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Vulval squamous cell cancer — does precursor lesion margin status affect recurrence-free survival after optimal surgical resection for early-stage disease?

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ABSTRACT

Objectives: Vulval cancer accounts for around 4% of all gynaecological malignancies and most tumours (> 90%) are of a squamous cell histotype. Most lesions arise on a background of differentiated VIN (dVIN) or lichen sclerosus (LS). Surgical treatment has undergone a paradigm shift with less radical surgery being attempted to preserve vulval structure and function, without compromising oncological outcome.

Material and methods: In this single site retrospective analysis, we consider the data from a tertiary oncology unit, to assess progression-free survival based on the presence of a precursor lesion at the margin of resection. 123 patients with FIGO stage 1 vulvar SCC (n = 33 1A, n = 90 1B) were included.

Results: One hundred five patients (85%) had an associated precursor lesion (dVIN and/or LS). Within the follow-up period, 33 patients (26.8%) had invasive recurrence, of which 24 (72.7%) had surgical resection margins which were positive for a precursor lesion. In patients with an acceptable microscopically clear invasive resection margin of > 2 mm the presence of a precursor lesion at the margin conveyed a higher risk of malignant recurrence when compared to those with completely clear margins (HR = 2.42; 95% CI 1.14–5.16).

Conclusions: This study adds to the available literature emphasising the clinical significance of dVIN or LS at the surgical margin of optimally resected disease. In those who have marginal involvement of a precancerous lesion, increased surveillance should be considered. Future work should explore the need for additional adjuvant therapy in this cohort.

Keywords: lichen sclerosus; precancer; surgery; vulval cancer; vulval intraepithelial neoplasia

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INTRODUCTION

Vulval cancer is a rare malignancy with approximately 1300 new cases every year in the United Kingdom accounting for 2% of cancer in females [1]. In addition, the disease is closely linked to deprivation meaning a diagnosis of vulval cancer is often compounded by complex social and health factors. These women find intensive follow up or the sequalae of more radical surgery destabilising to their wider social and financial health [2]. Despite improved survival over time, disease recurrence remains clinically significant; in those who receive treatment, local recurrence rates are 4% [3] annually and 40% at 10 years [4]. An improvement in risk stratifying those who are likely to recur would enable targeted intensive surveillance and treatment whilst reducing the burden on those who are unlikely to benefit. Therefore, more accurate recurrence predictors are a clinical priority.

Approximately 80% of vulval cancers are of a squamous cell carcinomas (SCC) histology with most associated with the oncovirus human papillomavirus (HPV); this is especially true in younger women [5–9]. The other route to carcinogenesis in vulval cancer is HPV independent and arises on the background of dVIN or LS [10–12].

Surgery is the cornerstone of treatment for vulval cancer [13]. The degree of surgical radicality is dictated by the balanced desire to preserve function whilst reducing the risk of disease recurrence and hence improve survival. Prognostic factors for recurrence include the patient's age, lesion size, depth of stromal invasion, lymph node involvement and

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lympho-vascular space invasion [14]. These factors cannot be influenced by surgery; however the dimensions of the surgical margin are but the impact of the surgical margin on survival remains controversial. Initial studies reported that a resection margin of < 8 mm is related to an increased risk of recurrence [14, 15] which resulted in more radical procedures and adjuvant radiotherapy which in turn incurred significant morbidity. However, a recent systematic review of prognostic factors in vulval cancer found a 4% annual local recurrence rate and crucially that a margin < 8 mm was not associated with an increased risk [16]. International guidelines agree that provided margins are microscopically clear of invasive diseaseclearance values of > 2 mm areacceptable. An area that remains unclear, is the relationship of a vulval precursor lesion at the surgical margin and disease recurrence. Vulval precursor lesions in the skin adjacent to and/or in the tumour margin are thought to be of prognostic value [17] and recently published data shows that independent presence of LS may strongly increase the risk of local recurrence [17–22].

The aim of this study was to determine the incidence of local recurrence and the recurrence free survival (RFS) in the presence of precursor lesions (LS/dVIN). Furthermore, it will explore the impact of LS/dVIN margin status (mm) on both recurrence and RFS. It is hoped this will improve the identification of those women at a greater risk of recurrence and will allow for better directed adjuvant therapy in addition to unnecessary radical of treatment.

Highlights

Vulval cancer is a morbid disease that often involves extensive surgery. Identifying the correct degree of radicality and those who could benefit from increased post operative surveillance is a clinical priority.

85% of Stage 1 vulval squamous cell carcinoma is associated with a precursor lesion of differentiated vulval intraepithelial neoplasia (dVIN) and/or lichen sclerosus (LS).

72% of those with invasive recurrence had surgical resection margins which were positive for a precursor lesion.

With an optimal initial malignant resection of > 2 mm, precursor margin status influences recurrence-free survival.

MATERIAL AND METHODS

Design and setting

A retrospective cohort study was performed including all patients who were surgically treated for primary vulval cancer in the Southeast of Scotland Cancer Network (SCAN). The network comprises four collaborating National Health Service (NHS) Boards: Borders, Dumfries & Galloway, Fife and Lothian serving a population of 1.5 million. The primary oncology referral centre where all surgical treatment was performed, was the Royal Infirmary of Edinburgh, which received on average 10 vulval cancer referrals a year.

Patients and treatment

Consecutive patients with vulval cancer who were diagnosed between January 2009 and December 2019 were included. Those with a primary diagnosis of The International Federation of Gynecology and Obstetrics (FIGO) stage 1 vulval SCC (pathologically and radiologically confirmed) who underwent primary surgical treatment by a subspecialty trained gynaecology oncologist were eligible for inclusion. Patients with multi-focal, FIGO II–IV or recurrent disease or who had undergone primary neo-adjuvant therapy/palliative radiation were excluded.

The surgical treatment consisted of either a radical vulvectomy or wide-local excision (WLE). Lymph node assessment, depending on the extent of disease, was assessed either by sentinel node sampling or unilateral or bilateral inguinofemoral lymph node dissection. Surgical intention was to achieve tumour-free margins of 1 cm where possible. After discussion at the specialist multi-disciplinary meeting, re-excision was recommended in cases of positive margins. Margin involvement was defined as histopathological invasive carcinoma or VIN3 within 8 mm of the surgical excision. Node positive patients were offered adjuvant radiotherapy. Patients with margins > 8 mm and negative nodes were offered close follow-up, which entailed 6 monthly clinical review for the first 3 years and annual thereafter.

Data collection

Histopathology was confirmed at consensus review by specialist gynaecology oncology pathologists. Data of patients with vulval SCC was extracted from a prospectively maintained regional clinical data base. Individual medical records were scrutinised as to determine eligibility for inclusion into the study. Margin status, defined as the maximal distance between invasive carcinoma and surgical resection, was reported as a categorical variable being grouped as 1. ≤ 2 mm 2. > 2–5 mm 3. > 5–8 mm and 4. >8 mm. Precursor lesions (LS or dVIN) present in resection margins indicated premalignant margin status and these were reported by a specialist gynaecology-oncology pathologist. Tumour stages were classified according to FIGO 2009 classification and agreed at regional multi-disciplinary meeting.

Variables recorded included age, size of tumour, stage, histological grade, and lymph-node status. Data collection, storage and analysis were in accordance with local governance protocols. Data analysis was performed using Microsoft Excel and Graphpad Prism version 9.4.0. A p value of < 0.05 was considered statistically significant and Kaplan–Meier curves were generated to assess survival.

Outcome

The primary outcome was recurrence free interval (RFI) defined as the time from primary histopathological

Table 1. Clinical and histopathological features of the study population

Clinical/ histopathological characteristics	Median (range)	Total patients
		n [%]
Age (at diagnosis)	60 (30–91)	
FIGO stage 2009		
1A		33 (27)
1B		90 (73)
Primary surgery		
Wide local excision		56 (46)
Hemi vulvectomy		4 (3)
Radical vulvectomy		63 (51)
Maximum dimension [mm]	44 (0.8–98)	
Grade of differentiation		
1		56 (46)
2		55 (44)
3		12 (10)
Background precursor lesion		105 (85)
dVIN		67 (63.3)
LS		14 (13.3)
Both		24 (22.8)
No precursor lesion		18 (14.6)
Margin precursor lesion		
Present		68 (55)
Absent		55 (45)
Status		
Alive		88 (72)
Died of vulval Ca		18 (15)
Died of intercurrent illness		7 (5)
Died of unknown cause		10 (8)

FIGO — International Federation of Gynecology and Obstetrics; dVIN — differentiated vulval intraepithelial neoplasia; LS — lichen sclerosus

diagnosis to local recurrence or death, measured in months. Recurrence was defined as time in months from initial treatment to any biopsy-proven suspicious lesion of the vulva or inguinal lymph nodes, in March 2021 at the time of data collection. Cause of death was determined from death certification or electronic General Practice (GP) records if available. The secondary outcome was the relation between precursor lesion presence in the margins and local recurrence.

In accordance with the journal's guidelines, we will provide our data for the reproducibility of this study in other centres if such is requested.

RESULTS

In total, 169 consecutive patients were identified with confirmed vulval SCC. Of these 46 patients were excluded from analysis due to presenting with stage II–IV disease. Therefore 123 patients with FIGO stage I vulval SCC (n = 33 1A, n = 90 1B) being included in the analysis. Median age at diagnosis was 63 years (range 30–91).

Clinical and histopathological characteristics of the study population are outlined in Table 1. The median tumour size was 44 mm (range 0.8–98 mm). Disease was more commonly grade 1 (n = 56) or grade 2 (n = 55) than grade 3 (n = 12). Most patients were treated by radical vulvectomy (n = 67) with the remainder undergoing a wide local excision (n = 56). Median follow up of these patients was 68 months (range 2–240 months). Overall recurrence rate was 35/123 (28.5%) with an average time to recurrence of 46.3 months. International Federation of Gynecology and Obstetrics 1A tumours showed a recurrence rate of 3/33 (9%) and 32/90 (35%) in stage 1B malignancies.

Surgical margin

Overall, 95 women had optimal surgical margin clearance of > 2 mm. Of those patients included in the study,

Table 2. Distribution of background precursor lesions, margin precursor lesions, overall recurrence rate and progression-free interval by cohort of surgical excision margin

Margin [mm]	n	Background precursor lesion n [%]	Margin precursor lesion n [%]	Overall recurrence n [%]	Recurrence-free interval [months]
≤ 2	28	25 (23.8)	21 (30.8)	12 (34.3)	9
> 2–< 5	36	31 (29.5)	20 (29.4)	5 (14.3)	28
> 5–< 8	24	20 (19)	13 (19.1)	8 (22.9)	39
>8	35	29 (27.7)	14 (20.7)	10 (28.5)	38.5
Total	123	105	68	35 (28.5)	
Optimal > 2	95	70 (73.7)	47 (49.5)	23 (24.2)	35

invasive tumour resection margin distance (mm) was distributed as ≤ 2 mm (n = 28), > 2–5 mm (n = 36), > 5–8 mm (n = 24), > 8 mm (n = 35); this data is as demonstrated (Tab. 2). In sub-group analysis it is demonstrated that recurrence rates were highest in the < 2 mm cohort at 12/35 (34.3). Beyond > 2 mm resection there was little difference in recurrence rate, in keeping with published data. As demonstrated in Table 2, the recurrence-free interval (RFI) for resection margins ≤ 2 mm was 9 months compared to 35 months in margins > 2 mm. Recurrence-free interval analysis, on surgical excision margin alone, demonstrated that margins > 2 mm confer a survival benefit over margins ≤ 2 mm. On analysis of categorical resection margins beyond 2mm there was no statistically significant difference.

Background precursor lesion

Analysis demonstrated the abundant presence of background high-risk lesions, with a total 105 (85%) of surgical specimens containing dVIN or LS. The distribution of lesions was even across all resection cohorts (≤ 2 mm, > 2–5 mm, > 5–8 mm and > 8 mm). Differentiated VIN had a higher prevalence in the patient cohort with 91 patients (73.9%) affected compared to LS (30.8%).

Most notably however only 18/123 (14.6%) cancers arose from precursor-independent changes. Furthermore, the demonstrated recurrence rate, independent of margin status, in precursor lesion positive patients was 35/123 (33.3%).

The presence of LS was associated with a high rate of disease recurrence and a progression-free interval of 23 months, compared to 25 and 34 months for dVIN and both lesions respectively.

Margin precursor lesion

In this series of 123 vulval SCC,68 patients (55%) demonstrated the presence of a high-risk precursor lesion within the margins of the surgical resection. Higher rates of margin lesions were seen in cases of lower margin cancer clearance with the ≤ 2 mm (21/28) and > 2–5 mm (20/36) cohorts both demonstrating rates of over 50% (Tab. 2). An excision margin of < 5 mm was associated with a statistically higher chance of margin precursor status being positive versus an excision clearance of > 5 mm.

Recurrence

Within the follow-up period, 35 patients had invasive recurrence, of which 26 (74.2%) had surgical resection margins which were positive for a precursor lesion. In patients with an acceptable microscopically clear invasive resection margin of > 2 mm, the presence of a precursor lesion at the margin conveyed a higher risk of malignant recurrence when compared to those with clear margins [hazard ratio (HR) = 2.42] For the cohort of patients with incomplete resection (≤ 2 mm) there was no statistically significant difference in recurrence (HR = 0.53) (Fig. 1 and 2)

Median recurrence free interval was 30.5 months (range 8.5–41) for positive precursor margins and the negative margin cohort demonstrated a median RFI of 32 months (10–97). With optimal > 2 mm resection margins there is a difference in the median recurrence free interval (RFI) from 40 to 25 months dependent on precursor lesion margin status. Including all the recurrences regardless of margin distance there's no statistical difference between those with positive or negative precursor margins in terms of the recurrence free interval.

DISCUSSION

Summary of main results

The primary aim of this study was to determine whether the presence of high-risk precursor lesions such as dVIN and LS influences recurrence and survival in vulval cancer. In this series we demonstrate that despite optimal (> 2 mm) pathological resection, the presence of high-risk precursor lesions within the margin, is associated with an increased risk of local recurrence compared to clear margins. There was, however, no demonstrable statistical difference in the recurrence-free interval between positive and

Table 3. Multivariate analysis of recurrence based on resection margin

Resection margin	HR	95% CI	p value
≤ 2 mm	2.42	1.14–5.16	0.0092**
> 2 mm	0.53	0.15–1.86	0.3234

HR — hazard ratio; CI — confidence interval

negative precursor margins Additionally despite analysis of the incomplete excision cohort (≤ 2 mm), demonstrating an increased risk of recurrence, this is statistically insignificant. This is likely due to small margin status rather than precursor status alone and an increase in data size would be needed to determine this.

Results in the context of published literature

The study demonstrates, alongside the literature, that incomplete (≤ 2mm) margin excision is associated with a higher risk of recurrence [23, 24] and with resection margins > 2 mm there was no difference in the recurrence-free interval. This is in keeping with published data from Pleunis et al. [13] who demonstrated in patients treated with primary surgery for vulval SCC, resection margins < 8 mm were not associated with an increased risk of recurrence. Surgical management between 2009–2019 aimed for clearance margins of 10 mm thus, this retrospective data analysis supports the British Gynaecological Cancer Society's (BGCS) adoption of > 2 mm recommendations in 2020. With less radical surgical excision and margins, patients will be less exposed to harmful and mutilating procedures. However as concluded in the systematic review from Te Grootenhuis et al. [16], the currently available data on margin status does not allow for true evidence-based medicine. They concluded that there is no lower limit (apart from involved margins) below which further treatment (either re-excision or adjuvant radiotherapy) to the vulva should be recommended. Being mindful of the significant morbidity associated with adjuvant radiotherapy to the vulva, the equivocal prognostic impact of margins on local recurrence rate, doctors should be reluctant before deciding to expose their patients to these potentially harmful adjuvant therapies.

Importantly this data demonstrates the significant of high-risk precursor lesions in determining patients' risk of recurrence. This data shows in patients receiving optimal surgical resection margins > 2 mm, in the presence of dVIN or LS, they are at a higher risk of cancer recurrence (p = 0.0092). These findings are in keeping with Te Grootenhuis et al. [3] who state the treatment of precursor lesions should be key in lowering the local recurrence rate and Bleeker et al. [20] who found that a combination of both dVIN and LS increase the risk of developing SCC to 19% over 10 years [20, 21]. Vulval cancer recurrence is often a new primary

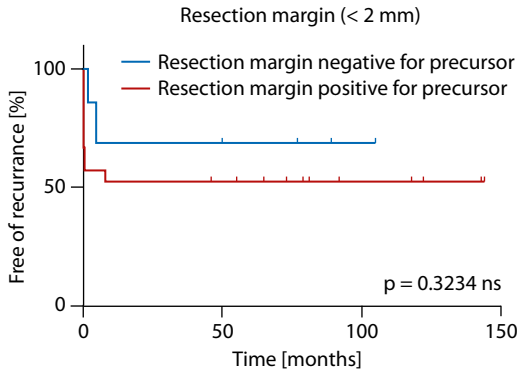

Figure 1. Kaplan–Meier curves to demonstrate the percentage of patients free of recurrent vulvar malignancy during the follow-up period (median 68 months) to compare those with initial invasive reaction margins (> 2 mm *i.e.* 'optimal' margins`) that were negative and those that were positive for precursor lesions (dVIN, LS or both). Log-Rank (Mantel-Cox); p = 0.3234ns, hazard ratio (HR) = 0.53, 95% confidence interval (CI) 0.15–1.86

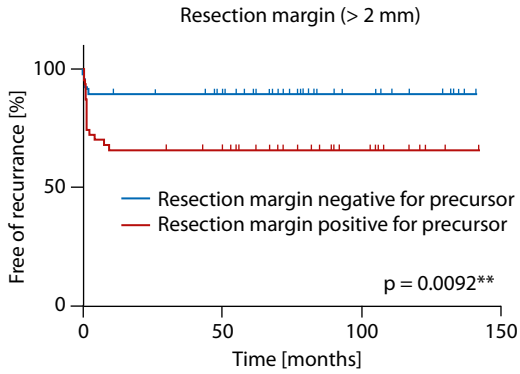

Figure 2. Kaplan–Meier curves to demonstrate the percentage of patients free of recurrent vulvar malignancy during the follow-up period (median 68 months) to compare those with initial invasive reaction margins (> 2 mm *i.e.* 'optimal' margins`) that were negative and those that were positive for precursor lesions (dVIN, LS or both). Log-Rank (Mantel-Cox); p = 0.0092**, hazard ratio (HR) = 2.42, 95% confidence interval (CI) 1.14–5.16

tumour triggered by the presence of lichen sclerosus or VIN at the margins [19, 22], however there is limited data on this. Precursor lesions and premalignant margin status demonstrate a risk of recurrence, however there is no current risk stratification in vulval cancer patients. This would allow closer follow-up or adjuvant therapy for those at high risk of recurrence, but equally allow the effective discharge of those low-risk patients.

Additionally, this data shows a significant increase in local recurrence rates related to the precursor presence regardless of its location. Patients with background lichen sclerosus or VIN had shorter progression-free survival. This is in line with the study of Te Grootenhuis et al. [16] demonstrating dVIN, LS, or both were associated with higher

rates of recurrence compared to patients without these lesions. This study emphasises the importance of comprehensive follow-up procedure and an earlier recourse to treatment in patients with persistent precursor disease at the resection margin who have undergone optimal surgical treatment. Treatment of underlying dermatoses must be one of the major focuses during follow-up. In patients with LS treatment with topical corticosteroids may reduce the risk for developing vulvar carcinoma [25]. This supports Yap et al. [19] who concluded that not the resection margin but the presence of lichen sclerosus is predictive for local recurrence or new tumours. Furthermore, in patients with complete resection and no precursor margin disease, clinicians can be confident that the risk of recurrence is low.

Strengths and weaknesses

This study is the largest UK-based retrospective data analysis performed to date since British National guidance changing to state 'as long as margins are microscopically clear of invasive disease, margins in the fixed specimen of > 2 mm are acceptable'.

The median recurrence rates for the centre of 35% are in line with international data that suggests rates of up to 40% at ten years.

The retrospective nature means the study is limited and data across all stages of disease was collected initially however post-hoc analysis demonstrated the numbers were too small for statistical interpretation. Due to this study having a small cohort size we are unable to demonstrate a statistically significant difference in recurrence-free survival based on precursor lesion status.

Implications for practice and future research

Although the findings align with current national guidelines aiming for resection margins of 2 mm, we also ask what the best way is of following up these women at higher risk of cancer recurrence. The active treatment of underlying dVIN or LS is the key strategy in reducing cancer recurrence. Particularly in LS, where effective treatments such as corticosteroids exist, clinicians must be focussed on recognising and treating early. There is a paucity of data on vulval SCC, leading to differing in clinical practice, risk stratification and furthermore follow-up. In keeping with international guidance, we can strong show the need for close follow-up in these patients. The development of more accurate risk stratification will allow for better directed adjuvant therapy and a reduction in the radicality of treatment, with improved recurrence-free survival. This study suggests in patients with adequate resection margins and no precursor margin disease, patient-initiated follow up strategies could be put in place.

CONCLUSIONS

This study adds to the available literature emphasising the clinical significance of dVIN or LS at the surgical margin of optimally resected disease. In those who have marginal involvement of a precancerous lesion, increased surveillance should be considered. Future work should explore the need for additional adjuvant therapy in this cohort.

Article information and declarations

Data availability statement

All data used in this manuscript is available on reasonable request.

Ethics statement

Local NHS Trust Ethics board approval for retrospective research.

Author contributions

All authors contributed equally.

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Conflict of interest

The authors declare no conflict of interest.

Supplementary material

None.

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