Cancer of the vulva and vagina

Mouton A
Gynaecological Oncology Unit, Dept of Obstetrics and Gynaecology, University of Pretoria
Correspondence to: Dr A Mouton: arrie.mouton@up.ac.za
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Introduction
Cancers of the vulva and vagina occur less commonly than the other genital tract tumours, accounting for approximately 9% of all cancers of the female genital tract worldwide.[1] Despite the adjacent status of the two organs the aetiology of cancers of the vulva and vagina are not always shared. Staging is also complex as tumours with a major vaginal component and a minor vulvar component are classified and staged as vulvar tumours. Similarly, tumours with a major vaginal component and a minor cervical component are classified as cervical tumours.

Cancer of the vulva

This disease occurs most commonly in or after the seventh decade of life[2] but invasive carcinoma has been reported in younger women with increasing frequency.[3] Invas ive disease is often seen associated with pre-invasive disease namely carcinoma in situ or vulvar intra-epithelial neoplasia grade 3 (VIN3)[4] in younger women, whereas in elderly patients invasive cancer may arise in a background of dystrophic epithelium caused by lichen sclerosus without any evidence of VIN3.

By far the most common histologic type of vulvar cancer is squamous carcinoma (90% of patients). Other histologic types are melanoma and basal cell carcinoma while carcinomas from the Bartholin gland are usually adenocarcinomas.

Recently three different histological patterns of vulvar carcinoma were described: basaloid, warty and keratinising, with two distinct aetiological pathways.[5] The basaloid and warty patterns represented a small portion. They are more common in young women, are more frequently found adjuvant to VIN3, are associated with human papillomavirus (HPV) and present the same risk factor profile as that of cervical cancer. The majority of basaloid or warty tumours (75-100%) are HPV DNA positive, whereas only 2% to 23% of the keratinising carcinomas are HPV positive.[6]

The increase in occurrence of vulvar cancer in young women does seemingly not correlate a change in referral patterns, smoking habits or screening.[7,8] Invasive disease is often seen in association with VIN3 in younger women.[9] Studies in Europe and North America have also shown an increase in the rate of VIN3 without an apparent increase in the numbers of patients with invasive carcinoma. It is not yet clear whether this discordance relates to a period of inherent latency in the disease or disconnect between VIN3 and invasive disease.[10]

It is known that lifestyle and sexual factors may increase an individual's risk for infection with HPV. Such infection as well as a history of genital warts increase the risk for development of vulvar carcinoma.[11] This was reported by Brinton et al in a case control study[12] where it was shown that an increased number of sexual partners, history of venereal warts, cigarette smoking and a history of abnormal cervical cytology were associated with increased risk. Patients who are immunocompromised because of HIV or other reasons for a suppressed immune system, e.g. secondary to long term use of corticosteroids, are also at risk of acquiring VIN3 or progressing to invasive cancer after HPV exposure because of their inability to eradicate the HPV from their lower genital tract epithelium.[13]

VIN3 lesions may arise anywhere on the vulva or perineum and usually present as an asymptomatic raised area though some lesions are associated with pruritus or pain. On inspection the basic change is that of pigment disorder in the epithelium with darkened hyperpigmented areas, white depigmented areas and red areas present in the lesion.

Vulvar carcinomas may be ulcerative or exophytic with single or multiple lesions present. Large confluent lesions may cover the entire vulvar skin.

Pre treatment evaluation and staging

While vulvar carcinoma is mainly clinically staged, recent developments have included some aspects of surgical staging in the treatment decision making tree. In particular this relates to the value of lymph node involvement and the use of sentinal node dissection. The single most important prognostic factor for this disease is the presence of lymph node metastases. This makes some component of surgical staging important and desirable in dealing with vulvar carcinoma.

Staging takes several important factors related to prognosis into account: tumour size, depth of invasion, lymph node involvement and presence of distant metastases. Palpation of the groin is inadequate to accurately stage the patient; of patients with clinically normal nodes, 16-24% will have nodal metastases on microscopy, while 24-40% of those with clinically enlarged nodes are negative at histological examination.[14] A meta-analysis of observational studies compared the following approaches of detecting lymph node metastases in vulvar cancer: sentinal lymph node biopsy (SLNB), groin ultrasound with or without fine needle aspiration, computed tomography, magnetic resonance and position emission tomography.[15] The most accurate test was SLNB (sensitivity 97%, 91% CI 91-100; negative likelihood ratio 0,12). Sensitivity for the other tests ranged between 45% and 86%.

Issues involving treatment

Early stage disease
For patients in Stage 1A the treatment of choice consists of radical local

Table I: Carcinoma of the vulva: FIGO staging system

Stage 0		Carcinoma in situ, VIN3
Stage I	Ia Ib	Lesions < 2 cm in size, confined to the vulva or perineum, no nodal metastases Lesions < 2 cm confined to the vulva or perineum and with stromal invasion < 1.0 mm*, no nodal metastases Lesions < 2 cm confined to the vulva or perineum and with stromal invasion > 1.0 mm*, no nodal metastases
Stage II		Tumour confined to the vulva and/or perineum; > 2 cm in greatest dimension; no nodal metastases
Stage III		Tumour of any size with adjacent spread to the lower urethra and/or the vagina, or the anus, and/or unilateral inguinofemoral lymph node metastases
Stage IV	IVa IVb	Tumour invades any of the following: upper urethra, bladder mucosa, rectal mucosa, pelvic bone, and/or bilateral regional node metastases Any distant metastasis including pelvic lymph nodes

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

Table II: Carcinoma of the vulva: definitions of treatment

Treatment	Definition
Surgery alone	Surgery as first therapy and no other mode(s) of therapy within 90 days from the date of surgery. Subsequently, patients can be given any further treatment.
Radiotherapy alone	External radiotherapy and/or Brachytherapy as first form of therapy and no other form(s) of therapy within 90 days from the end of teletherapy/brachytherapy. Subsequently, patients can be given any further treatment.
Radio-surgery	Brachytherapy and/or external radiotherapy as first therapy and then surgery within 60 days from the end of brachytherapy/teletherapy. Subsequently, patients can be given any further treatment.
Neo-adjuvant chemotherapy + surgery	Two to four cycles of chemotherapy as first therapy and then surgery. Subsequently, patients can be given any further treatment.
Surgery + adjuvant radiotherapy	Surgery as first therapy and then external radiotherapy and/or Brachytherapy within 90 days from the date of surgery. Subsequently, patients can be given any further treatment.
Surgery + adjuvant chemotherapy	Surgery as first therapy and then chemotherapy within 90 days from the date of surgery.
Chemo-radiotherapy	Radiotherapy with chemotherapy (either neo-adjuvant, concomitant or sequential) administered together or at least within 90 days from the end of either therapy.
Adjuvant hormonal therapy	Surgery or radiotherapy or chemo-radiotherapy as first therapy and then hormonal therapy within 90 days from the end of surgery/radiotherapy/chemotherapy. Subsequently, patients can be given any further treatment.

excision without lymphadenectomy (LND) in patients with less than 1 mm stromal invasion, since inguinofemoral lymph node metastases are rare (< 1%).[16]

For stage 1B where the lesion has > 1 mm of stromal invasion, the risk of inguinofemoral lymph node metastases is > 8%. Patients with stage 1B disease should undergo radical local excision with inguinofemoral LND.[17] The choice of unilateral or bilateral LND depends on the location of the lesion.

Primary radiotherapy is generally avoided for management of early vulvar cancer because of associated morbidity. Primary groin irradiation was compared to primary groin dissection in a Cochrane review. Despite only three studies meeting inclusion criteria, it was concluded that although primary groin irradiation is associated with less morbidity, it resulted in more recurrences than surgery.[18]

Positive margins

There is some evidence for benefit of postoperative radiotherapy in a

patient with positive or close margins (< 8 mm).[19] However, re-excision should be considered for positive or very close margins to avoid radiotherapy side-effects and complications.

There have been few studies addressing the role of adjuvant radiotherapy to reduce local or groin recurrences in early stages of node negative vulvar cancer. The Gynecological Oncology Group (GOG) has completed a prospective trial to evaluate the role of adjuvant radiotherapy in patients with high risk tumours (> 4,1 mm in diameter, positive margins or lymphovascular space invasion) but with negative groin metastasis (GOG145). Awaiting the results and unless those results suggest otherwise, it appears reasonable to consider adjuvant radiotherapy for patients with high-risk primary tumours but with negative nodes.

Sentinel lymph node biopsy (SLND) is under investigation as an alternative to inguinofemoral LND. There are no randomised trials comparing SLND to traditional inguinofemoral LND, but multiple case studies have been published. Efforts are continuing to improve the accuracy of SLND including identifying the most effective approach to lymphatic mapping and investigating the case of advance pathologic methods to detect micro metastasis.[20] The best candidates for intra-operative lymphatic mapping are women with uninfected tumours limited to the lateral vulva, with no palpable enlarged groin nodes and no history of vulvar surgery that could disrupt to lymphatic drainage.

Complications of treatment
As treatment has evolved into less extensive procedures, the associated morbidity and complications have become less problematic. The worst limiting morbidities continue to be associated with the node dissection.

Sedlis et al[21] noted that, because node positivity is the exception rather than the rule, three fourths of patients will experience the morbidity of node dissection without benefit. In the Netherlands, 80% of patients, particularly those over the age of 74, did not have a groin node dissection preformed.[22] Less radical dissections in the groin have lesser, but still significant morbidity. Patients with positive nodes, patients who had post operative radiation therapy, patients over the age of 65 years and patients who had the saphenous vein removed were at greater risk of having complications in the groin.

Recurrence
Adequate surgery on the vulva results in 85-90% local control of the disease, even among patients with positive lymph nodes. The predominant site of recurrence is on the vulva; even when radical surgery is preformed recurrences at local site are three times as common as recurrences in the groin, pelvis or destined sites.

Local recurrences
Between 43 and 54% of all recurrences will occur on the vulva.[23] The risk of local recurrence increases as a function of depth of invasion and primary lesion size. A margin of 8 mm or less has been associated with local failure.[24] In a series of 37 patients with recurrences after conservative therapy, the GOG reported that the median time to recurrence on the vulva was 35.9 months and median survival after local recurrence was 52.4 months.[25] This data support the hypothesis of Rowley and coworkers[26] that recurrences of the vulva, particularly those remote from the initial site, may well represent re-occurrences rather than recurrences in the classic sense. Many recurrences in the vulva are amendable to consideration for re-excision.

Rouzier et al[27] carefully followed up patients with relapse to determine whether the site of recurrence was of prognostic importance. Outcome after local recurrences was 73% survival at one year and 50% survival at five years. Those patients with positive nodal status, large tumours, close margins and deep invasion were at high risk of death.

Groin recurrence
Six to thirty percent of recurrences will occur in the groin depending in part on the frequency of groin node involvement at the time of initial diagnosis.[28] Recurrences in the groin occur primarily if the groin is neglected or if the groin nodes are found to be involved at the onset of therapy. In the GOG series with 37 recurrences after conservative therapy, the median time to recurrence in the groin was seven months and the median time of survival after groin recurrence was only 9.4 months with 91% of those with groin recurrences succumbing to disease.

Distant recurrence
Pelvic recurrence occurs rarely, in approximately 5% of all cases.[28] Of all recurrences, 8-23% are distant and are associated with a dismal prognosis. Chemotherapy for recurrent or metastatic disease has not been extensively studied nor proven to be of great value. Patient age, performance status and toxicity have limited the delivery of therapy.

Follow up
Regular follow up for patients after treatment is universally recommended. Most schedules include visits every 3-4 months for the first 1-2 years with less frequent visits through five years. The recommended schedules are more empiric than based on the time frame of relapse. Oonk and coworkers[29] identified 65 patients with recurrent disease; 42 of these recurrences were found at a routinely scheduled screening examination. Symptoms were present in 21 of the 42 patients, however, so at least half of these lesions could have been found in the same time frame at an unscheduled appointment. The risk of second primaries other than the vulva, such as cervical cancer, is also noted to be a reason for routine follow up. Other issues related to the patient's treatment such as urinary incontinence, may also justify close monitoring.

Summary
After assessment of the available evidence the following recommendations can be made:

- A radical wide local excision of the vulvar lesion, sufficient to achieve a 1 cm gross margin, decreases the risk for local recurrence.
- If depth of invasion is greater than 1 mm, the risk of lymph node involvement merits a surgical assessment of the groin.
- Ipsilateral (or sometime bilateral) groin node dissection can be performed through separate incisions conserving as much healthy skin as possible. All the nodal tissue medial to the iliofemoral vessels and above the deep fascia should be removed.
- Sentinel node evaluation is a step forward but the false-negative rate has not been sufficiently defined to recommend this modality for routine use.
- Patients with positive inguinal nodes at groin dissection should receive radiation therapy.
- For patients who have unresectable primary disease or who would require exenteration where nodes are palpably suspicious, fixed and/or ulcerated, chemo-radiation is the preferred option.
- Exenterative procedures may rarely be required, particularly for recurrences.
- No treatment has been constantly shown to be effective for patients with groin recurrence.
- Chemotherapy for recurrence of metastatic disease has not been proven to be of value.

Cancer of the vagina
Vaginal intraepithelial neoplasia (VAIN) and small invasive vaginal cancers may be detected as a result of abnormal findings on a Papanicolau smear.

Most cases with VAIN have had cervical intraepithelial neoplasia (CIN) lesions before or concurrently. The same aetiology, namely infection with high risk strains of HPV, is true for CIN, VAIN, cervical as well as vaginal cancer.

Most invasive cancers of the vagina are metastatic tumours. Therefore many histologic types are encountered.

Primary vaginal squamous carcinomas can arise anywhere in the vaginal mucosa. Invasive carcinomas typically infiltrate sub-vaginal tissues beneath the site of mucosal origin. Although tumours originating in the vagina can spread to invade the cervix, tumours that involve both sites are conventionally classified as cervical cancer. Depending on the location and extent of the primary tumour, vaginal cancer can spread to involve any of the nodal groups in the pelvis. The external and internal iliac nodes are most commonly involved, but can also spread to common iliac or pre-sacral nodes or with involvement of the recto vaginal septum. For early lesions surgery may have a place and exenterative surgery may have a place for advanced lesions. The mainstay of treatment however remains radiotherapy with or without chemotherapy.

Cervical cytology policy for patients after hysterectomy

Patients having had treatment for CIN lesions and for cervical carcinoma are followed clinically with use of cytology of the vault. Patients who have had hysterectomy for benign reasons have a very small risk to develop VAIN at a later stage and this risk does not warrant regular cytologic follow-up. To never take a smear is also not good as new strains of HPV may be encountered by any patient. A safe midway option is to recommend cytologic assessment of the vault every 5-10 years in such cases.

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