SQUAMOUS CELL CARCINOMA OF THE VULVA

Effective Date: September 2013

The recommendations contained in this guideline are a consensus of the Alberta Provincial Gynecologic Oncology Team and are a synthesis of currently accepted approaches to management, derived from a review of relevant scientific literature. Clinicians applying these guidelines should, in consultation with the patient, use independent medical judgment in the context of individual clinical circumstances to direct care.

BACKGROUND

Cancer of the vulva represents approximately 5% of all gynecological malignancies. The incidence of vulvar cancer in North America is the highest, world wide, at a rate of 1.63 per 100,000 women. [1] Vulvar cancer typically affects older women (peak age of diagnosis is 75 years); [2] however, it appears to be increasing among younger women. [3,4] The most common histology is squamous cell carcinomas (90%), with the remaining 10% comprised of melanomas, adenocarcinomas, basal cell carcinomas, and sarcomas. [5] Staging is based on the Federation Internationale de Gynecologie et d'Obstetrique (FIGO) [6] classification system, which was updated in 2010. [7] A detailed description of this staging system can be found in the Appendix.

The median survival time for cancer of the vulva is 104.2 months and the five-year survival rate is 62.3% overall. [8] 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. [8] Likewise, increasing patient age negatively impacts survival: the 5-year survival rate (all vulvar cancer) is 96.0% for individuals aged 20-60 years vs. 68.8% for individuals aged 70 years and older. [8]

The purpose of this guideline is to recommend options for the management of vulvar cancer, based on the best evidence available.

GUIDELINE QUESTIONS

- What is the role of post-operative, adjuvant radiotherapy in early stage vulvar cancer?
- What is the role of definitive radiotherapy or chemoradiotherapy in advanced stage vulvar cancer?
- What is the role of sentinel lymph node biopsy in patients with clinically negative nodes, with tumours < 2 cm?
- What is the role of surgery in patients with metastasis to the inguinofemoral nodes?
- What is the most appropriate follow-up schedule for advanced stage patients treated with chemoradiotherapy only?

DEVELOPMENT

This guideline was reviewed and endorsed by the Alberta Provincial Gynecologic Oncology Tumour Team. Members of the Alberta Provincial Gynecologic Oncology Tumour Team include gynecologic oncologists, radiation oncologists, medical oncologists, pathologists, nurses, and pharmacists. Evidence was selected and reviewed by a working group comprised of members from the Alberta Provincial Gynecologic Oncology Tumour Team and a Knowledge Management Specialist from the Guideline Utilization Resource Unit. A detailed description of the methodology followed during the guideline development process can be found in the Guideline Utilization Resource Unit Handbook.

SEARCH STRATEGY

Entries to the Medline and EMBASE databases and clinical practice guideline databases (e.g. National Guidelines Clearinghouse, CancerView, etc.) were searched for evidence relevant to this topic. Search terms included: neoplasm AND vulva or vulvar, with limits of studies in humans, clinical trials, and studies in English. Studies that did not report response rates or survival rates were further excluded.

The initial search in 2011 returned a total of 55 relevant studies, which included clinical trials, retrospective studies, and case studies. The search was repeated in 2013 and returned a total of three relevant citations.

Existing guidelines considered for this review include the following: Society of Obstetricians and Gynaecologists of Canada guidelines (2006), [9] National Cancer Institute guidelines (2009), [10] the Royal College of Obstetricians and Gynaecologists guidelines (2006), [11] and the BC Cancer Agency (BCCA) guidelines (2000). [12] An effort was made to either adapt or adopt the most appropriate guidelines from other sources so that work wasn't duplicated. An evidence based perspective was used to draft proposals. Where evidence was weak, recommendations were based on group consensus.

TARGET POPULATION

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

RECOMMENDATIONS

I. Pre-Operative Investigations

Investigations should include:

- History and clinical exam, biopsy
- Chest x-ray
- Blood work (CBC, LFT, renal function studies)

The following investigations could be considered, as clinically indicated:

- CT chest/abdomen/pelvis
- Examination under anesthesia (EUA) cytoscopy +/- sigmoidoscopy/protoscopy, as clinically indicated

II. Primary Treatment

- Patients with a locally advanced primary or nodal disease should be referred for multidisciplinary clinical evaluation.
- An expert pathology review should be performed by a pathologist with experience in gynecologic pathology.
- Surgical management of the primary tumour and the lymph nodes depends on the size and location of the primary tumour (Table 1). [13]
- Radical radiotherapy could be considered as an alternative to surgery in patients deemed unsuitable for surgery because of site or extent of disease, or where preservation of the clitoris or anal sphincter is desired.
- In patients with tumours >2 cm, chemoradiotherapy could also be considered as an alternative to surgery in patients deemed unsuitable for surgery because of site or extent of disease, or where preservation of the clitoris or anal sphincter is desired.

Table 1. Surgical management of squamous cell carcinoma of the vulva

Tumour size (cm)	*Invasion (mm)*	*Location*	*Recommended surgery*
<2	<1	lateral or central	consider wide local excision
<2	<5	lateral	consider radical local excision with unilateral lymphadenectomy
<2	<5	central *	consider radical local excision with bilateral lymphadenectomy
<2	>5	lateral	consider radical vulvectomy with unilateral or bilateral lymphadenectomy
<2	>5	central *	consider radical vulvectomy with bilateral lymphadenectomy; separate groin incisions and unilateral lymphedenectomy for select early lesions may reduce morbidity
>2	any	lateral or central	consider radical vulvectomy with bilateral lymphadenectomy; separate groin incisions and unilateral lymphadenectomy for select early lesions may reduce morbidity

* Up to 1 cm from midline

- Chemoradiotherapy is recommended, as primary definitive treatment in patients with extension to adjacent perineal structures and/or positive nodes.
  - Chemotherapy options include: fluorouracil (5-FU) alone, 5-FU plus cisplatin, or 5-FU plus mitomycin-C, or cisplatin alone, based on patient factors (i.e. renal insufficiency, ototoxicity, deafness)
  - Radiotherapy volume and dose will be individualized by the radiation oncologist.

III. Adjuvant Treatment

- ***Stage IA:*** the preferred treatment for stage IA disease is wide local excision (WLE) only.
- ***Stage IB:*** post-operative radiotherapy could be considered for close positive margins, at the discretion of the radiation oncologist.
- ***Stage II:*** post-operative radiotherapy could be considered for close positive margins, at the discretion of the radiation oncologist.
- ***Stage III:***
  - Patients who are pathologically node positive should be referred to radiation oncology for clinical evaluation.
  - For patients with one lymph node metastasis (<5 mm and no extracapsular extension) post-operative radiotherapy is not recommended.
  - For patients with two or more lymph node metastases (≥5 mm) or three or more lymph node metastases (<5 mm), and for patients with positive nodes with extracapsular spread, post-operative radiotherapy is recommended.
  - If findings are positive for a unilateral groin node dissection for a small (<2 cm) lateral lesion, dissection of the contralateral groin is recommended.
  - Adjuvant local radiotherapy should also be considered for close margins.

- ***Stage IVA and IVB:*** for patients with invasion to regional (2/3 upper) structures or distant sites, with or without positive nodes, post-operative radiotherapy is recommended.
  - Adjuvant local radiotherapy should also be considered for close margins.

IV. Follow Up and Surveillance

Patients treated with chemoradiotherapy as primary definitive treatment should be seen as follows:
- Clinical exam at 4-6 weeks
- 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
- If imaging or biopsy is positive, consider salvage surgery.

Long-term follow-up of all patients should include:
- 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

DISCUSSION

For stage IA disease, the preferred treatment is wide local excision alone; groin node dissection is not indicated because the risk of metastasis is low. [13,14] However, the management of stage IB disease depends on the size, location, and depth of the tumour. [9,11,15] For tumours <2 cm with <5 mm invasion, wide local excision (WLE) with complete unilateral lymphadenectomy can be considered for lateral tumours, while WLE with bilateral lymphadenectomy can be considered for central tumours. For tumours <2 cm with >5 mm invasion, radical vulvectomy with unilateral or bilateral lymphadenectomy can be considered for lateral tumours, while 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.

For patients who are not candidates for surgery, radiation therapy or chemoradiotherapy could be considered for primary definitive treatment, as an alternative to surgery. However, salvage surgery should be considered if no response is documented after three months.

For node positive vulvar cancer, the preferred treatment (e.g. radiation therapy or inguinal lymphadenectomy), post-vulvectomy, remains uncertain. Results from a Gynecologic Oncology Group (GOG) RCT showed that, with a median follow-up of 74 months, the cancer-related death rate was significantly higher for pelvic node resection versus 45-50 Gy pelvic and groin radiation (51% vs. 29% at 6 years; HR 0.49, 95% CI 0.28-0.87; P=.015). Furthermore, six-year overall survival was significantly better for patients with clinically suspected or fixed ulcerated groin nodes who underwent radiation therapy compared with those who underwent node resection (P=.004). However, the relative risk of progression was 39% in radiation patients (95% CI 0.17-0.88, P=.02). In this study, greater than 20% positive ipsilateral groin nodes (number positive/number resected) was significantly associated with contralateral lymph node metastasis, relapse, and cancer-related death. [16,17] Unilateral or bilateral radiotherapy could be given at the discretion of the radiation oncologist in patients with more than two micrometastases, one macrometastases, and/or extracapsular spread.

Among patients with squamous carcinoma of the vulva and nonsuspicious (N0-1) inguinal nodes (n=48), a GOG trial showed that, following radical vulvectomy, groin radiation (50 Gy) to 3 cm resulted in excessive

groin relapse (18.5%), as compared with node dissection (0%), while node dissection resulted in better progression-free interval (p=.03) and survival (p=.04). [18] A recent Cochrane review on this topic concluded that surgery is still to be considered the first choice treatment for the groin nodes, but that individual patients not medically fit for surgery could be treated with primary radiotherapy. [19] The Society of Obstetricians and Gynaecologists of Canada (2006) recommend that patients with either three or more micrometastases in the groin with node size > 10 mm, with extracapsular spread, or with bilateral microscopic groin metastases should receive postoperative bilateral groin and pelvic radiation. [9] The recommendation was made on the basis that the presence of extracapsular tumour cells and a node size of greater than 15 mm both have been shown to negatively impact survival. [20,21]

Preoperative chemoradiotherapy may be used for the primary management of unresectable tumours. [22] A GOG trial [23] among patients (n=46) with N2/N3 lymph nodes evaluated the efficacy of preoperative split course of radiation (47.6 Gy to the primary and lymph nodes) with concurrent chemotherapy (cisplatin/5-FU). Following treatment, the lymph nodes became resectable in 95% of patients who completed treatment (38 of 40 patients); local control was achieved in the lymph nodes in 97% (36 of 37 patients) and in the primary area in 76% (29 of 38 patients). Disease-free survival was 50%.

For advanced vulvar cancer, neoadjuvant radiation with or without chemotherapy followed by radical surgery should be considered the best option for management. [9,11] However, this may be associated with more morbidity than either radiotherapy or chemotherapy alone with surgery. An alternative is to use two to four cycles of neoadjuvant chemotherapy followed by surgery. If there is still significant disease, consideration can be given to radiotherapy followed by a further assessment for possible surgery. Chemotherapy options include fluorouracil (5-FU) alone or in combination with cisplatin or mitomycin-C, based on patient factors. The dosing regimen for 5-FU is 1000 mg/m^2 IV days 1-4 and 29-32 of radiotherapy. [24] Cisplatin should be given as 50 mg/m^2 IV on days 1 and 29 of radiotherapy. [24,25] Mitomycin C is given as 15 mg/m^2 IV on day 1 of radiotherapy. [26,27] 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 (see discussion above on management of groin nodes). [11] Intensity modulated radiation therapy (IMRT) is currently considered experimental in patients with locally advanced vulvar cancer; however, in the future it may well have a role in the management of these patients. Beriwal, et al. (2008) showed that, among patients with stage II-IVA cancer (n=18), preoperative treatment with 5-FU and cisplatin plus twice-daily IMRT during the first and last weeks of treatment resulted in a 78% (14 of 18 patients) rate of surgery. Among these surgical patients, a response was observed in 100% (nine complete responses and five partial responses) and the recurrence rate was 21% (three patients; all partial responders). [28]

DISSEMINATION

- Present the guideline at the local and provincial tumour team meetings and weekly rounds.
- Post the guideline on the Alberta Health Services website.
- Send an electronic notification of the new guideline to all members of CancerControl Alberta.

MAINTENANCE

A formal review of the guideline will be conducted at the Annual Provincial Meeting in 2015. If critical new evidence is brought forward before that time, however, the guideline working group members will revise and update the document accordingly.

GLOSSARY OF ABBREVIATIONS

Acronym	Description
CBC	complete blood count
CI	confidence interval
CT	computed tomography
EUA	examination under anesthesia
FIGO	Federation Internationale de Gynecologie et d'Obstetrique
FU	Fluorouracil
HR	hazard ratio
IMRT	intensity modulated radiation therapy
LFT	liver function tests
PET-CT	positron emission tomography, computed tomography
RCT	randomized controlled trial
RR	relative risk
RT	radiotherapy
WLE	wide local excision

CONFLICT OF INTEREST

Participation of members of the Alberta Provincial Gynecologic Oncology Team in the development of this guideline has been voluntary and the authors have not been remunerated for their contributions. There was no direct industry involvement in the development or dissemination of this guideline. CancerControl Alberta recognizes that although industry support of research, education and other areas is necessary in order to advance patient care, such support may lead to potential conflicts of interest. Some members of the Alberta Provincial Gynecologic Oncology Team are involved in research funded by industry or have other such potential conflicts of interest. However the developers of this guideline are satisfied it was developed in an unbiased manner.

REFERENCES

[1] Cancer Research UK. Vulval cancer - UK incidence statistics. URL: http://info.cancerresearchuk.org/cancerstats/types/vulva/incidence/#Worldwide. Last updated: June 4, 2010 (retrieved: January 12, 2011).

[2] Crum CP. Carcinoma of the vulva: epidemiology and pathogenesis. Obstet Gynecol. 1992;79:448–54.

[3] Jones, R.W., J. Baranyai, and S. Stables, Trends in squamous cell carcinoma of the vulva: the influence of vulvar intraepithelial neoplasia. Obstet Gynecol, 1997. 90(3): p. 448-52

[4] Joura, E.A., et al., Trends in vulvar neoplasia. Increasing incidence of vulvar intraepithelial neoplasia and squamous cell carcinoma of the vulva in young women. J Reprod Med, 2000. 45(8): p. 613-5

[5] Jemal A, Tiwani RC, Murray T, Ghafoor A, Samuels A, Ward E, et al. Cancer Statistics 2004. CA Cancer J Clin 2004;54:8–29.

[6] Shepherd J. Revised FIGO staging for gynaecological cancer. Br J Obstet Gynaecol 96(8):889-92, 1989.

[7] 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.

[8] Kosary CL. National Cancer Institute: SEER Survival Monograph. URL: http://seer.cancer.gov/ publications/survival/surv_vulva.pdf. Retrieved: January 12, 2011.

[9] 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.

[10] National Cancer Institute. Vulvar Cancer Treatment. URL: http://www.cancer.gov/cancertopics/pdq/ treatment/vulvar/HealthProfessional/page5. Retrieved: June 10, 2010.

[11] Luesley, et al. and the Royal College of Obstetricians and Gynaecologists. Management of vulval 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.

[12] BC Cancer Agency. Cancer Management Guidelines: Gynecology Vulva: Management. URL: http://www.bccancer.bc.ca/HPI/ CancerManagementGuidelines/Gynecology/Vulva/default.htm. Retrieved on June 10, 2010.

[13] GOG 173 Study. Unpublished results from the SGO Meeting in San Francisco in 2010.

[14] Hacker NF, Van der Velden J. Conservative management of early vulvar cancer. Cancer 1993;71(4 Suppl):1673–7.

[15] Stehman FB, Bundy BN, Dvoretsky 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.

[16] Kunos C, Simpkins F, Gibbons H, Tian C, Homesley H. Radiation therapy compared with pelvic node resection for node-positive vulvar cancer: a randomized controlled trial. Obstet Gynecol. 2009 Sep;114(3):537-46.

[17] Homesley HD, Bundy BN, Sedlis A, Adcock L. Radiation therapy versus pelvic node resection for carcinoma of the vulva with positive groin nodes. Obstet Gynecol. 1986 Dec;68(6):733-40.

[18] Stehman FB, Bundy BN, Thomas G, Varia M, Okagaki T, Roberts J, Bell J, Heller PB. Groin dissection versus groin radiation in carcinoma of the vulva: a Gynecologic Oncology Group study. Int J Radiat Oncol Biol Phys. 1992;24(2):389-96.

[19] van der Velden K, Ansink A. Primary groin irradiation versus primary groin surgery for early vulvar cancer. Cochrane Database of Systematic Reviews 2001, Issue 4. Art. No.: CD002224.

[20] 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.

[21] van der Velden J, van Lindert AC, Lammes FB, ten Kate FJ, Sie-Go DM, Oosting H, et al. Extracapsular growth of lymph node metastases in squamous cell carcinoma of the vulva. Cancer 1995;75:2885–90.

[22] Blake P. Radiotherapy and chemoradiotherapy for carcinoma of the vulva. Best Pract Res Clin Obstet Gynaecol 2003;17:649–61.

[23] 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.

[24] Cunningham MJ, Goyer RP, Gibbons SK, Kredentser DC, Malfetano JH, Keys H. Primary radiation, cisplatin, and 5-fluorouracil for advanced squamous carcinoma of the vulva. Gynecol Oncol. 1997 Aug;66(2):258-61.

[25] Leiserowitz GS, Russell AH, Kinney WK, Smith LH, Taylor MH, Scudder SA. Prophylactic chemoradiation of inguinofemoral lymph nodes in patients with locally extensive vulvar cancer. Gynecol Oncol. 1997 Sep;66(3):509-14.

[26] Lupi G, Raspagliesi F, Zucali R, Fontanelli R, Paladini D, Kenda R, di Re F. Combined preoperative chemoradiotherapy followed by radical surgery in locally advanced vulvar carcinoma. A pilot study. Cancer. 1996 Apr 15;77(8):1472-8.

[27] 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.

[28] 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.

APPENDIX

Staging of cancer of the vulva is based on the Federation Internationale de Gynecologie et d'Obstetrique (FIGO) classification system (2010):

Stage I: Tumor confined to the vulva

- IA: lesions ≤2 cm in size, confined to the vulva or perineum and with stromal invasion ≤1.0 mm *, no nodal metastasis
- IB: lesions >2 cm in size or with stromal invasion >1.0 mm *, confined to the vulva or perineum, with negative nodes

Stage II: Tumor of any size with extension to adjacent perineal structures (1/3 lower urethra, 1/3 lower vagina, anus) with negative nodes

Stage III: Tumor 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 extracapsular spread

Stage IV: Tumor invades other regional (2/3 upper urethra, 2/3 upper vagina), or distant structures

- IVA: tumor 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
- IVB Any distant metastasis including pelvic lymph nodes

* The depth of invasion is defined as the measurement of the tumor from the epithelialstromal junction of the adjacent most superficial dermal papilla to the deepest point of invasion.