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No. 370-Management of Squamous Cell Cancer of the Vulva

This Clinical Practice Guideline has been prepared by the Society of Gynecologic Oncology of Canada (GOC) Guidelines Committee, and reviewed by the Society of Obstetricians and Gynaecologists of Canada (SOGC)'s Clinical Practice – Gynaecology and Guideline Management and Oversight committees and approved by the Executive and Board for GOC and by the Board of the SOGC.

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Key Words: Squamous cell vulvar cancer, sentinel lymph nodes, chemoradiation, surgery.

KEY MESSAGES

1. Any suspected lesion present on the vulva should be referred to an appropriate clinician for vulvar biopsy.
2. Once squamous cell cancer of the vulva is diagnosed, a referral should be made to a gynaecologic oncologist.
3. Vulvar SCC cases with extensive disease should be assessed prior to treatment in a multidisciplinary setting and multidisciplinary surgical teams.
4. Squamous cell cancer of the vulva has a high recurrence rate due to its association with HPV and skin dysplasia

Abstract

Objective: This guideline reviews the clinical evaluation and management of squamous cell cancer (SCC) of the vulva with respect to diagnosis, primary surgical, radiation, or chemotherapy management and need for adjuvant treatment with chemotherapy and/or radiation therapy. Other vulvar cancer pathologic diagnoses are not included in the guideline.

Intended Users: The first part of this document which includes recommendations 1 through 3 is for general gynaecologists, obstetricians, family doctors, registered nurses, nurse practitioners, residents, and health care providers with a focus on the

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presentation, diagnosis, and updated information about surgical procedures performed by subspecialists. The surgical management and treatment of advanced vulvar cancer are intended for gynaecologic oncologists, radiation oncologists, and medical oncologists who treat these complex patients. This guideline is intended to provide information for interested parties who may follow these patients once treatment is complete.

Target Population: Adult women (18 years and older) with SCC of the vulva. Excluded from these guidelines are women with preinvasive disease.

Options: Women diagnosed with SCC of the vulva should be referred to a gynaecologic oncologist for initial evaluation, consideration for primary surgery and inguinal lymph node assessment, and potentially adjuvant radiation and/or chemotherapy. All cases of vulvar cancer should have access to discussion at a multidisciplinary cancer case conference. Women who would otherwise require radical surgery such as abdominal-perineal resection or exenterative procedures may be considered for primary treatment with radiation and/or chemotherapy.

Evidence: For this guideline, relevant studies were searched in PubMed, Medline, and the Cochrane Systematic Reviews using the following terms, either alone or in combination, with the search limited to English language materials: vulva, vulvar cancer, inguinofemoral lymph node dissection, sentinel nodes, systemic chemotherapy, radiotherapy, neoadjuvant, adjuvant, primary, exenteration, survival, follow up. The initial search was performed in September 2016 with a final literature search in May 2017. Relevant evidence was selected for inclusion in the following order: meta-analyses, systematic reviews, guidelines, randomized controlled trials, prospective cohort studies, observational studies, non-systematic reviews, case series, and reports. Additional significant articles were identified through cross-referencing the identified reviews. The total number of studies identified was 286, and 78 studies were included in this review.

Validation Methods: The content and recommendations were drafted and agreed upon by the principal authors. The Executive and Board of the Society of Gynecologic Oncology of Canada reviewed the content and submitted comments for consideration, and the Board of the Society of Obstetricians and Gynaecologists of Canada approved the final draft for publication. The quality of evidence was rated using the criteria described in the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology framework (Table 1). The interpretation of strong and weak recommendations is described in Table 2. The Summary of Findings is available upon request.

Benefits, harms, and/or costs: These guidelines are to encourage physicians in the appropriate use of sentinel inguinal lymph node assessment for SCC of the vulva. The committee also promotes the centralization of treatment of vulvar cancer in specialized treatment centres.

Guideline update: Evidence will be reviewed 5 years after publication to decide whether all or part of the guideline should be updated. However, if important new evidence is published prior to the 5-year cycle, the review process may be accelerated for a more rapid update of some recommendations.

Sponsors: This guideline was developed with resources funded by the Society of Gynecologic Oncology of Canada and the Society of Obstetricians and Gynaecologists of Canada.

Summary Statements:

1. Clinical trials have demonstrated the clinical efficacy of the human papillomavirus vaccine in reducing the burden of vulvar intraepithelial neoplasia and, potentially, vulvar cancer (high).
2. Early stage vulvar cancer is well managed with local surgical excision and assessment of inguinal lymph node status for those with International Federation of Gynecology and Obstetrics stage IB and resectable stage II tumours (high).
3. The morbidity of inguinofemoral lymph node dissection for vulvar cancer can be significant and sentinel lymph node biopsy can reduce these complications (high).
4. There is a detection rate for inguinofemoral sentinel lymph nodes of 87% per groin when using a combination of radioactive colloid and blue dye (moderate).
5. Lateralized squamous cell cancer of the mid to posterior vulva ($>$1 cm from the midline) can forgo bilateral surgical assessment of clinically normal inguinofemoral lymph nodes (high).
6. Adjuvant radiation treatment improves overall survival when given for inguinofemoral macrometastases (high) and close surgical margins for squamous cell cancer of the vulva (low).
7. The addition of chemotherapy as a radiation sensitizer to radiation treatments may improve overall outcomes (low).
8. Primary radiotherapy can be used when surgery is either not an option or would cause extreme morbidity (moderate).
9. There is a paucity of data for the systemic treatment of surgically unresectable squamous cell cancer of the vulva, advanced disease with distant metastases, or recurrent disease previously treated with surgery, and/or radiation with or without chemotherapy, but platinum-based therapies currently demonstrate the greatest activity available (low).
10. Squamous cell cancers of the vulva have a high recurrence rate due to their association with human papillomavirus and skin dysplasia (high).
11. Vulvar squamous cell cancer with nodal recurrence is typically fatal and its treatment should be individualized and guided by the size of disease and previous treatment (low).

Recommendations:

1. Any worrisome vulvar lesion should be referred to an appropriate clinician for vulvar biopsy. Punch biopsies of adequate size (at least 4 mm wide) and depth (to subcutaneous fat) are most likely to achieve pathologic diagnosis (strong, high).
2. Once vulvar squamous cell cancer is diagnosed, a referral should be made to a gynaecologic oncologist (strong, high).
3. Clinicians should strongly recommend the human papillomavirus vaccine for all females 9 to 45 years of age to reduce the burden of all human papillomavirus–related diseases (strong, high).
4. Inguinal sentinel lymph node mapping for surgical staging of vulvar cancer is appropriate for unifocal tumours, $<$4 cm in widest diameter, of squamous cell histology, and where lymph nodes are not clinically suspicious (strong, high).
5. Surgeons developing skills in sentinel lymph node mapping for vulvar cancer staging should perform a minimum of 10 correlated cases of sentinel lymph node biopsy with subsequent complete inguinofemoral lymph node dissection prior to sentinel node mapping alone to reduce false-negative rates (strong, high).
6. Adjuvant radiation, including both inguinal and pelvic fields, should be given for any inguinofemoral lymph node macrometastasis ($\geq$5 mm), 2 or more micrometastases ($<$5 mm), or extracapsular spread (strong, high).
7. We suggest that adjuvant radiotherapy should be given for close ($\leq$10 mm on fresh and $\leq$8 mm on fixed pathologic specimens) and positive surgical margins for squamous cell cancer of the vulva

Table 1. Key to Grading of Recommendations, Assessment, Development and Evaluation (GRADE)

Strength of the recommendation	Definition
Strong	Highly confident of the balance between desirable and undesirable consequences (i.e., desirable consequences outweigh the undesirable consequences; or undesirable consequences outweigh the desirable consequences).
Weak[a]	Less confident of the balance between desirable and undesirable consequences.
Quality level of a body of evidence	Definition
High|++++	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate|+++0	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low|++00	Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.
Very low|+000	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[a] Weak recommendations should not be misinterpreted as weak evidence or uncertainty of the recommendation.
Examples: Strong, moderate|+++0: strong recommendation, moderate quality of evidenceWeak, Low|++00: weak recommendation, low quality of evidence.
Adapted from: Schünemann H, Bro_zek J, Guyatt G, et al. (editors). The GRADE Handbook. GRADE Working Group, 2013. Available at: http://gdt.guidelinedevelopment.org/app/handbook/handbook.html. Accessed on August 3, 2018.

Table 2. Judgement and interpretation of strong and conditional recommendations

Judgement/interpretation	Strong recommendation "We recommend. . ..."	Conditional recommendation "We suggest. . .."
Judgement by guideline panel	It is clear to the panel that the net desirable consequences of a strategy outweighed the consequences of the alternative strategy.	It is less clear to the panel whether the net desirable consequences of a strategy outweighed the alternative strategy.
Implications for patients	Most individuals in this situation would want the recommended course of action, and only a small proportion would not.	Most individuals in this situation would want the suggested course of action, but many would not.
Implications for clinicians	Most individuals should receive the intervention. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator.	Clinicians should recognize that different choices will be appropriate for each individual and that clinicians must help each individual to arrive at a management decision consistent with his or her values and preferences.
Implications for policy makers	The recommendation can be adopted as policy in most situations.	Policy making will require substantial debate and involvement of various stakeholders.

Adapted from: Schünemann H, Bro_zek J, Guyatt G, et al. (editors). The GRADE Handbook. GRADE Working Group, 2013. Available at: http://gdt. guidelinedevelopment.org/app/handbook/handbook.html. Accessed on August 3, 2018.

if surgical re-excision is not feasible or has potential for high surgical morbidity (weak, low).

8. The addition of radiosensitizing chemotherapy to adjuvant radiation may be beneficial; however, the evidence is extrapolation from cervical and anal canal cancer protocols (weak, low).
9. Chemotherapy should be considered as a radiosensitizer in primary radiation treatment (weak, low).
10. Primary radiotherapy should be given to patients who are not candidates for radical surgery, or where surgery would compromise the function of an organ (i.e., urethra, anus) (strong, moderate).
11. Patients with extensive vulvar squamous cell cancer that would require primary exenterative procedures for surgical removal should be assessed in a multidisciplinary setting with surgical and radiation teams for consideration of primary chemoradiation. When surgery is the preferred primary treatment for locally advanced squamous cell cancer of the vulva, a comprehensive approach is recommended for optimal results, including specialized surgical teams, which may include gynaecologic oncology, general surgery, plastic surgery, and urology (strong, high).
12. There is currently insufficient evidence to offer recommendations for a specific systemic chemotherapy combination, duration, or method of delivery for the treatment of squamous cell cancer of the vulva (weak, low).
13. There is a need for large cooperative group trials to determine the best treatment for women requiring systemic chemotherapy for squamous cell cancer of the vulva (strong, high).
14. All women previously treated for vulvar cancer benefit from long-term follow-up provided by an experienced health care provider able to detect any recurrence or second gynaecologic malignancy (weak, low).

INTRODUCTION

Cancer of the vulva is a rare malignancy that affects between 1 and 2 women in 10 000 annually[1]. It accounts for about 5% of the malignancies of the female genital tract[2]. Rare subtypes include adenocarcinomas, melanomas, or others[3], but the vast majority of tumours are SCC. This document will focus on SCC of the vulva.

Over the past decade there have been several advances in the identification, management, and prevention of vulvar cancer affecting the overall course of this disease. Historically, vulvar cancer was characterized by late presentation and radical surgical intervention with low OS[4]. With increased levels of education and awareness patients are now presenting earlier for evaluation. Overall, the 5-year survival rate related to vulvar cancer is increasing, with improvements in operative morbidity resulting from refinements in surgical techniques and radiation[1].

The first vulvar cancer guidelines of the FIGO were published in 1988, with updates in 1994 and 2009. The 1988 guideline included the surgical evaluation of lymph nodes for prognostic and treatment planning noting the inaccuracy of clinical estimation of lymph node metastases at the time of diagnosis[5]. Although the 1994 guidelines subdivided stage I disease and further delineated the prognostic significance of lymph node–positive disease[6], it was not until the 2009 revision that our more nuanced understanding of the prognoses associated with the extent of nodal metastasis was highlighted[7]. Specifically, the similarity in survival between stage I and II node-negative disease versus the heterogeneity in survival within stage III (node-negative and node-positive disease) is clearly outlined. This revised staging system has been successfully validated in the clinical setting[8]. Nodal status is one of the most important prognostic factors to consider in the management of vulvar cancer[9], and therefore recent efforts have focused on developing increasingly sophisticated methods of nodal evaluation, within the context of reduced operative morbidity.

The incidence of vulvar cancer has been considered bimodal in its age distribution, with a younger cohort of patients developing HPV-associated disease and an older cohort developing non–HPV-associated disease, often in a background of vulvar dystrophy such as lichen sclerosus[10]. With the introduction of the HPV vaccine a decade ago the landscape of vulvar cancer is likely to change significantly in the near future, and population studies are already showing the changing clinical environment with reduced HPV genotype prevalence associated with vulvar cancer[11].

ABBREVIATIONS

FIGO	International Federation of Gynecology and Obstetrics
GROINNSS-V	GROningen INternational Study on Sentinel nodes in Vulvar cancer
HPV	human papillomavirus
IFLD	inguinofemoral lymph node dissection
OS	overall survival
SCC	squamous cell cancer
SLNB	sentinel lymph node biopsy

PRESENTATION AND DIAGNOSIS

Early signs and symptoms of vulvar SCC can include itching not relieved by steroid creams or antifungals, pain, burning, thickening of the skin with white or reddish patches, and scaling of the skin[3]. As the condition worsens a mass may develop with ulceration, bleeding, fluid discharge from the tumour, increasing pain, and enlarged lymph nodes within the inguinal area[3]. With any skin complaint, the most important steps in diagnosis are the physical examination and skin biopsy, both of which are often delayed as women try over-the-counter medications for relief or doctors prescribe medications without assessing the lesion[3]. Any identified lesion on visual inspection or colposcopy should be biopsied with either a punch biopsy (minimum 4 mm diameter) or wide excision prior to treatments with steroid cream[12]. An adequate punch biopsy should be taken from the area of strongest clinical suspicion for disease and must be sufficiently deep to include full-thickness skin with some of the underlying subcutaneous fat[12]. Clinically suspicious nodes may be assessed by fine-needle aspiration. When advanced disease is suspected on physical examination, further investigation with computed tomography scan, positron emission tomography scan, cystoscopy, and sigmoidoscopy may be performed to help confirm advanced metastatic disease prior to treatments[3].

Recommendations

1. Any worrisome vulvar lesion should be referred to an appropriate clinician for vulvar biopsy. Punch biopsies of adequate size (at least 4 mm wide) and depth (to subcutaneous fat) are most likely to achieve pathologic diagnosis (strong, high).

2. Once vulvar squamous cell cancer is diagnosed, a referral should be made to a gynaecologic oncologist (strong, high).

Pre-invasive Disease

This guideline will not address the management of pre-invasive disease of the vulva, but we refer you to the American College of Obstetricians and Gynecologists guideline, "Management of Vulvar Intraepithelial Neoplasia," for further information[13].

Impact of HPV Vaccine

Results from recently completed phase III clinical trials demonstrate that a widely disseminated HPV vaccine program has the potential to decrease the burden of HPV-associated precancers and cancers[14–17]. It is estimated that approximately 80% of vulvar SCCs usually found in younger women are HPV associated[18]. The magnitude of reduction in vulvar cancer incidence with HPV vaccination will be not be evident for some time, but it is expected to be significant[18]. For detailed information about the HPV vaccine and its impacts, readers should refer to *Contemporary Clinical Questions on HPV Related Disease and Vaccinations,*[18] where there is strong evidence supporting the use of the HPV vaccine for all females 9 to 45 years of age.

Summary Statement

1. Clinical trials have demonstrated the clinical efficacy of the human papillomavirus vaccine in reducing the burden of vulvar intraepithelial neoplasia and, potentially, vulvar cancer (high).

Recommendation

3. Clinicians should strongly recommend the human papillomavirus vaccine for all females 9 to 45 years of age to reduce the burden of all human papillomavirus–related diseases (strong, high).

Surgically Resectable Early Stage Vulvar Cancer

Stage I vulvar cancer is divided into FIGO stage IA: tumour confined to the vulva or perineum, ≤ 2 cm in size with stromal invasion ≤ 1 mm, and FIGO stage IB: tumour confined to the vulva or perineum, >2 cm in size or with stromal invasion >1 mm depth of invasion[8]. From a surgical perspective, stage IA lesions can be managed by wide local excision with clear macroscopic margins without nodal evaluation due to the exceptionally low frequency of lymph node metastases. Stage IB and surgically resectable stage 2 lesions require a radical wide local excision of the vulva with a 1- to 2-cm margin extending to the inferior fascia layer of the urogenital diaphragm with assessment of the ipsilateral lymph nodes in a well-lateralized lesion (at least 1 cm from the midline) or bilateral lymph node assessment in a midline lesion or a lesion on the anterior vulva[19]. Radical wide local excisions and inguinal lymph node assessment should be performed by specialists in gynaecologic oncology. Lymph node assessment can be done by either complete IFLD or sentinel lymph node mapping depending on tumour size and the presence or absence of clinically enlarged lymph nodes. Procedure selection criteria will be discussed in the following section (Figure 1). The remainder of this document discusses the specialized procedures provided by a gynaecologic oncology service that are required to adequately evaluate and treat women with SCC of the vulva.

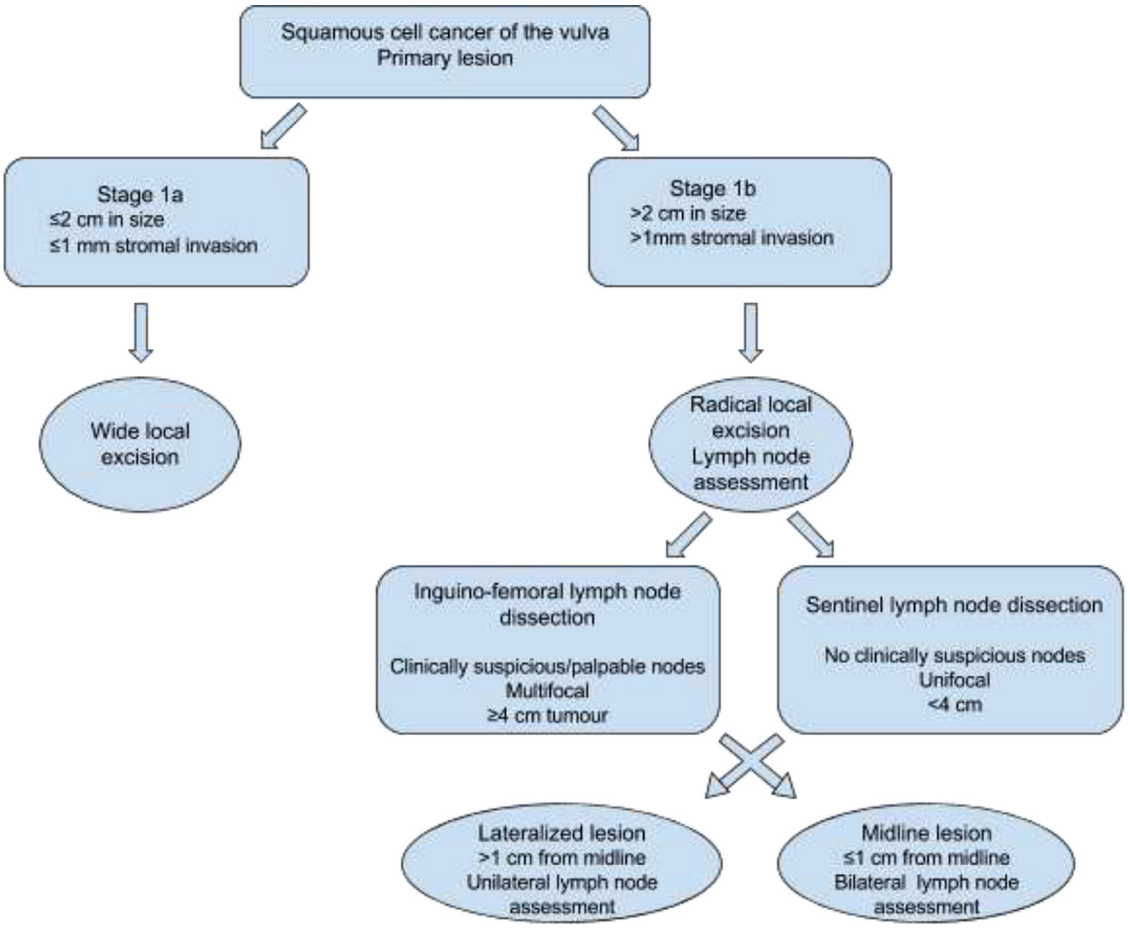
Summary Statement

2. Early stage vulvar cancer is well managed with local surgical excision and assessment of inguinal lymph node status for those with International Federation of Gynecology and Obstetrics stage IB and resectable stage II tumours (high).

Sentinel Inguinal Lymph Node Assessment

Over the past decade there has been a gradual shift towards offering SLNB in vulvar cancer over IFLD, with an acceleration in the uptake of SLNB after the publication of the GROINSS-V trial in 2008[20]. GROINSS-V was a multicentre observational study in which patients with a negative sentinel lymph node no longer underwent IFLD. Recurrence rates in the inguinal region were similar between the SLNB and IFLD groups. This trial has highlighted several important criteria in offering SLNB over IFLD. Specifically, tumours should be unifocal, <4 cm in widest diameter, SCC, with no clinically suspicious nodes[20]. Also, a small study (27 patients) has suggested that it is possible to repeat sentinel nodes in recurrent disease; however, the procedure appears technically challenging, has a lower success rate, and is not accepted standard of care[21]. Small retrospective trials suggest that SLNB can be performed after vulvar surgery within a reasonable time frame (less than 3 months)[22]. Clinical consideration may be given for using an SLNB approach in patients who require a full IFLD to help target specific lymph nodes within the nodal bundle for ultrastaging by the pathologist. It has been noted that surgical operator experience and centre procedural knowledge base play a significant role in the rate of groin recurrence[21]. In the

Figure 1. Surgical treatment of early-stage SCC of the vulva.



GROINSS-V trial, the failure rate was 36% in the first 2 years of procedure implementation but 15% per subsequent year (or afterwards). Expert opinion suggests that a minimum of 10 correlated cases (SLNB followed by IFLD) should be performed to ensure a sufficiently low false-negative rate. To evaluate whether mid to posterior vulvar lesions between 1 and 2 cm from the midline could forgo a bilateral lymph node assessment, Gynecologic Oncology Group 173 did a subgroup analysis of laterally ambiguous lesions and found no sentinel lymph nodes mapped to the contralateral groin[23]. A study also assessed that if there is a positive unilateral SLNB and the other side has a negative SLNB, the risk for contralateral non-SLN metastases appears to be low (0 of 28 patients)[24]. In a recent publication by Covens et al., a meta-analysis found the detection rate of sentinel nodes to be 87% per groin using a combination of radioactive colloid and patent blue dye[25].

The morbidity of an IFLD procedure is significant: wound dehiscence, seroma formation, infections, thrombosis, and chronic lymphedema. As a result of these findings, and in association with improved quality of life,[26] SLNB may be a better alternative than IFLD for many patients.

Summary Statements

3. The morbidity of inguinofemoral lymph node dissection for vulvar cancer can be significant and sentinel lymph node biopsy can reduce these complications (high).
4. There is a detection rate for inguinofemoral sentinel lymph nodes of 87% per groin when using a combination of radioactive colloid and blue dye (moderate).
5. Lateralized squamous cell cancer of the mid to posterior vulva (>1 cm from the midline) can forego bilateral surgical assessment of clinically normal inguinofemoral lymph nodes (high).

Recommendations

4. Inguinal sentinel lymph node mapping for surgical staging of vulvar cancer is appropriate for unifocal

tumours, <4 cm in widest diameter, of squamous cell histology, and where lymph nodes are not clinically suspicious (strong, high).

5. Surgeons developing skills in sentinel lymph node mapping for vulvar cancer staging should perform a minimum of 10 correlated cases of sentinel lymph node biopsy with subsequent complete inguinofemoral lymph node dissection prior to sentinel node mapping alone to reduce false-negative rates (strong, high).

Advanced Vulvar Cancer

Although surgical resection with or without adjuvant treatment has long been the standard of care in smaller lesions, the management of advanced disease, including unresectable primary disease, disease that would otherwise require an extensive surgical procedures such as abdominal-perineal excision or exenteration, or disease involving fixed or ulcerated nodes, has varied over the past several decades. Since the 1980s external beam radiotherapy with or without the use of interstitial brachytherapy has been the mainstay in the management of advanced vulvar cancer[27]. Recent advances in surgical technique for exenterative procedures have demonstrated lower rates of mortality and morbidity than previously reported[28]. Chemotherapy alone has also been demonstrated to result in disease regression or stability[29–31], but chemoradiation remains the preferred option of most clinicians.[32,33] Although preoperative chemoradiation generally decreases the size and resectability of tumours, the morbidity of surgery after radiation is not insignificant[33]. Primary chemoradiation treatment (doses >55 Gy) for unresectable lesions can offer comparable survival rates to chemoradiation followed by surgery while avoiding the potential surgical complications[34].

Adjuvant Radiotherapy

There are 2 clinical scenarios in which adjuvant radiotherapy following surgery is recommended: lymph node metastases ≥5 mm (Table 3), and close/positive surgical margins. Homesley et al. conducted a randomized controlled trial in inguinal node–positive patients identified by complete groin node dissections that randomized women to surgical ipsilateral pelvic lymph node dissection to the affected side versus bilateral radiotherapy to the groin and pelvic lymph nodes[35]. The 2-year survival was improved in the radiotherapy group (75% vs. 56%, $P = 0.03$), but this advantage was limited to inguinal macrometastases. In the update published in 2009 the 6-year OS difference was no longer present (51% vs. 41%, $P = 0.18$), but still in favour of radiotherapy[36]. However, cancer-specific mortality remains higher in the patients treated with pelvic lymphadenectomy rather than with radiotherapy (51% vs. 29%, $P = 0.015$).

Table 3. Indications for adjuvant radiotherapy of metastatic groins lymph nodes

1 lymph node micrometastasis (<5 mm)	No adjuvant radiotherapy
Any lymph node macrometastasis (≥5 mm)	Adjuvant radiotherapy, including inguinal and pelvic fields
2 or more lymph node micrometastases (<5 mm)	Adjuvant radiotherapy, including inguinal and pelvic fields
Any extracapsular spread	Adjuvant radiotherapy including inguinal and pelvic fields

In Gynecologic Oncology Group 88, patients with clinically normal inguinal nodes following radical vulvectomy were randomized to either bilateral groin dissection or groin radiotherapy[37]. The study was prematurely closed because there were 8 disease-related deaths in the radiotherapy arm, 5 of which had nodal relapse. A subsequent analysis showed that inadequate radiotherapy techniques were used and the patients were likely underdosed[38]. Further studies showed if adequate radiotherapy is used there is no difference in outcome between nodal dissection and radiotherapy to the nodes[39]; however, groin node dissection and radiotherapy carry a different spectrum of toxicity that must be considered. Radiation to the pelvis has demonstrated equivalence to pelvic node dissection and therefore pelvic radiation is also included, in lieu of pelvic node dissection[36].

At present there are no reported prospective trials of intensity-modulated radiotherapy, which uses advanced computer programs and imaging to deliver higher doses of radiation to tumours with minimal dosing to surrounding tissues, in the management of vulvar cancer. In retrospective and preliminary trials, IMRT techniques have resulted in superior tissue sparing and lower complication rates[40–42]; however, extrapolation from anal cancer suggests a higher rate of marginal misses and locoregional failure.[43,44]

It is widely accepted that margins of ≥10 mm on fresh tissue and ≥8 mm on pathology fixed specimen are considered adequate[45]. A meta-analysis of literature and 148 patients seen at Leiden, The Netherlands, showed no difference in local recurrence between <8 mm and ≥8 mm; however, 40% of patients received additional treatment. Tumour-positive margin was the only independent risk factor for local recurrence in multivariable analysis[46]. Similarly, Woelber et al. reported 286 patients who did not receive any adjuvant therapy[47]. There was no difference in local recurrence <8 mm versus ≥8 mm (12.6% and 10.2%), with no recurrences identified in 36 patients if the margin was ≥11 mm. However, Ignatov et al. showed improvement in

survival in 65 cases with close or positive margins (≤10 mm) who received adjuvant radiotherapy[48]. The 5-year OS of patients with close/positive surgical margins without radiation was 29% versus 68% with radiation. Notably, patients with close/positive surgical margins who received radiation of the vulva had a 5-year survival rate equivalent to that of patients with negative margins (>10 mm) (68%).

Chemotherapy in Addition to Adjuvant Radiation

The use of chemotherapy as a radiosensitizer in the treatment of vulvar cancer is largely based on extrapolation from cervical and anal canal cancer protocols, generally using a combination of 2 of the following agents: cisplatin, mitomycin C, fluorouracil, paclitaxel, and ifosfamide[49]. The addition of chemotherapy may be beneficial in node-positive vulvar SCC patients when more than 1 node is involved[50]. Analysis of the National Cancer Database of 473 patients who received concomitant chemotherapy and radiotherapy showed median survival without and with adjuvant chemotherapy of 29 months and 44 months, respectively ($P = 0.001$), resulting in a 38% reduction in the risk of death (hazard ratio 0.62, 95% confidence interval 0.48−0.79, $P < 0.001$)[50].

Surgery Versus Primary (Chemo)Radiotherapy

There are no randomized trials comparing surgery with the combination of chemotherapy and radiotherapy. Patients receiving primary (chemo)radiotherapy often have more advanced stage disease, poorer overall health, and centrally located disease. The largest series in the literature from 3 institutions thus far has collected 46 patients undergoing primary chemoradiation (median stage III, size 5 cm) and 222 patients undergoing surgery (median stage I, 3 cm)[51]. The OS was significantly longer for patients who had primary surgery, 131 months versus 70 months (P value <0.01), but there was no statistical difference in PFS ($P = 0.38$). Published data for stage III and IV patients treated with chemoradiation versus surgery (33 and 30 patients, respectively), with a median follow-up of 31 months, identify no difference in OS (76% vs. 69%, respectively) or PFS[52].

Primary (Chemo)Radiotherapy

Primary radiotherapy with concomitant chemotherapy in treatment of stage III and IV vulvar cancer is reserved for patients in whom surgery is not a feasible option. Various trials have used radiotherapy with maximal dosing from 47−65 Gy (dose per fraction about 2 Gy) in addition to weekly cisplatin or mitomycin C with or without 5-fluorouracil.[33,49,53,54] Complete pathological response is about 70%,[33] with a 5-year survival of about 50%[53]. It appears that the dose per fraction should be kept at 1.8−2 Gy and the total dose should be ≥60 Gy. The treatment time should be kept under 8 weeks.

Summary Statements

6. Adjuvant radiation treatment improves overall survival when given for inguinofemoral macrometastases (high) and close surgical margins for squamous cell cancer of the vulva (low).
7. The addition of chemotherapy as a radiation sensitizer to radiation treatments may improve overall outcomes (low).
8. Primary radiotherapy can be used when surgery is either not an option or would be extremely morbid moderate).

Recommendation

6. Adjuvant radiation, including both inguinal and pelvic fields, should be given for any inguinofemoral lymph node macrometastasis (≥5 mm), 2 or more micrometastases (<5 mm), or extracapsular spread (strong, high).
7. We suggest that adjuvant radiotherapy should be given for close (≤10 mm on fresh and ≤8 mm on pathology fixed specimen) and positive margins for squamous cell cancer of the vulva if surgical re-excision is not feasible or has potential for high surgical morbidity (weak, low).
8. The addition of radiosensitizing chemotherapy to adjuvant radiation may be beneficial; however, the evidence is extrapolation from cervical and anal canal cancer protocols (weak, low).
9. Chemotherapy should be considered as a radiosensitizer in primary radiation treatment (weak, low).
10. Primary radiotherapy should be given to patients who are not candidates for radical surgery, or where surgery would compromise the function of an organ (i.e., urethra, anus) (strong, moderate).

SURGICAL EXENTERATION AND RECONSTRUCTION

To achieve optimal surgical margins, resection of vulvar SCC tumours may leave large defects. Most often, primary defect closure will be achievable. However, to prevent excessive tension or in scenarios where there is poor tissue mobility, myocutaneous flaps or skin grafting may be necessary[55]. A collaborative approach with plastic surgery teams is to be encouraged in complex situations. Although locally advanced tumours with urethral, extensive vaginal, or anal involvement can be managed with primary

exenterative surgery, it is preferred, nowadays, to offer primary chemoradiation in such clinical situations.[55,56]

Recommendation

11. Patients with extensive vulvar squamous cell cancer that would require primary exenterative procedures for surgical removal should be assessed in a multidisciplinary setting with surgical and radiation teams for consideration of primary chemoradiation. When surgery is the preferred primary treatment for locally advanced squamous cell cancer of the vulva, a comprehensive approach is recommended for optimal results, including specialized surgical teams, which may include gynaecologic oncology, general surgery, plastic surgery, and urology (strong, high).

Systemic Chemotherapy in Vulvar Cancer

Systemic chemotherapy is offered to patients with advanced or recurrent disease not amenable to surgical resection or radiation treatment. Additionally, neoadjuvant chemotherapy may be considered in women with locally advanced disease who would otherwise require an exenterative procedure, as a reduction in tumour size may allow for a less morbid operation.

There are no randomized control trials to guide selection of the most optimal chemotherapy regimen for SCC of the vulva in the neoadjuvant, adjuvant, or palliative setting. Conclusive evidence is hampered by low patient volumes at each treatment centre. Current publications include phase II trials, prospective data collection, retrospective reviews, and case reports.

The first group to publish a case report on systemic chemotherapy for unresectable vulvar cancer was Shimizu et al., using a combination of bleomycin, vincristine, mitomycin C, and cisplatin[29]. The patient had a complete clinical response and was eligible for a radical vulvectomy with inguinal node dissection. Other clinical trials had mixed results using bleomycin as the base of their chemotherapy regimens[31,57], and due to the concerns of high chemotherapy toxicity, including pulmonary fibrosis, further publications have focused on platinum-based treatments.[58–62] A recent pooled analysis looked at systemic agents used and the clinical outcomes of 97 patients with stage III/IV vulvar cancer who required neoadjuvant chemotherapy or had already received radiation treatment[63]. Of the 3 chemotherapy regimens, the 5-year survival rate was 53% for bleomycin, 58% for cisplatin combined with 5-fluorouracil, and 74% for a cisplatin/paclitaxel combination.

There are few studies published on targeted agents in vulvar cancer that demonstrate some activity against SCC of the vulva. Cetuximab and erlotinib, targeted agents for epidermal growth factor receptor (EGFR), have been used in a few case reports.[64–66]

Summary Statement

9. There is a paucity of data for the systemic treatment of surgically unresectable squamous cell cancer of the vulva, advanced disease with distant metastases, or is recurrent disease previously treated with surgery, and/or radiation with or without chemotherapy; but platinum-based therapies currently demonstrate the greatest activity available (low).

Recommendations

12. There is currently insufficient evidence to offer recommendations for a specific systemic chemotherapy combination, duration, or method of delivery for the treatment of squamous cell cancer of the vulva (weak, low).
13. There is a need for large cooperative group trials to determine the best treatment for women requiring systemic chemotherapy for squamous cell cancer of the vulva (strong, high).

Recurrence Rates and Survival

All women treated for vulvar SCC will require close follow-up. Moreover, as vulvar SCC may be a manifestation of HPV disease or other underlying chronic vulvar disease (lichen sclerosus, Paget's disease, etc.), long-term surveillance is mandatory[67]. Based on a study by Oonk et al. in 2003, close follow-up of women treated for SC vulvar cancer is associated with earlier detection of recurrences and consequently identification of smaller tumours[68].

From 12% to 37% of patients will experience a recurrence after their initial treatment.[69–71] As shown by Gonzalez et al., most vulvar cancer recurrences will occur in the first 2 years[72]. Nevertheless, 35% of relapses arise 5 years or more after the initial diagnosis. Lymph node status is the strongest predictor of survival, disease site recurrence, and metastatic disease[69]. Other recurrence risk factors include the clinical cancer stage, tumour size, depth of invasion, and lymphovascular space invasion (LVSI)[69]. Advanced age is also a poor prognostic factor. Recent data suggest that HPV-induced vulvar SCC tends to have a better prognosis than non–HPV-associated disease,[73] similar to the head and neck literature.

The following are 5-year OS rates by stage based on the FIGO statistics on patients with vulvar SCC from 1999 to 2001[74]:

- Stage I: 78.5%
- Stage II: 58.8%
- Stage III: 43.2%
- Stage IV 13%

There are no definitive studies to guide optimal follow-up strategy for patients treated for vulvar SCC, but most authors agree on a targeted history and a complete physical examination of the perineum, special attention to scars and skin bridges, as well as inguinal examination and appropriate follow-up of any abnormal cytology of the cervix or anus. Any suspicious lesion should be biopsied. No routine imaging is required unless there is a specific complaint or finding on examination. One is encouraged to inquire about the body image and potential post-treatment sexual dysfunction or chronic pain. A medical encounter every 6 months for the first 2 years followed by an annual visit subsequently is reasonable for early stage patients. Advanced stage patients may benefit from more frequent visits every 3 to 4 months for 2 years, then every 6 months for 3 years, and then annually. Annual cervical cytology should be performed.

Vulvar cancer relapse can be categorized as local or distant. Twenty percent of patients will experience a local recurrence[67]. Any local relapse (or skin bridge recurrence) amenable to surgical resection should be excised.[69–71] Local reconstruction or grafting could be necessary in a previously treated patient. Unresectable local recurrences should be treated by radiation therapy in a patient with no prior radiation or in whom maximal tolerable doses were not reached. Otherwise, the only curative option left is exenterative surgery. Well-selected patients may achieve long-term survival with exenterative surgery.[55,56]

Vulvar SCC nodal recurrence is most often fatal[56]. Treatment of nodal recurrence should be individualized and guided by the size of disease and previous treatment. Great caution should be exercised in the surgical resection of nodal recurrences in women with previous groin irradiation[71]. In formerly untreated patients, recent data suggest that the addition of postoperative (chemo)radiation to a resectable inguinal node recurrence may reach a 5-year OS of 50%[75]. Unresectable nodes are typically treated with palliative radiation therapy for symptom control[76].

Distant recurrence is defined by any disease arising beyond the vulvar boundaries or the groin. Pelvic lymph node recurrence should be considered as a distant relapse. Isolated pelvic lymph node recurrence in a patient not previously treated with pelvic radiation therapy should be addressed with chemoradiation. Metastatic disease will otherwise be treated by palliative systemic therapy[71].

Summary Statements

10. Squamous cell cancers of the vulva have a high recurrence rate due to their association with human papillomavirus and skin dysplasia (high).
11. Vulvar squamous cell cancer with nodal recurrence is typically fatal and its treatment should be individualized and guided by the size of disease and previous treatments (low).

Recommendation

14. All women previously treated for vulvar cancer benefit from long-term follow-up provided by an experienced health care provider able to detect any recurrence or second gynaecologic malignancy (weak, low).

CONCLUSIONS

Vulvar cancer remains a heterogeneous disease, and a standard treatment algorithm cannot be applied to all patients; each patient requires careful clinical evaluation with attention given to clinical findings, pathology, and comorbid status. Surgically resectable vulvar SCCs require groin node assessment, with the preferred method being sentinel lymph node dissection by appropriately trained gynaecologic oncologists. Adjuvant radiation, including both inguinal and pelvic fields, should be given for any inguinofemoral lymph node metastasis and for close or positive margins where further surgical excision is not possible. For tumours that exceed a size or are in a location that would have significant surgical morbidity, primary (chemo)radiation treatment of these vulvar cancers is successful, and consideration of its use in lieu of surgery should involve multidisciplinary teams. There is a paucity of data for the systemic treatment of advanced-stage vulvar SCC, but platinum-based treatments are currently the most active available.

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