Current insights into the aetiology, pathobiology, and management of local disease recurrence in squamous cell carcinoma of the vulva
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Current insights into the aetiology, pathobiology and management of local disease recurrence in squamous cell carcinoma of the vulva: a review paper

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Running Title: Local disease recurrence in vulval squamous cell carcinoma
Abstract

Squamous cell carcinoma of the vulva is predominantly a disease of the elderly, where the mainstay of treatment is radical surgery. Local vulval recurrence (LVR) is a significant problem for these patients, and the rates of recurrence have not improved over the last three decades. Disappointingly, we still lack an understanding of how LVRs develop and the best approach to prevent and manage the condition. This review discusses recent insights into the key prognostic factors that influence the risk of recurrence, focusing on the role of tumour-adjacent non-neoplastic epithelial disorders, which are thought to play a causative role.

Main body of text

Background

Vulval cancer comprises only 6% of all gynaecological malignancies reported in the UK, with squamous cell carcinoma (VSCC) making up 90% of all cases. It is predominantly a disease of the elderly with three-quarters of cases affecting those aged over 60 years. Radical vulvectomy is the mainstay of treatment for VSCC, with the extent of surgery depending on a number of factors that include: the size of the tumour; its location and proximity to vital organs; fitness to tolerate major surgery; FIGO stage; and wishes of the patient. Recurrent disease is common following primary treatment in VSCC with more than half of the cases recur locally involving the vulvoperineal area. The rate of local vulval recurrence (LVR) has not changed over time and affects at least 1 in 4 patients following primary treatment. Inadequate surgical excision has always been thought to be the main reason attributed to the development of LVR, but this belief is increasingly being challenged by new evidences. Furthermore, a number of studies have showed that other clinicopathological factors are equally important in determining the timing, pattern and frequency of LVR following surgery; in particular, the presence of non-neoplastic but dysplastic epithelium found adjacent to the primary tumour. The latter is of particular interest given that more than two-thirds of VSCC cases arise in a background of histologically abnormal or dysplastic epithelium such as vulval intraepithelial neoplasia (VIN) or Lichen Sclerosus (LS).

Managing LVR can be challenging especially in the elderly population who often have other medical comorbidities and in those who have previously received extensive surgery or exposure to radiotherapy. Further surgery is often associated with physical and psychosexual comorbidities and, in some instances, can result in the loss of urinary and bowel functions. Disappointingly, we still lack an understanding of how LVRs develop and the best approach to prevent and manage the condition.
This review discusses recent insights into the key prognostic factors that influence the risk of LVR and focuses on the role of non-neoplastic epithelial disorders (NNEDs), which are thought to arise from a field of molecularly altered epithelium termed a “field of cancerization”.

**The dual pathobiology of VSCC**

Like squamous cell carcinoma of the head and neck (HNSCC), VSCC is known to arise through HPV-dependent and independent routes (see Figure 1). The current disease paradigm holds that following persistent infection with high-risk (HR)-HPV strains, women are at risk of developing usual or classical type vulvar intraepithelial neoplasia (uVIN), which subsequently progress into basaloid or warty type squamous cell carcinoma (SCC) \(^{12,13}\). It is estimated that 40% of all VSCC cases arise through the viral-dependent route; interestingly, the prevalence of HR-HPV positive tumours is 20% higher in the United States compared to the UK \(^{14-19}\). Most cases of the tumour test positive for HPV16 and, to a lesser extent, HPV18 and HPV33 \(^{20}\). HPV-associated tumours typically affect younger women, aged <65 years, and the incidence in this age group is reportedly increasing in the UK and elsewhere \(^1\). This increase is a reflection of the rising incidence of the precursor lesion, uVIN, in young women, due in part, to the rise in the prevalence of infection with HR-HPV strains \(^{20}\). Although women with uVIN often suffer debilitating physical and psychosexual symptoms, the risk of progression to VSCC is substantially lower than that of cervical intraepithelial neoplasia; current estimates of disease progression are less than 10% \(^{21}\).

The virus independent route is associated with the development of keratinising tumours in a background of differentiated intraepithelial neoplasia (dVIN) or Lichen Sclerosus (LS) \(^{12,13}\). It is thought that the primary trigger of carcinogenesis in this setting is chronic inflammation, which results in repeated injury, scarring and ultimately, sclerosis of the affected epithelium. The sustained episodes of cell renewal and repair, which accompanies chronically inflammation, are associated with DNA damage and a high probably of mutation or silencing of tumour suppressor genes (TSGs), which, over time can result in oncogenic transformation \(^{22}\). Nevertheless, it remains unclear if LS gives rise to dVIN as there is no clear-cut connection between the two conditions. Similarly, it is also unclear whether dVIN, like uVIN, is a precursor lesion in HPV-negative VSCC. Women within this age group are usually older (> 65 years) and critically they are also more likely to have other medical co-morbidities, which may pose particular challenges in managing their cancer.

Although the current theory suggests that VSCC may arise through these two distinct pathways, our recent study has shown that resected tumour specimens from almost a third of patients were found to have LS, uVIN and dVIN co-existing with each other \(^7\). This finding raises the question as to
whether the two routes to VSCC development are mutually exclusive. Understanding the underlying
pathobiology which leads to the development of VSCC is crucial as many studies have found that the
presence of NNEDs found adjacent to the primary tumour appears to influence the rate and pattern
of local recurrence\textsuperscript{7-10,23,24}. Furthermore, in other HPV-associated cancers, such as HNSCC and anal
cancer, there is compelling evidence to suggest that HPV-positivity confers a survival advantage.
However, despite this clear-cut correlation in these two diseases, studies on VSCC have failed to
demonstrate that HR-HPV positivity is an independent predictor of disease-free survival\textsuperscript{19,25-27}. The
difficulty in revealing the expected association with HPV status in women with VSCC may flow in part
from the frequency with which uVIN co-exists alongside LS and dVIN, both of which impose an
increased risk of LVR development\textsuperscript{7}. It is also worth noting that the detection HR-HPV DNA in
tumour specimens does not necessarily indicate the presence of transcriptionally active virus given
that the virus might have undergone integration, become methylated and transcriptionally silent\textsuperscript{28}.
Alternatively, the presence of HR-HPV DNA might constitute a transient reactivation or new infection
that is not necessarily related to viral-driven oncogenesis\textsuperscript{29}. Due to the complexity of the HPV life
cycle, the significance of HR-HPV DNA positivity in VSCC remains unclear. Further studies are
required to measure the levels of expression of the HR-HPV oncogenes and its surrogate markers (E7,
p16\textsuperscript{INK4a} and MCM7); these biomarkers would confirm if oncogenesis is driven through the HR-HPV
route.

**Topography of VSCC recurrence**

Like HNSCC, our recently published study, along with two others, has identified two different
patterns of local recurrence in VSCC (Figure 2). A local vulval recurrence can occur on a site
previously occupied by or distant to the primary tumour\textsuperscript{7,8,23}. This pattern of local recurrence was
first described in SCC of the oral cavity and upper respiratory tract\textsuperscript{30}, and, like VSCC, the former can
be derived from both HPV-dependent and HPV-independent routes. Molecular profiling of HNSCC
has identified three distinctive patterns of local recurrence. Tumours that arise on a site previously
occupied by the primary tumour are termed a local relapse (LR), and are thought to be a true local
recurrence, while tumours that occur at least 2cm or more away from the primary tumour are
termed second field tumours (SFT) or second primary tumours (SPT) and are thought to constitute
new tumours that could be genetically related (SFT) or unrelated (SPT) to the primary tumour\textsuperscript{31}.
Although still speculative, it is thought that both SFT and SPT arise within an area of genetically
altered pre-neoplastic epithelium contiguous with the primary tumour that has a propensity to
undergo malignant transformation\textsuperscript{32}. 
Unlike HNSCC, a detailed examination of the topography of local recurrences in vulval cancer has not been adequately described. As such, very few retrospective cohort studies have attempted to categorise LVR based on the site and time at which the disease recurs following primary surgery. Bosquet et al. defined “recurrence” as a disease which relapses within five years of treatment while those that relapse after five years were termed a “re-occurrence” 33. Both Regauer et al. and Oonk et al. postulated that disease which recurs locally within 3 months of treatment is primarily due to treatment failure, while van der Velden et al. described a “true” local recurrence as a disease which recurs within 2cm of or “near” to the excision scar 9 34 35. However, it is important to note that the definitions of local recurrence used by these authors are purely hypothetical and based on observational studies and, unlike the case for HNSCC, were not based on molecular profiling.

**Clinico-pathological determinants of LVR**

Tumour-free pathological margins of 8mm or more, measured after formalin fixation, is considered to be the gold standard practice to minimise local disease recurrence. The current surgical practice advocates the removal of at least 15mm of disease-free tissue, lateral and deep margins, so that after fixation a ≥8mm histological cancer-free margins can be achieved to avoid LVR 36. This recommendation is based on a study conducted by Heap et al. on a small retrospective cohort 37. The study found that none of the patients with pathological margins of ≥8mm had recurrent disease, and local recurrence was only found in those with pathological margins of <8mm. While a number of independent studies support these findings 23 38, other more recent studies, which interrogated pathological margins in addition to other clinical-pathological determinants, dispute the notion that inadequate excision margin is the sole reason that contributes to LVR 5-7. After an extensive review of the literature, we have identified 27 independent retrospective cohort studies which have assessed the clinicopathological factors that determine LVR (see Table 1). Collectively, these studies found, that in addition to inadequate excision margins, there were other clinical determinants that influenced the risk of LVR. These included: groin node metastasis; the presence of Lichen Sclerosis (LS) and vulvar intraepithelial neoplasia (usual and differentiated type VIN) adjacent to the primary tumour; older age group; tumour size; tumour multifocality; histology grade; lymphovascular invasion (LVSI); perineural invasion; site of tumour; the type of surgery performed; and others 4-7 9 11 23 33 34 37-52. However, it remains unclear which of the risk factors best predict LVR, as each study identified different predictors, and none were in total agreement with each other.

The inconsistencies in the findings from each retrospective study can be attributed to a number of possibilities. Firstly, different methodologies were used in each study to collect and analyse its results; secondly, the majority of these studies were conducted in a single institution where clinical
practice in managing VSCC can be substantially different; thirdly, there was a lack of consistency in the clinical determinants used in each study; fourthly, the definition for LVR varies between each study and, at times, used interchangeably with distant metastasis; and lastly, there was lack of consensus in defining what constituted a true LVR. As a result, these studies failed to identify the common prognostic variable(s) involved in LVR. Taking into the account the limitations of these studies, we conducted an analysis of our cohort to evaluate all potential clinicopathological determinants previously implicated in the development of LVR \(^7\). We also dichotomized local recurrences into LR or SFT/SPT, according to the definitions obtained from molecular studies on HNSCC. Interestingly, our results showed that more than half of the cases of local recurrence occurred at a site distant to the primary tumour; we also found that the presence of LS appeared to be the only clinical determinant that reliably predicts LVR. These patients were not at greater risk of developing distant metastasis when compared to other clinical determinants evaluated, suggesting that local disease recurrence probably occurs as a result of the ongoing chronic inflammatory dermatosis associated with the residual LS. Although we have yet to perform molecular profiling of the tumour specimens obtained in our study, we believe that LVR (both SFT and SPT) originate from a “field” of molecularly altered epithelium that has acquired the necessary genetic changes to undergo malignant change. Contrary to previous beliefs, they do not occur as a result of inadequate excision margins as described by Heap and colleagues. It is also worth highlighting that Heap et al. drew their inferences solely from unadjusted estimates, and their findings could be confounded by other clinicopathological variables that were not evaluated in their study.

Field cancerization and LVR

The concept of field cancerization was first proposed by Slaughter et al. in 1953, who studied the histology of dysplastic epithelial tissue at tumour-adjacent surgical margins in an attempt to explain the reason for the development of multiple primary tumours and local recurrence in the oral cavity and upper respiratory tract \(^{30}\). In the original study, histological examinations were performed on normal tissue at surgical margins adjacent to the tumour. This study revealed the presence of multiple independent primary lesions and evidence of hyperplastic or atypical epithelium in seemingly histologically normal tissue contiguous with the primary tumour. Since the development of molecular biology, the concept of field cancerization has now been redefined in molecular terms. Mutation or epigenetic silencing of growth promoting or tumour suppressor genes predisposes epithelium to undergo oncogenic transformation, allowing genetically altered cells to expand and colonise large areas of the epithelium. This phenomenon partly explains the multifocality of tumours, as secondary tumours or local recurrences, such as SFT and SPT, emerge some years later.
after removal of the primary tumour. The multifocality and multicentricity of vulval neoplasia, its propensity to recur locally but at sites distant from the primary disease, point to this tumour arising within a field of cancerization in which at least some of the molecular abnormalities present in the primary tumour will be detected in adjacent histologically normal epithelium.

As more than two-thirds of VSCC arise on a background of atypical skin in the form of uVIN, dVIN, or LS \(^{11}\), it is plausible that these non-neoplastic epithelial disorders arise from molecularly altered epithelium that is generated through virus-dependent and independent routes. As such, NNEDs may constitute pathological biomarkers which indicate the presence of a molecularly altered field of epithelium. In the case of uVIN, these lesions are derived from HR-HPV infected epithelium that has acquired additional molecular changes that have progressed to high-grade VIN. Several studies performed on HIV-infected women revealed the presence of multifocal HPV-associated warts and uVIN lesions/condylomata in the genital tract of HIV-positive women pointing to the existence of a cancer field in these patients \(^{53,54}\). Using molecular analyses involving X chromosome inactivation, Rosenthal and colleagues revealed that high-grade VIN lesions contiguous with VSCC were of clonal origin, raising the possibility that these VSCCs were derived from molecularly altered clones within the VIN lesions \(^{55}\). However, the question of whether HR-HPV infection per se generates a cancer field is currently unclear. Although data for VSCC is unavailable, a recent study performed in HNSCC has revealed that normal epithelium obtained from resection margins were uniformly HPV negative, suggesting that at least in this disease, HR-HPV may not generate a field of molecularly altered epithelium. This finding supports the notion that unlike HPV negative HNSCC, HR-HPV-positive HNSCC exhibits lower rates of local recurrence \(^{56}\).

While uVIN is a putative precursor lesion for HPV-positive VSCC, it is still debatable whether LS is a precursor lesion for the HPV-negative counterpart. Although recent evidence shows that residual LS that remains after excision of the primary tumour increases the risk of local recurrence \(^{7-9}\), the absolute risk of recurrence in these women is not well defined. The notion that LS generates a field of cancerization, much like that observed in HPV-negative HNSCC, is a strong but as yet unproven concept. However, such an idea is not without foundation. It is now well established that chronic inflammation, coupled with sustained episodes of wound-healing, can predispose epithelial tissue to oncogenic transformation \(^{57}\). It is still unclear whether inflammation plays a permissive or promoting function in the generation or expanding “initiated” (i.e. mutated) cells. Chronic inflammation is associated with abnormal cytokine and growth factor production which can fuel the expansion of molecularly altered or premalignant cells. A number of studies have shown that LS lesions overexpress p53 protein and, in a significant proportion of cases, harbour mutated TP53 genes \(^{22,58}\).
The induction of p53 is most likely associated with a DNA damage response, induced through the production of reactive oxygen species (ROS) or by ischaemic stress, both of which are produced during chronic inflammation. Increased levels of ROS are associated with the recruitment of the epigenetic modulator, DNMT1, to CpG-rich islands upstream of promoters of both growth regulatory (i.e. p16INK4A) and genes involved in the DNA damage response. Chronic or sustained bouts of inflammation also cause alterations to the underlying stroma, converting normal fibroblasts into myofibroblasts which produce cytokines, chemokines and growth factors that can promote the growth of pre-malignant epithelial cells. An overwhelming body of evidence now supports a key role of the stromal microenvironment in field cancerization and the development of both primary tumours and local recurrences. This is particularly relevant as previous clinical studies which evaluated the risk of LVR following an en bloc vulvectomy, and a triple incision, showed no difference in risk despite the removal of less “normal” tissue in the latter. Therefore, removing excessive non-neoplastic skin during primary surgery may not have prevented the development of LVR as the adjacent skin bought together to close the wound may have already undergone a “field transformation” that may eventually give rise to an LVR.

The challenges in managing local V SCC recurrence

The treatments for LVR have not changed over the last three decades, and surgical excision continues to be the only treatment modality for cure. Surgery, however, may not be suitable for all patients and the procedures can be challenging especially in those who have previously had wide radical excision or radiotherapy. Reconstructive surgery is often required following primary excision to restore anatomy and function, as extensive scarring from previous surgery often reduces tissue volume and renders its flexibility to achieve primary closure. As a result, a skin flap is often harvested to cover the defect left after radical surgery. For a tumour which recurs and encroaches the urethra, anus or vaginal, pelvic exenteration followed by reconstructive surgery may be required to remove the disease completely if the patient is physically fit enough to undergo the operation. For those patients who previously had radiotherapy to their vulval, wound breakdown following subsequent surgery is common because irradiated skin often has an inadequate blood supply and a slow healing rate, making skin grafting unsuitable for most of them.

Squamous cell carcinomas, in general, are radiosensitive, but several studies have revealed poor treatment responses for large tumours when used alone without surgery. However, radiotherapy alone has been used successfully to treat low volume disease which recurs in the vulva. The use of concurrent chemotherapeutic agents such as 5-flourouracil, Mitomycin C and platinum agents with irradiation have proved effective in managing large volume disease in patients who are radiotherapy...
naïve or in those who are physically unfit for surgery \textsuperscript{67}. Neoadjuvant chemoradiotherapy followed by surgery is still superior to chemoradiotherapy alone in treating local recurrences, as overall survival is significantly better in those who can have surgery \textsuperscript{67}. Concurrent chemoradiotherapy may also be used to reduce the tumour volume before surgery, sparing those patients who required an exenterative surgery from having a simple radical excision; but defunctioning colostomy may be necessary in cases where the tumour recurs in close proximity to the anorectal canal \textsuperscript{2}. Nevertheless, as VSCC mostly affects the elderly population, only a small number of patients are physically fit enough to endure such forms of aggressive triple therapies that involve chemoradiation and surgery. As currently chemotherapeutic agents are used as an adjunct to radiotherapy or surgery and in palliative setting, there is a need to look for new chemotherapeutic drugs that can be used as a lone therapy for VSCC so that we are less reliant on surgery.

\section*{Conclusion}

Currently, there is a paucity of knowledge regarding the timing, topography and aetiology of local VSCC recurrence. The notion that inadequate surgical excision margins are the driver for local recurrence is increasingly being challenged by studies utilising more sophisticated statistical analysis to evaluate the clinical determinants which predict LVR. Based on current evidence, we hypothesise that LVR arises within a field of molecularly altered epithelium that is generated as a result of chronic inflammation or infection with oncogenic HPV strains. We suggest that LVRs develop in a pre-existing field of molecularly altered epithelium from clones that have acquired the necessary mutations to undergo malignant transformation. Future studies should utilise molecular profiling techniques to identify the molecular changes present in these pre-cancerous fields so that potential biomarkers or gene signatures can be determined, and these used to stratify patients into those who are most likely at risk of developing local recurrences. Unlike HNSCC, the contiguous nature and ease of accessibility of the vulva made this organ an ideal model to study how the field of cancerization develops and the key molecular changes that predispose cells within the field to tumour formation. This analysis would allow us to develop field therapies that could be administered short- or long-term to delay or prevent local VSCC recurrence. In the case of LS-associated VSCC, where chronic inflammation appears to play a vital role in disease pathology and tumour recurrence, the use of topical steroids may prevent or delay local recurrences by reducing inflammation and re-establishing a more "normal" stromal microenvironment.

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Disclosure of Interests
The authors declare no conflict of interest

Contribution to Authorship
JKWY, CWD and DML conceived the idea for the review, participated in its design and coordination, and provided final approval of the version to be published. JKWY, DO and SN performed a systematic review of the literature. JKWY and DO wrote the paper. CWD and DML critically reviewed the manuscript and contributed intellectual opinion. All authors read and approved the final manuscript.

Details of ethics approval
Not applicable

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References


Sites of Local recurrences

Local Relapse (LR)

Site of Primary Tumour

Second Field Tumour (SFT)

or

Second Primary Tumour (SPT)
## Table 1: Clinico-pathological determinants associated with local VSCC recurrence (LVR)

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Cohort size (n)</th>
<th>Location of LVR (n)</th>
<th>Determinants associated with LVR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yap et al. [7]</td>
<td>2016</td>
<td>201</td>
<td>LVR= 66 episodes, LR= 29 episodes; SFT= 26 episodes</td>
<td>LR and SFT: Lichen Sclerosis</td>
</tr>
<tr>
<td>Holthoff et al. [43]</td>
<td>2015</td>
<td>94</td>
<td>LR* recurrence in primary tumour = 31 'recurrent tumour' = 9</td>
<td>Perineural invasion</td>
</tr>
<tr>
<td>Iacoponi et al. [51]</td>
<td>2013</td>
<td>87</td>
<td>LR* = 23</td>
<td>Tumour size</td>
</tr>
<tr>
<td>Larsson et al. [40]</td>
<td>2012</td>
<td>133</td>
<td>LR* = 31</td>
<td>None identified</td>
</tr>
<tr>
<td>Stankevici et al. [41]</td>
<td>2012</td>
<td>107</td>
<td>LR* = 65</td>
<td>Site of primary cancer (midline disease)</td>
</tr>
<tr>
<td>Woelber* et al. [5]</td>
<td>2011</td>
<td>102</td>
<td>LR* = 10</td>
<td>Excision margins not significant</td>
</tr>
<tr>
<td>Regauer [9]</td>
<td>2011</td>
<td>75</td>
<td>LR* = 35</td>
<td>Presence of Lichen Sclerosus adjacent to main tumour</td>
</tr>
<tr>
<td>Szurukowski et al. [39]</td>
<td>2010</td>
<td>59</td>
<td>LR* = 10</td>
<td>Multifocal disease</td>
</tr>
<tr>
<td>Groenen et al. [6]</td>
<td>2010</td>
<td>93</td>
<td>LR* = 18</td>
<td>None identified</td>
</tr>
<tr>
<td>Tantipalakorn et al. [8]</td>
<td>2009</td>
<td>121</td>
<td>LR=26 (primary*13, remote13)</td>
<td>Primary recurrence= excision margins&lt;8mm; remote recurrence= Presence of Lichen Sclerosus adjacent to main tumour</td>
</tr>
<tr>
<td>Woelber* et al. [52]</td>
<td>2009</td>
<td>103</td>
<td>LR* = 8</td>
<td>None identified</td>
</tr>
<tr>
<td>Cheng et al. [45]</td>
<td>2009</td>
<td>100</td>
<td>LR* = 20</td>
<td>Lymphovascular invasion, lymph node metastasis</td>
</tr>
<tr>
<td>Ayhan et al. [44]</td>
<td>2008</td>
<td>91</td>
<td>LR* = 8</td>
<td>Surgery type, lymph node metastasis, advanced stage disease, ulcerative lesion, tumour size</td>
</tr>
<tr>
<td>Yoder et al. [50]</td>
<td>2008</td>
<td>78</td>
<td>LR* = 11</td>
<td>Histological grade, incomplete resection, depth of invasion</td>
</tr>
<tr>
<td>Chan et al. [38]</td>
<td>2007</td>
<td>90</td>
<td>LR* = 13</td>
<td>Excision margins, groin node metastasis</td>
</tr>
<tr>
<td>Woolden et al. [42]</td>
<td>2006</td>
<td>125</td>
<td>LR* = 29</td>
<td>Age &gt;74 years</td>
</tr>
<tr>
<td>Bosquet et al. [33]</td>
<td>2005</td>
<td>330</td>
<td>LR* = 64 (30= reoccurrence; 34= recurrence)</td>
<td>Recurrence: Inguinal nodal metastasis; Re-occurrence: None identified</td>
</tr>
<tr>
<td>Van der Velden et al. [34]</td>
<td>2004</td>
<td>76</td>
<td>LR* = 15</td>
<td>Triple incision (vs en bloc)</td>
</tr>
<tr>
<td>Rouzier et al. [23]</td>
<td>2002</td>
<td>215</td>
<td>LR* = 13; distant recurrence= 13, Skin bridge recurrence= 7</td>
<td>Depth of invasion, incomplete resection margins</td>
</tr>
<tr>
<td>De Hullu et al. [46]</td>
<td>2002</td>
<td>253</td>
<td>LR* = 18 at 2 years; 32 at 4 years</td>
<td>Excision margins &lt;8mm</td>
</tr>
<tr>
<td>Maggino et al. [49]</td>
<td>2000</td>
<td>502</td>
<td>‘perineal’ =94</td>
<td>FIGO stage, lymph node metastasis, Lymphovascular space invasion</td>
</tr>
<tr>
<td>Preti et al. [10]</td>
<td>2000</td>
<td>101</td>
<td>LR* = 18</td>
<td>FIGO stage IVa, groin node metastasis</td>
</tr>
<tr>
<td>Fonseca-Moutinho et al. [4]</td>
<td>2000</td>
<td>56</td>
<td>LR* = 11 at 2 years LR* = 15 at 5 years</td>
<td>FIGO stage IVa, groin node metastasis</td>
</tr>
<tr>
<td>Look et al. [48]</td>
<td>1993</td>
<td>154</td>
<td>‘recurrence* = 25</td>
<td>Lymph node metastasis</td>
</tr>
<tr>
<td>Lingard et al. [47]</td>
<td>1992</td>
<td>90</td>
<td>LR* = 16</td>
<td>Multifocal disease, tumour size (stage), inadequate excision margins</td>
</tr>
<tr>
<td>Heaps et al. [37]</td>
<td>1990</td>
<td>135</td>
<td>LR* = 21</td>
<td>Excision margins &lt;8mm, depth of invasion, tumour thickness, lymphovascular space invasion, keratinizing tumour, mitotic activity</td>
</tr>
</tbody>
</table>

*Potential duplication of cohorts; LR – local recurrence, LVR – local vulval recurrence, SFT – second field tumour

*site of LR not defined; 'the appearance of tumour in a new location after treatment, or in the same location after a minimum disease-free period of 6 months; 'recurrence defined as 'vulva'; 'de novo: >3 months after definitive surgery; 'LR defined as tumour recur at a site remote from initial tumour; 'statistical analysis of recurrence included distant metastasis; 'recurrence: development of SCC in a previously treated vulva/groin within 5 years, reoccurrence: development of SCC in vulva/groin after 5 years; 'LR: at or near the site of vulvectomy scar; primary tumor site recurrence (up to and including 2 cm from the vulvectomy scar); 'LR: >2cm from vulvectomy scar; 'recurrence' was defined as new appearance of tumour after therapy with radical intent, unsure if also encompassed distant recurrence