



Provincial Vulva Cancer Treatment Guidelines

Approved at the Provincial Gyne-Oncology Guideline Meeting
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Clinical practice guidelines have been developed after multi-disciplinary consensus based on best available literature. As the name suggests, these are to be used as a guide only. These guidelines do not replace physician judgment which is based on multiple factors including, but not limited to, the clinical and social scenario, comorbidities, performance status, age, available resources and funding considerations. The Saskatchewan Cancer Agency disclaims all liability for the use of guidelines except as expressly permitted by the Agency. No portion of these guidelines may be copied, displayed for redistribution to third parties for commercial purposes or any non-permitted use without the prior written permission from the Agency.

Recommendations for drug treatment presented in the Agency's guidelines for a cancer site may not reflect provincial cancer drug funding. Please refer to the current Saskatchewan Cancer Agency drug formulary at www.saskcancer.ca for information on cancer drug listing and funding.

Benefits and risk of the proposed treatment should be discussed with patient.

Participating in clinical trials is encouraged when available. Involvement of a multidisciplinary team is strongly recommended.

Contents:

- 1) [Background and Epidemiology](#)
- 2) [Guideline Development](#)
- 3) [Target Population](#)
- 4) [Referral](#)
- 5) [Diagnosis and Work Up](#)
- 6) [FIGO Stage of Vulvar Cancer](#)
- 7) [Management of Early Vulvar Cancer](#)
- 8) [Management of Advanced vulvar Cancer](#)
- 9) [Adjuvant Treatment](#)
- 10) [Follow up and Surveillance](#)
- 11) [Discussion](#)
- 12) [References](#)

1) **Background and Epidemiology:**

Vulvar cancer is not common. It represents about 4 to 5% of all gynaecologic cancers. The incidence of vulvar cancer in North America is the highest, worldwide, at a rate of 1.63 per 100,000 women. Because it is uncommon, and it presents in many different skin lesion types, it is often not recognized or diagnosed early. Vulvar cancer typically affects older women. The median survival time for cancer of the vulva is 104 months and the five-year survival rate is 62.3% overall. Stage of diagnosis impact survival rates: the 5-year survival for stage I and stage II squamous cell carcinoma is 93.3% and 78.7%, respectively, versus 52.7% and 28.7% for stage III and stage IV squamous cell carcinoma, respectively. More than 75% of these cancers occur in women over age 55 and 30% in women over 75(1).

The staging is based on the International Federation of Obstetrics and Gynecology (FIGO) classification system, which was updated in 2009.

Vulvar cancer is a squamous cell type 85% of the time, though malignant melanoma occurs in 5-10%, and malignant melanoma is as aggressive on the vulva as it is elsewhere. It spreads locally through the skin, but also embolizes to the regional lymph nodes in the inguinal area. Prognosis is based on stage: the size of the lesion, the depth of invasion, the presence of disease in lymph nodes and the presence of any distant metastases to the urethra, rectum, bone, liver, and lungs.

Vulvar cancer has bimodal pattern of incidence, with Human Papilloma Virus infection (HPV) related cancer peaking in the 6th decade. This infection appears to be becoming more common and the proportion of vulvar cancer that is related to HPV is increasing (2). Differentiated vulvar cancer peaks at a later age and is more commonly associated with chronic skin conditions such as Lichen Sclerosus (LS). In fact, it is now recognized that women with LS have a 3-5% probability of developing vulvar cancer. Women with LS should therefore be closely followed. Biopsies should be taken to rule out cancer, especially when there are areas of hyperkeratosis (3). ‘

2) **Guideline Development:**

Existing guidelines considered for this review include the following: Society of Obstetricians and Gynaecologists of Canada guidelines (2006), National Cancer Institute guidelines (2009), the Royal College of Obstetricians and Gynaecologists guidelines (2006), the BC Cancer Agency (BCCA) guidelines, (2000), and Alberta health Services Guideline, 2011 (5-98).

3) **Target population:**

The recommendations outlined in this guideline will apply to adults over the age of 18 years with squamous cell carcinoma of the vulva. This guideline does not address patients with other less common vulvar cancer subtypes such as adenocarcinoma, basal cell carcinoma, and melanoma.

4) **Referral (when to refer):**

- Biopsy all suspicious lesions of the vulva
- Biopsy any lesion on the vulva which is not easily identified or does not respond to a short course of a topical treatment
- The biopsy may diagnose a pre-invasive disease, but this should be further evaluated at colposcopy as the biopsy may not be deep enough to diagnose an invasive cancer
- Sometimes more than one biopsy may be clinically indicated.
- Management of vulvar cancer is complex and requires multidisciplinary involvement. All patients should be referred to a gynecologic oncologist for surgery or radiotherapy or both if the clinical exam or biopsy results are positive for vulvar cancer or If suspicious on clinical presentation.
- An expert pathology review should be performed by a pathologist with experience in gynecologic pathology for discussion at multi-disciplinary tumour board rounds, which will triage patients for further management.

5) Diagnosis and Work-up:

- History and clinical examination, including pelvic examination
- Investigations:
 - Vulvar and / or groin lymph node biopsy
 - Chest x-ray
 - Blood work (CBC, LFT, renal function studies)
- Imaging (optional for > Stage 2) can include:
 - MRI pelvis, CT abdomen; chest x-ray;
 - CT /PET optional

The following investigations could be considered, as clinically indicated on individual case basis:

- CT chest/abdomen/pelvis
- PET-CT
- Examination under anesthesia (EUA) cystoscopy+/-sigmoidoscopy / proctoscopy

6) FIGO Stage of Vulvar Cancer:

Staging of cancer of the vulva is based on the Federation Internationale de Gynecologie et d'Obstetrique (FIGO) classification system (10), which was updated in 2010 (11).

Stage 1	Tumour confined to the vulva
IA:	Lesions ≤ 2 cm in size, confined to the vulva or perineum and with stromal invasion ≤ 1.0 mm *
IB:	Lesions > 2 cm in size or with stromal invasion > 1.0 mm *, confined to the vulva or perineum, with
<i>Stage II:</i>	Tumour of any size with extension to adjacent perineal structures (1/3 lower urethra, 1/3 lower Vagina, anus) with negative nodes
<i>Stage III:</i>	Tumour of any size with or without extension to adjacent perineal structures (1/3 lower urethra, 1/3 lower vagina, anus) with positive inguino-femoral lymph nodes
IIIA:	(i) With 1 lymph node metastasis (≥ 5 mm) or (ii) 1–2 lymph node metastasis (es) (< 5 mm)
IIIB:	(i) With 2 or more lymph node metastases (≥ 5 mm) or (ii) 3 or more lymph node metastases (< 5 mm)
IIIC:	With positive nodes with extra capsular spread
<i>Stage IV:</i>	Tumour invades other regional (2/3 upper urethra, 2/3 upper vagina), or distant structures
IVA:	Tumour invades any of the following: (i) upper urethral and/or vaginal mucosa, bladder mucosa, rectal mucosa or fixed to pelvic bone or (ii) fixed or ulcerated inguino-femoral lymph nodes

Primary Treatment of Invasive Squamous Cell Vulvar Cancer

Surgical management of the primary tumour and the lymph nodes depends on the size and location of the primary tumour. There is a role for sentinel node sampling in tumours < 2 cm in size.

7) Management of Early Vulvar cancer (Stage 1):

Early lateralized disease

Early disease central location

Early disease: Central Location and not possible to preserve sphincters & clitoris

Tumour size (cm)	Depth of invasion (mm)	Location	Recommended treatment	Adjuvant treatment
<2 cm	< 1 mm	Central/ lateral	Consider wide local excision	*Further excision/ adjuvant vulvar radiation
<2	> 1mm	Central	Consider radical local excision with bilateral lymphadenectomy	**Further excision ** adjuvant vulvar radiation not reexcision if nodes negative ***Adjuvant groin radiation if nodes positive
<2	>1 mm	Lateral	Consider radical local excision with unilateral lymphadenectomy	*Further excision/ adjuvant vulvar radiation ** adjuvant vulvar radiation not reexcision if nodes negative ***Adjuvant groin radiation if nodes positive
> 2	Any depth	Lateral/ central	Consider radical vulvectomy with unilateral / bilateral lymphadenectomy	*Further excision/ adjuvant vulvar radiation ** adjuvant vulvar radiation, not reexcision if nodes negative ***Adjuvant groin radiation if nodes positive

* if Unfavorable primary features:
Margins <8mm

**Depth > 5 mm and CLS positive

***Unfavorable nodes:
≥ 2 positive
or 1 through capsule

Primary radical radiotherapy is an alternative option for patients unsuitable for surgery and preservation of clitoris and anal sphincter is required.

Sentinel Node Assessment:

The sentinel lymph node (SLN) concept was successfully introduced initially in melanoma (12) and is standard of care in breast cancer (sensitivity of 88.6%– 91.2% and a negative predictive value (NPV) of 91.1%– 95.7%). It has a significant impact on postoperative morbidity for a large percentage of breast cancer patients. The systematic regional lymphadenectomy concept

assumes after the formation of a local tumour lesion, cancer cells spread in a stepwise manner from the primary lesion to their regional lymph nodes and finally to vital organs and it does not take into account the complex developmental and tumour biologic characteristics

The sentinel lymph node (SLN) is defined as the first node in a lymphatic basin that receives drainage from the primary tumour.

SLN can accurately predict the status of the nodes in the corresponding regional lymphatic basin making complete regional lymphadenectomy in the presence of a negative SLN unnecessary

The SLN procedure has been reported to have a detection rates in the range of 60%–90% for gynecologic malignancies, it is better when combined with radioisotope mapping. Currently, there are two mapping methods described for the detection of SLNs; Blue dye (include isosulfan blue, blue violet, and methylene blue) and radioactive tracer (it contains technetium-99m (Tc-99m) radioisotope bound to nanoparticles like colloidal sulphur or human albumin (12, 13).

Several investigators have reported a high rate of successful sentinel node identification in combination with the low incidence of false-negative sentinel node histology, in early-stage unifocal vulvar cancer patients with low groin recurrence rate and excellent survival (14, 15).

Management of Clinical Stage II and III:

Chemo-radiotherapy is an alternative option for patients with tumours > 2 cm unsuitable for surgery because of extent of tumour and preservation of clitoris and anal sphincter is required

Radical vulvectomy and bilateral inguinofemoral lymphadenectomy is indicated in those when groin lymph nodes are not clinically suspicious.

8) Management of Advanced Vulvar Cancer:

It includes Stage III or IV tumours where the primary lesion involves anus, rectum, rectovaginal septum, and/or upper urethra/bladder, or the presence of bulky groin nodes

Chemo-radiation is recommended as primary treatment in patients with advanced disease such as extension to perineal structures and positive nodes.

In order to determine the radiation field, the nodal status must be determined by surgical exploration by gynecologic oncologists for positive nodes. Chemo-radiation may be used as a single modality for treatment or it may be combined with delayed surgery when the residual tumour has shrunk enough to allow excision (3). However, this may be associated with more morbidity than either radiotherapy or chemotherapy alone with surgery.

Chemotherapy options include (5-FU) alone, 5-FU and cisplatin based on patient factors (renal function, ototoxicity, age, etc.)

Larger, but still respectable lesions, may require techniques of grafts or flaps to obtain complete removal of the lesion with an adequate margin (8 mm microscopic margins). This may require the expertise of plastic surgery in selected cases.

Surgery for vulvar cancer is associated with significant morbidities and possible complications. These include wound break down, wound infection, lymphedema, deep venous thrombosis, lymphocyst formation and others.

9) Adjuvant Treatment:

- Stage 1A: No adjuvant treatment is indicated
- Stage 1B: Postoperative radiotherapy could be considered for close positive margins if re-excision is not possible
- Stage II: Postoperative radiotherapy could be considered for close positive margins if re-excision is not possible
- Stage III A: postoperative groin radiation is not indicated
- Stage IIIB and IIIC: postoperative groin radiation is indicated
- Stage IVA and IVB: postoperative local radiation could be considered depending upon close positive margins

10) Follow Up and Surveillance:

Those patients who are treated with chemo-radiotherapy, as primary definitive treatment:

Clinical exam at 4-6 weeks after completion of treatment

- Other tests as clinically indicated (i.e. suspicious clinical exam): Imaging with CT or PET-CT, as indicated
- Examination under anesthesia (EUA) with biopsy, post-treatment, if outpatient exam is not possible (patient factor)

If imaging or biopsy is positive, salvage surgery may be considered

Long-term follow-up:

Ideally the initial evaluation should be done by a gynecologic oncologist to confirm healing and to evaluate for recurrences. When followed by a family physician or generalist, and if there is a suspicion for recurrence, patient should be referred back to a Gynecologic Oncologist

Early recurrences may be amenable to radical surgery such as pelvic exenteration or to radiation therapy if not already treated with maximal tolerable doses. Routine investigations are done only as clinically indicated.

Follow Up Protocol

- Year 1: every three months, or as clinically indicated
- Year 2: every four months, or as clinically indicated
- Years 3-5: every six months, or as clinically indicated
- Annually after, or as clinically indicated

The use of sentinel lymph node biopsies has been well-studied in melanoma and certainly has a place in the management of vulvar melanoma if the facilities are available. There is an increasing body of literature on the use of sentinel node biopsy for the management of squamous cell cancers of the vulva and it will likely become the standard of care.

11) Discussion:

For stage IA disease, the treatment is wide local excision alone; groin node dissection is not indicated because the risk of metastasis is very low (17).

The management of stage IB disease depends on the size, location, and depth of the tumour (5, 18). For tumours <2 cm wide local excision (WLE) or radical vulvectomy with complete unilateral lymphadenectomy can be considered for lateral tumours, while WLE or radical vulvectomy with bilateral lymphadenectomy can be considered for central tumours. For the treatment of any tumours >2 cm, radical vulvectomy with complete bilateral lymphadenectomy should be considered (7, 9). For women who are not candidates for initial surgical management, radiation therapy or chemo-radiotherapy could be considered for primary definitive treatment.

Adjuvant unilateral or bilateral radiotherapy in patients with more than two micrometastases, one macrometastases, and/or extra capsular spread is usually recommended (5). The recommendation was made on the basis that the presence of extra capsular tumour cells and a metastasis size of greater than 15 mm both have been associated with poor survival (19, 20).

Surgery is the first choice treatment for the groin nodes; primary radiotherapy should be kept as a reserve for individual patients not medically fit for surgery.

Preoperative chemo-radiotherapy may be used for the primary management of unresectable tumours and following treatment there is high chance that these lymph nodes can become resectable (21, 22).

For advanced vulvar cancer, neoadjuvant radiation with or without chemotherapy followed by radical surgery if there is still biopsy proven residual disease should be considered. However, this may be associated with more morbidity than either radiotherapy or chemotherapy alone with surgery.

Chemo-radiation is recommended as primary treatment in patients with advanced disease such as extension to perineal structures and positive nodes.

Chemotherapy options include fluorouracil (5-FU) alone or in combination with cisplatin, based on patient factors. The dosing regimen for 5-FU is 1000 mg/m² IV days 1-4 and day 29-32 of radiotherapy. Cisplatin should be given as 50 mg/m² IV on days 1 and 29 of radiotherapy (9, 23, 24). Dose reductions could be considered in the elderly (>70 years of age) and in those with evidence of vasculitis (e.g. diabetes).

The role of surgery for the removal of positive groin nodes is unclear. Intensity modulated radiation therapy (IMRT) can be used with locally advanced vulvar cancer.

The treatment is usually complex and it can be associated with significant complications. It is a relatively uncommon gynecological cancer, this is best evaluated by a gynec-oncologist when it is diagnosed and should be referred immediately.

12) References:

1. Ansink AC; Hientz AP. Epidemiology and etiology of squamous cell carcinoma of the vulva. *Eur J Obstet Gynecol Reprod Biol* 1993;48:111-5
2. Sturgeon SR, Brinton La, Devessa SS, Kurman RJ. In situ and invasive vulvar cancer incidence trends (1973-1987). *Am J Obstet Gynecol* 1992;166:1482-5
3. MacLean AB, Jones RW, Scurry J, Neill S. Vulvar Cancer and the Need for Awareness of Precursor Lesions. *Journal of Lower Genital Tract Disease* 2009; 13: 115-117
4. Homesley HD, Management of Vulvar Cancer. *Cancer* Nov. 15, 1995;76:10:2159-2170.
5. Faught W, et al. and the Society of Obstetricians and Gynaecologists of Canada. Management of squamous cell carcinoma of the vulva. *J Obstet Gynaecol Can* 2006;28(7):640–645.
6. National Cancer Institute. Vulvar Cancer Treatment. URL: <http://www.cancer.gov/cancertopics/pdq/treatment/vulvar/HealthProfessional/page5>. Retrieved: June 10, 2010.
7. Luesley, et al. and the Royal College of Obstetricians and Gynaecologists. Management of vulvar cancer. 2006. Published by the RCOG Press at the *Royal College of Obstetricians and Gynaecologists*, 27 Sussex Place, Regent's Park, London NW1 4RG. URL: www.rcog.org.uk.
8. BC Cancer Agency. Cancer Management Guidelines: Gynecology Vulva: Management. URL: <http://www.bccancer.bc.ca/HPI/CancerManagementGuidelines/Gynecology/Vulva/default.htm>. Retrieved on March 10, 2011.
9. Alberta health Service. Cancer Management Guidelines: Gynecology Squamous cell cancer of vulva: Management. URL: <http://www.albertahealthservices.ca/hp/if-hp-cancer-guide-gyne006-vulva.pdf> retrieved Nov 2012
10. Shepherd J. Revised FIGO staging for gynaecological cancer. *Br J Obstet Gynaecol* 96(8):889-92, 1989
11. FIGO Committee on Gynecologic Oncology. Revised FIGO staging for carcinoma of the vulva, cervix, and endometrium. *International Journal of Gynecology and Obstetrics* 105 (2009) 103–104
12. Morton DL, Wen DR, Wong JH, Economou JS, Cagk LA, Storm FR, et al. Technical details of intraoperative lymphatic mapping for early stage melanoma. *Arch Surg* 1992;127:392–9.
13. Levenback C, Burke TW, Morris M, Malpica A, Lucas KR, Gershenson DM. Potential applications of intraoperative lymphatic mapping in vulvar cancer. *Gynecol Oncol* 1995;59:216–20.
14. Terada KY, Coel MN, Ko P, Wong JH. Combined use of intraoperative lymphatic mapping and lymphoscintigraphy in the management of squamous cell cancer of the vulva. *Gynecol Oncol* 1998;70:65–9.
15. Ate G.J. Van der Zee, Maaik H. Oonk, Joanne A. De Hullu, Anca C. Ansink, Ignace Vergote, Sentinel Node Dissection Is Safe in the Treatment of Early-Stage Vulvar Cancer *J Clin Oncol* 26:884-889.
16. Hampl M, Hantschmann P, Michels W, et al: Validation of the accuracy of the sentinel lymph node procedure in patients with vulvar cancer: result of a multicentre study in Germany. *Gynecol Oncol* 2008;111:282-288.

17. Hacker NF, Van der Velden J. Conservative management of early vulvar cancer. *Cancer* 1993;71(4 Suppl):1673–7.
18. Stehman FB, Bundy BN, Dvoretzky PM, Creasman WT. Early stage I carcinoma of the vulva treated with ipsilateral superficial inguinal lymphadenectomy and modified radical hemivulvectomy: a prospective study of the Gynecologic Oncology Group. *Obstet Gynecol* 1992;79:490–7.
19. Paladini D, Cross P, Lopes A, Monaghan JM. Prognostic significance of lymph node variables in squamous cell carcinoma of the vulva. *Cancer* 1994;74:2491–6.
20. Van der Velden J, van Lindert AC, Lammes FB, ten Kate FJ, Sie-Go DM, Oosting H, et al. Extra capsular growth of lymph node metastases in squamous cell carcinoma of the vulva. *Cancer* 1995;75:2885–90.
21. Blake P. Radiotherapy and chemoradiotherapy for carcinoma of the vulva. *Best Pract Res Clin Obstet Gynaecol* 2003;17:649–61.
22. Montana GS, Thomas GM, Moore DH, Saxer A, Mangan CE, Lentz SS, Averette HE. Preoperative chemo-radiation for carcinoma of the vulva with N2/N3 nodes: a gynecologic oncology group study. *Int J Radiat Oncol Biol Phys*. 2000 Nov 1;48(4):1007-13
23. Thomas G, Dembo A, DePetrillo A, Pringle J, Ackerman I, Bryson P, Balogh J, Osborne R, Rosen B, Fyles A. Concurrent radiation and chemotherapy in vulvar carcinoma. *Gynecol Oncol*. 1989 Sep;34(3):263-7.
24. Beriwal S, Coon D, Heron DE, Kelley JL, Edwards RP, Sukumvanich P, Zorn KK, Krivak TC. Preoperative intensity-modulated radiotherapy and chemotherapy for locally advanced vulvar carcinoma. *Gynecol Oncol*. 2008 May;109(2):291-5.

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