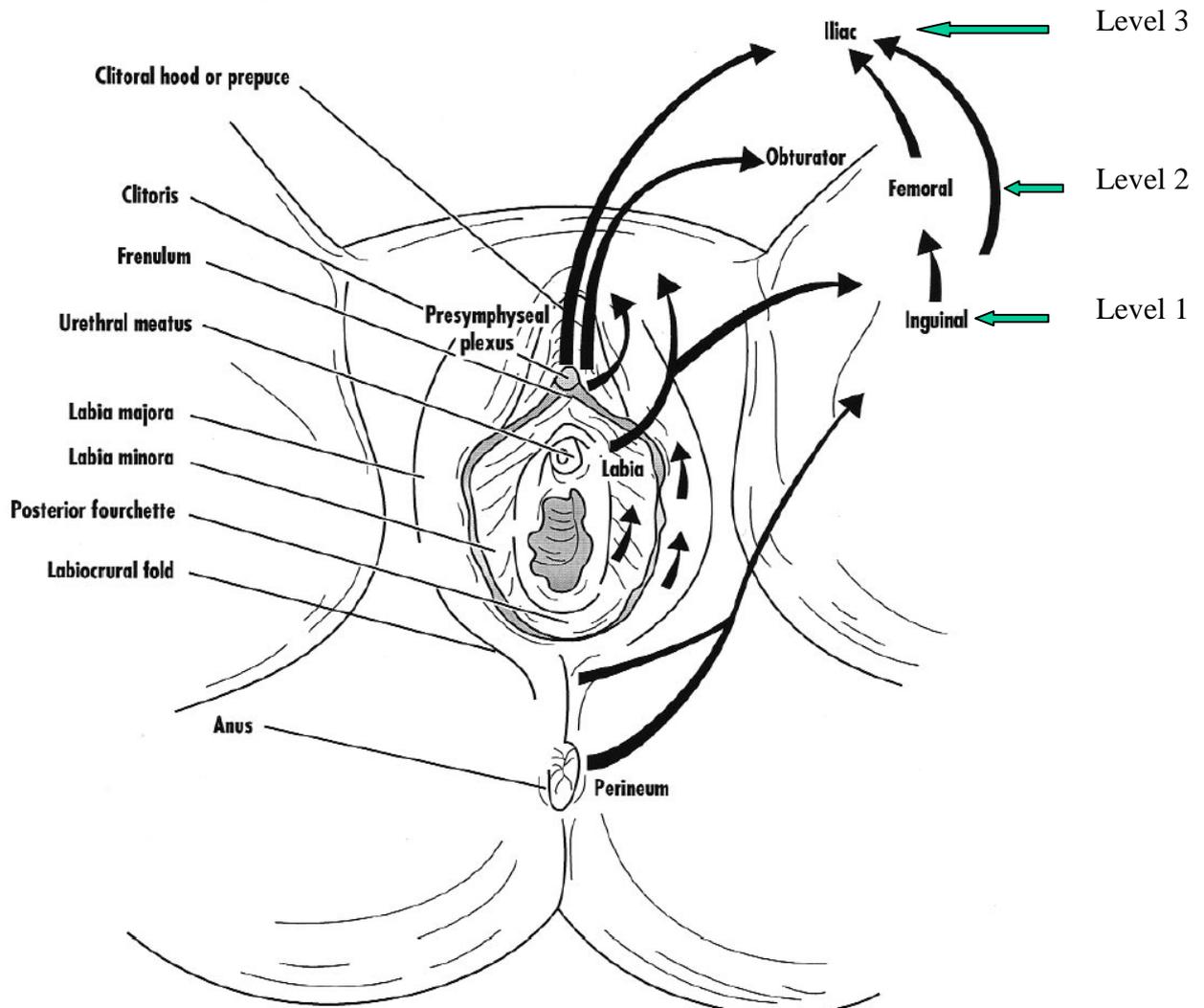
- Indications:
  - Gross tumour, which cannot be removed surgically without endangering function of anal sphincter or urethra.
  - Insufficient surgical margins: the margins of resection either not free of tumour or close ( $\leq 8$ mm on fixed specimen).
- Site of primary tumour in vulva, PTV-T: minimum 64 Gy
- Subclinical disease in vulva, PTV-V: 50 Gy in 1.7-1.8 Gy/fraction, though dose should be increased to 56 Gy in the areas of prior major surgery.
- Nodal sites: No indications for radiotherapy.

*Patients node positive on lymphadenectomy:*

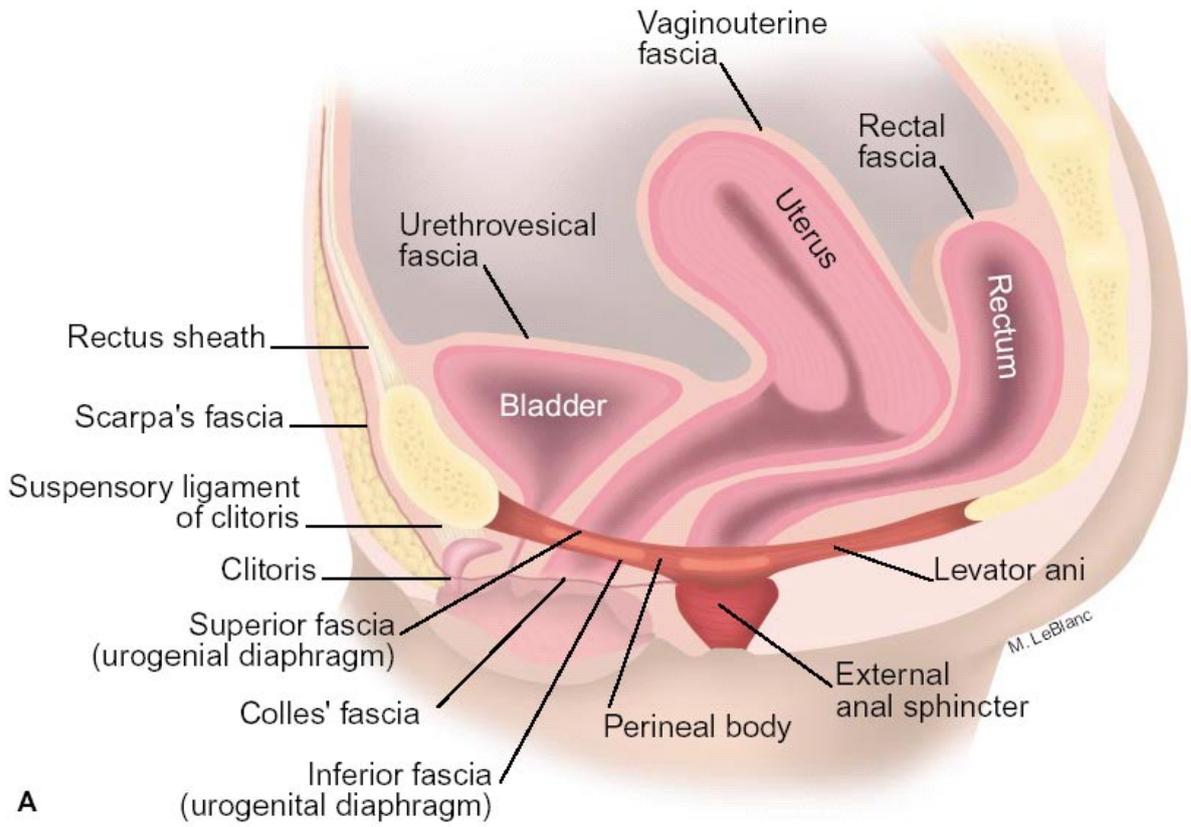
- Indications:
  - Gross tumour, which cannot be removed surgically without endangering function of anal sphincter or urethra.
  - Insufficient surgical margins: the margins of resection either not free of tumour or close ( $\leq 8$ mm on fixed specimen).

- Irradiation of the whole vulva to the sub-clinical dose may be considered for patients with positive lymph nodes, even if the surgical margins are sufficient.
- Site of primary tumour in vulva, PTV-T: minimum 64 Gy
- Subclinical disease in vulva, PTV-V: 50 Gy in 1.7-1.8 Gy/fraction, though dose should be increased to 56 Gy in the areas of prior major surgery.
- Gross tumour at nodal site, if any, PTV-N: minimum 64 Gy
- Subclinical nodal disease, Principle of “plus one level” and prophylactic RT:  
PTV-RN-1+2 and PTV-RN-3, as appropriate: 50 Gy in 1.7-1.8 Gy/fraction, though dose should be increased to 56 Gy in the areas of prior major surgery.

## Appendix 12.3: Anatomy of vulvar region & nodal levels



**Figure 14-1.** Anatomy and lymphatic drainage of the vulva and perineum. Lymphatic channels from the posterior vulva run anterior through the labia, and then laterally to the groin nodes. Lymphatic channels from the perineum and tissue lateral to the labiocrural fold traverse the upper medial thigh.



**Appendix 12.4: Example – target & patient fixation:**