

Management of Squamous Cell Cancer of the Vulva

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Abstract

Objectives: To review and make recommendations regarding the management of early and advanced squamous cell cancer of the vulva.

Options: Radical vulvectomy and groin dissection or more conservative surgery in early squamous cell vulvar cancer; chemotherapy and radiation followed by consideration of surgery in advanced disease.

Outcomes: Risk of inguinal lymph node metastases, risk of tumour recurrence, patient morbidity, patient survival.

Evidence: Follows the quality of evidence assessment of the Canadian Task Force on the Periodic Health Examination (Table 1).

Key Words: Vulvar cancer, inguinal lymph nodes, vulvectomy, radiation, chemotherapy

Recommendations:

1. Stage IA lesions (≤ 2 cm diameter and ≤ 1 mm stromal invasion) can be managed by radical local tumour excision without inguinofemoral node dissection. (II-2B)
2. Stage IB unilateral lesion (≤ 2 cm diameter, > 1 mm stromal invasion and ≥ 1 cm from the midline) is treated by radical wide local excision completed by an ipsilateral inguinofemoral node dissection; a central lesion (within 1 cm from the midline) requires bilateral inguinofemoral node dissection. (II-2B)
3. 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. (II-2B)
4. Advanced cancer of the vulva should be treated with primary radiation and concomitant chemotherapy, followed by consideration of surgical resection. (II-2B)

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INTRODUCTION

Cancer of the vulva accounts for approximately 5% of all female genital tract malignancies and occurs most frequently in women between the ages of 65 and 75. The vast majority (90%) are squamous cell carcinomas, and other histologic lesions including melanomas, adenocarcinomas, basal cell carcinomas, and sarcomas account for the remaining 10%.¹ This document addresses only the management of squamous cell lesions.

The presentation of vulvar cancer and its most appropriate treatment have changed significantly over time. Early in the 20th century, the majority of patients presented with advanced disease. Treatment was primarily local excision, with only 20% to 25% of patients surviving five years. The development of radical en bloc vulvectomy and inguinal node dissection improved survival, but also resulted in major operative morbidity and physical and psychological sequelae.^{2,3}

Partly as a result of improved education of primary health care providers and of patients, cancer of the vulva usually

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Table 1. Criteria for quality of evidence assessment and classification of recommendations

Level of evidence*	Classification of recommendations†
I: Evidence obtained from at least one properly designed randomized controlled trial.	A. There is good evidence to support the recommendation that the condition be specifically considered in a periodic health examination.
II-1: Evidence from well-designed controlled trials without randomization.	B. There is fair evidence to support the recommendation that the condition be specifically considered in a periodic health examination.
II-2: Evidence from well-designed cohort (prospective or retrospective) or case-control studies, preferably from more than one centre or research group.	C. There is poor evidence regarding the inclusion or exclusion of the condition in a periodic health examination.
II-3: Evidence from comparisons between times or places with or without the intervention. Dramatic results from uncontrolled experiments (such as the results of treatment with penicillin in the 1940s) could also be included in this category.	D. There is fair evidence to support the recommendation that the condition not be considered in a periodic health examination.
III: Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.	E. There is good evidence to support the recommendation that the condition be excluded from consideration in a periodic health examination.

*The quality of evidence reported in these guidelines has been adapted from the Evaluation of Evidence criteria described in the Canadian Task Force on the Periodic Health Exam.⁴⁰

†Recommendations included in these guidelines have been adapted from the Classification of Recommendations criteria described in the Canadian Task Force on the Periodic Health Exam.⁴⁰

presents now as a lesion localized to the vulva. Patients often seek medical consultation at the onset of symptoms, and physicians recognize the value and importance of a thorough vulvar examination and biopsies.⁴ Fundamental to the understanding of treatment for vulvar cancer is knowledge of the patterns of tumour growth and lymphatic drainage of the vulva.

In 1988, the International Federation of Gynecology and Obstetrics (FIGO) introduced a new surgical/pathological staging system, replacing a clinical staging system for vulvar carcinoma. A surgical staging system was instituted because of the clinical inaccuracy of estimating node status and the prognostic significance of histologically proven inguinal node metastasis. Modifications were made in 1994 with Stage I further divided into IA and IB (Table 2).⁵ A standard treatment for vulvar cancer cannot be applied to all patients. Each patient requires careful clinical evaluation; her treatment plan must be based on clinical findings, and the plan should be altered when appropriate, depending on surgical/pathological outcome as well as co-morbidity factors. Surgical therapy is tailored to the individual patient, and novel techniques for inguinal node evaluation are currently under investigation. A spectrum of patients and tumour distribution has been identified, and the treatment approach to each group differs accordingly.

The quality of evidence reported in these guidelines has been described using the Evaluation of Evidence criteria outlined in the Report of the Canadian Task Force on the Periodic Health Exam (Table 1).⁶

MICROINVASIVE VULVAR CANCER

The International Society for the Study of Vulvar Disease (ISSVD) has defined microinvasive or superficially invasive vulvar cancer as a squamous carcinoma of ≤ 2 cm diameter with a depth of invasion of ≤ 1 mm. The deepest point of invasion is measured from the epithelial stromal junction of the most superficial adjacent dermal papilla.⁷ It is now widely accepted that only lesions with 1 mm or less of invasion and no vascular space permeation are not at risk for nodal metastases.^{5,8} Such lesions are classified as Stage IA and may be treated with a radical wide local excision also referred to as deep partial vulvectomy⁹ (tumour-free margin of 1–2 cm) without inguinofemoral lymphadenectomy. A radical wide local excision facilitates obtaining a negative deep margin by excising the lesion down to fascia. Should final pathology analysis reveal greater than 1 mm of invasion with a nonmidline lesion, then an ipsilateral inguinofemoral lymphadenectomy should be performed.^{10,11}

Recommendation

1. Stage 1A lesions (≤ 2 cm diameter and ≤ 1 mm stromal invasion) can be managed by radical wide local tumour excision without inguinofemoral node dissection. (II-2B)

EARLY VULVAR CANCER (STAGE I)

Therapy for small lesions confined to the vulva is not standardized. As a general principle, the procedure of choice is that which minimizes physical and psychosocial morbidity and maximizes the opportunity of cure. From a surgical

Table 2. FIGO staging for vulvar cancer (1994)

FIGO Stage	Clinical / Pathologic Findings
Stage 0	Carcinoma in situ, intraepithelial carcinoma
Stage I	Tumour ≤ 2 cm in greatest diameter, confined to the vulva or perineum; nodes are negative
IA	As above with stromal invasion ≤ 1.0 mm
IB	As above with stromal invasion 1 mm
Stage II	Tumour confined to the vulva and/or perineum, > 2 cm in greatest dimension, nodes are negative
Stage III	Tumour of any size with 1. Adjacent spread to the lower urethra and/or the vagina and/or the anus 2. Unilateral regional lymph node metastasis
Stage IVA	Tumour invades any of the following: Upper urethra, bladder mucosa, rectal mucosa, pelvic bone, or bilateral regional node metastasis
Stage IVB	Any distant metastasis including pelvic lymph nodes

FIGO, International Federation of Gynecology and Obstetrics.⁵

perspective, both the primary lesion and the inguofemoral lymph nodes must be considered in treatment planning.

Historically, en bloc radical vulvectomy and bilateral inguofemoral lymphadenectomy was the standard of care for all patients with cancer of the vulva.^{2,3} Although survival rates were very good, such radical surgery was associated with significant morbidity including wound breakdown, cellulitis, and chronic lymphedema. Moreover, the impact, on both body image and on sexual function, was profound.¹² Anderson and Hacker reported sexual arousal in the radical surgery patients at the eighth percentile, and body image amongst the same group at the fourth percentile, compared with a control group of women who had not undergone vulvectomy.¹³

A more conservative surgical excision rather than en bloc dissection generates two major concerns. The first is that the nature of the disease is a diffuse one and therefore the whole vulva may require treatment. The second is that if an en bloc dissection is not performed, the skin bridge (the skin between the lesion and the nodal resection) will be at high risk as a site for recurrence. Fortunately, available data have not substantiated these concerns. Radical local excisions (removal of the tumour with a 1–2 cm margin of normal tissue, carried down to fascia or symphysis pubis) with inguofemoral node dissection through separate incisions has provided at least an equal opportunity of cure.^{5,14} It is important when there is greater than 1 mm of invasion that an inguofemoral lymphadenectomy be performed, because there is an escalating risk of lymph node metastases in lesions with deeper stromal invasion. The prognosis from inguinal recurrent disease if the groin is not dissected is dismal, with up to 90% of patients dying from the

disease.¹⁵ If the primary lesion is unilateral, defined as ≥ 1 cm away from the midline, then an ipsilateral groin dissection is sufficient.¹⁶ Only one report has shown positive contralateral nodes with negative ipsilateral nodes in Stage I disease for a cumulative incidence of 0.4% (2/476) patients. If clinically positive groin nodes are found in an ipsilateral dissection for a small primary lesion, dissection of the contralateral groin is advocated.^{4,5}

Midline lesions (< 1 cm from the midline) require bilateral inguofemoral node dissection.

The technique of inguofemoral node dissection through separate incisions, initially described by Byron et al. and subsequently modified by Hacker et al., has provided several benefits.^{17,18} Postoperative hospital stay has decreased significantly, with chronic lymphedema occurring in 20% of patients compared with a previously reported incidence of between 32% and 65%.^{19,20}

Recommendation

2. Stage IB unilateral lesion (≤ 2 cm diameter, > 1 mm stromal invasion, and ≥ 1 cm from the midline) is treated by radical wide local excision completed by an ipsilateral inguofemoral node dissection; a central lesion (within 1 cm from the midline) requires bilateral inguofemoral node dissection. (II-2B)

Sentinel Node Assessment

The sentinel node, in the context of carcinoma, refers to the first node in the lymphatic basin that receives primary lymphatic flow. Much of the early work in this area was a component of the management of cutaneous melanomas, where sentinel node biopsy is now the standard of care.²¹ The identification and subsequent detailed pathologic

examination of the sentinel node aims to provide full nodal evaluation and decreased morbidity. The logic or hypothesis behind this has been that if the sentinel node is negative, all remaining nodes will be negative, and a complete groin dissection can be avoided. In cancer of the vulva, the sentinel node is located in the inguinofemoral lymph node basin.

Sentinel nodes are identified by peritumoral intradermal injection of isosulfan or patent blue dye, alone or preferably in conjunction with radioactive ^{99m}Tc -labelled sulfur colloid. Lymph nodes are subsequently identified by groin dissection and gamma counting and then submitted for frozen section, immunohistochemical staining, and multiplane sectioning.^{22,23}

Several investigators have reported a high rate of successful sentinel node identification in combination with the low incidence of false-negative sentinel node histology.^{24,25} However, safety and clinical utility remain to be proven. Until results are available from larger clinical trials assessing the value of examining sentinel node histology in which no further lymphadenectomy is performed, sentinel node biopsy should be considered an experimental procedure.

CLINICAL STAGE II OR III

Patients in whom the groin nodes are *not* clinically suspicious should be treated with a radical vulvectomy and bilateral inguinofemoral lymphadenectomy. Two surgical approaches can be used: (1) the separate three-incision approach and (2) the en bloc 1-incision procedure.^{17,18} There may also be a role for sentinel node biopsy in patients without obvious inguinofemoral node involvement.²² When inguinal nodes are suspicious or positive, the en bloc dissection should be used to diminish the possibility of retrograde lymphatic permeation leading to skin bridge recurrences. Data from Hacker et al. and Homesley et al. concluded that pelvic node metastases occurred only in the presence of clinically suspicious groin nodes or three or more positive unilateral groin nodes.^{26,27} A gynaecological oncology group study reported that radiation therapy to the pelvis and groin was superior to pelvic lymphadenectomy as adjunct therapy when there were two or more positive inguinal nodes.²⁸ The two-year survival rate for the radiation therapy group was 68%, compared with 54% for the pelvic lymphadenectomy group. There was no difference with only one node positive. The groups were not separated into less than three nodes versus three or more nodes positive; therefore, it is not possible to determine whether those with two nodes positive would benefit from radiation therapy. More recently, investigators have demonstrated that the morphology of a positive inguinal lymph node may also determine prognosis. The presence of extracapsular tumour cells and a node size of greater than 15 mm both have a

significant negative impact on survival.^{29,30} Berek and Hacker have used a node size threshold of 10 mm as a predictor of poor outcome.⁵

Therefore, adjunctive radiation therapy should be used when there are three or more micrometastases in the inguinal nodes, one micrometastasis > 10 mm in diameter, any evidence of extracapsular spread, or with bilateral microscopic groin metastases. The benefit of radiation therapy for two positive unilateral nodes remains to be determined.^{5,29,30}

Recommendation

3. Patients with three or more micrometastases in the groin, with node size > 10 mm, with extracapsular spread, or with bilateral microscopic metastases, should receive postoperative bilateral groin and pelvic radiation. (II-2B)

ADVANCED VULVAR CANCER

Advanced disease, although uncommon, presents a difficult management problem. 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. A surgical approach might include radical vulvectomy and inguinal node dissection with a posterior, anterior, or total pelvic exenteration. There is potential for high operative morbidity and mortality with additional long-term psychological and physical morbidity. In addition, for patients with fixed groin nodes, surgery alone is rarely curative.^{13,31} As an alternative to such radical surgery, Boronow proposed in 1973 an approach using both radiation therapy and surgery.³² In 1982, Boronow reported 26 patients with primary tumour treated with combined therapy,³³ 65% of whom were alive between one and 11 years post treatment. No patient required exenteration. The radiation therapy component was brachytherapy (11 patients), external beam and brachytherapy (14 patients), or external beam alone (1 patient). Surgery was radical vulvectomy plus or minus inguinal/pelvic lymphadenectomy. Hacker et al. similarly reported eight patients with advanced vulvar lesions (and no evidence of fixed pelvic nodes or distant spread) treated with external radiation therapy and individualized surgical resection. Five of the eight patients (62.5%) were alive without clinical disease between 15 months and 10 years after therapy.³⁴ Surgery was possible four to six weeks following radiation therapy. In four patients (50%), there was no residual tumour within the surgical specimen, suggesting that vulvar lesions responded to radiation more like squamous cell carcinoma of the skin than of the cervix or vagina. The radiation field was limited to the vulvar lesion alone in those patients with clinically nonsuspicious groin nodes, but extended to include groin and pelvic nodes in those patients with suspicious or positive groin nodes. Boronow et al. updated their

experience in 1987, reporting a five-year survival rate of 75% in 37 patients with primary advanced disease.³⁵

Thomas et al. in 1989, and Landoni et al. in 1996, reported on the use of concurrent chemotherapy in addition to primary radiotherapy. Up to 60% of patients achieved complete response, although with an increase in local toxicity.^{36,37} On the basis of all available data, preoperative radiation with or without chemotherapy should be regarded as primary therapy, followed by consideration of surgical resection, in a patient who would otherwise require a primary exenterative procedure.^{38,39} Clearly, optimal management of advanced vulvar cancer is complex and requires a multidisciplinary approach. This group of patients should be managed in a tertiary cancer centre by appropriately trained personnel.

Recommendation

4. Advanced cancer of the vulva should be treated with primary radiation and concomitant chemotherapy, followed by consideration of surgical resection. (II-2B)

CONCLUSION

The presentation of vulvar cancer and its most appropriate treatment have significantly changed over time. Early cancer of the vulva is now managed by less radical surgery and treatment of advanced tumours requires a multimodality approach. Appropriate treatment requires an understanding of tumour biology and growth, and vulvar and pelvic anatomy, and relevant oncological consultation where indicated.

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