Article published online: 2021-06-03

Original Article

Vulval Cancer: When should I Stop Resecting? Identifying the Factors that Predict Recurrence

Abstract

Context: Vulval cancer surgery has become more conservative and it is important to understand whether resection margins alone influence recurrence rates or whether other prognostic factors should be considered when planning treatment. **Aims:** The aim of this study is to define factors that predict vulval cancer recurrence, enabling development of a recurrence prediction model. **Settings and Design:** This was a retrospective descriptive analysis of new vulval squamous cell carcinoma cases in a gynecological oncology center (January 1, 2007 to December 31, 2013). **Subjects and Methods:** Analysis of tumor characteristics and treatments. Patient outcomes were recorded, identifying recurrences, and subsequent interventions. **Statistical Analysis Used:** Univariable and multivariable logistic regression tools applied to determine recurrence risk factors. **Results:** Seventy patients underwent primary vulval surgery. Bilateral groin node dissection was performed in 26/70 (37.1%) cases and unilateral groin node dissection in 9/70 (12.9%) cases. 57/70 (82%) cases had a negative vulval resection margin, with 67% <8-mm margin. 18/70 (26%) patients underwent adjuvant treatment. Overall recurrence rate of 21/70 (30%): 14/70 locally and 7/70 at the groin. Median survival was 84.2 months and median disease-free interval was 19.1 months. Factors that were statistically significant in predicting recurrence were positive groin histology, lymphovascular space invasion (LVSI), and disease stage. **Conclusions:** We reported a reduction in the size of tumor-free margins at primary excision. The recurrence rate of 30% is within the previously reported range, suggesting that factors aside from resection margin (LVSI, stage, and groin node involvement) are also important in predicting recurrence. These factors should be incorporated into a prediction model when planning adjuvant treatment.

Keywords: *Recurrence factors, resection margin, vulval cancer*

Sarah Louise Platt, Claire Louise Newton, Pauline J Humphrey[1], Joya P Pawade[2], Vivek V Nama[3]

Department of Gynaecological Oncology, St Michael's Hospital, University Hospitals Bristol NHS Foundation Trust, [1]Bristol Haematology and Oncology Centre, University Hospitals Bristol NHS Foundation Trust, [2]Department of Pathology, University Hospitals Bristol NHS Foundation Trust, Bristol, [3]Department of Gynaecology, Croydon Health Services NHS Trust, Thornton Heath, UK

Introduction

In 2014, 1289 new cases of vulval cancer were reported in the UK, with a crude mortality rate of 1.5/100,000 women.[1] Recurrence rates range from 15% to 33%, mostly in the vulva and groin.[2] Several prognostic variables can influence recurrence and overall survival: disease-free margin, depth of invasion, lymphovascular space invasion (LVSI), the size of the primary tumor, and stage of the disease.[3,4]

Surgical management of vulval cancer has previously been defined by large vulval excisions that achieve the required margins and depth to reduce recurrence, usually at the expense of significant patient morbidity. Sacrificing continence mechanisms to achieve margin status impacts on the quality of life, so there has been a shift toward suboptimal margins.

Heaps *et al*. recommend that a minimum of 8 mm is an acceptable tumor-free margin.[5] De Hullu *et al*. reported a small but significant increase in the overall recurrence rate with more conservative surgery.[6] The study also highlighted that surgical margins were prone to shrinkage and excision margins of 2 cm should be considered to ensure a tumor-free margin of at least 8 mm. Our evidence to define a "good margin" is in these two studies. These conclusions were reinforced in Van der Velden's Cochrane review, although also acknowledged that the main observational studies are over 10 years old.[6-9] The recent AGOCaRE-1 multicenter study concluded that tumor-free margin distance may not be as significant as first thought, but this did not include UK centers.[10]

Depth of tumor invasion also influences the risk of recurrence. Hacker *et al*. reported a depth of invasion above

How to cite this article: Platt SL, Newton CL, Humphrey PJ, Pawade JP, Nama VV. Vulval cancer: When should I stop resecting? Identifying the factors that predict recurrence. Indian J Med Paediatr Oncol 2019;40:358-64.

Submitted: 04-Aug-2017
Accepted in Revised Form: 18-Apr-2018
Published: 04-Dec-2019

Address for correspondence:
Dr. Sarah Louise Platt, Department of Gynaecological Oncology, St Michael's Hospital, Southwell Street, Bristol, BS2 8EG, UK.
E-mail: sarah.platt@uhbristol.nhs.uk

Access this article online
Website: www.ijmpo.org
DOI: 10.4103/ijmpo.ijmpo_138_17
Quick Response Code:

1 mm as significant in predicting nodal metastasis, with risk increases proportionally to depth.[11] Subsequently, inguinofemoral lymphadenectomy is now recommended for tumor depth >1 mm.

Following excision, adjuvant treatment is recommended if margins are involved, but other factors have been less influential in guiding treatment decisions. Currently, no prediction model exists to identify recurrences irrespective of margin status. The aim of this study was to further define these factors, aiding the development of a recurrence prediction model.

Subjects and Methods

All new cases of squamous cell carcinoma of the vulva treated in our center from January 1, 2007 to December 31, 2013 were reviewed to determine factors that influence recurrence in vulval cancer. In 2007, expansion of the minimum dataset for histopathological reporting of vulval neoplasms was introduced by the Royal College of Pathologists and to maintain consistency, all cases were reviewed from 2007.

Cases were identified through patient coding and electronic patient records. Data were collected from electronic patient records, patient notes, and pathology database to ensure full details of demographics, pathological features, and recurrences were available for analysis.

Patients had their definitive surgery performed by a designated gynecological oncologist. Tumors were excised with a 2-cm healthy skin and tissue excision margin wherever possible. If this was not achieved, the decision-making and reasoning were recorded carefully; for example, to preserve continence. If the depth of invasion on biopsy was ≥1 mm, ipsilateral or bilateral groin node dissection was performed either as a combined procedure or as a subsequent procedure. Bilateral groin node dissection was required in tumors of the labia minora, central tumors within 1 cm of the midline, or large lateral lesions of >2 cm, while ipsilateral dissection was performed in the remaining cases. In some cases, full groin node dissection was not performed despite being clinically indicated due to significant patient comorbidities.

The surgical technique and approach was in keeping with a previous review of vulval cancer management in this region by Falconer *et al*.[12] Analysis of adherence to these standards [Table 1] in this cohort allows for comparison of management with the 1997–2002 cohort and can further differentiate trends in surgical management. A small group of patients (n = 3) were eligible for participation in the GROINSS-VI trial, assessing the role of sentinel lymph node dissection in the management of vulval cancer. However, two of these cases were still within the "learning curve" component of the trial, so a full groin node dissection was performed in addition to the sentinel node detection and biopsy. Histological samples were examined by the pathology team, led by an experienced gynecological histopathologist (JP). Information was recorded according to the Royal College of Pathologists' minimum dataset [Table 2].[3]

Patients were followed up by a gynecological oncologist for a total of 5 years. Any patient suspected to have a recurrence had biopsies taken. Treatments provided for recurrent disease were recorded.

Vulval radiotherapy (45 Gy in 25 fractions) was administered postoperatively if the resection margin was positive or tumor-free margin <8 mm and re-excision was not possible without compromising either urinary or fecal continence. Groin radiotherapy was also administered (to a total of 50.4 Gy in 28 fractions) if groin nodes demonstrate spread. Our local protocol indicates that radiotherapy to the groins is required when there are one or more macroscopically involved inguinal nodes (≥5 mm); two or more microscopically involved inguinal lymph

Table 1: Surgical technique standards (Falconer *et al*.)

All cancers should have an accurately recorded FIGO stage
All patients with vulval cancer must have definitive surgery performed by the designated gynecologist with oncology interest
Tumors should be excised, ideally with a 2-cm healthy tissue excision margin down to the inferior fascia of the urogenital diaphragm and the fascia over the symphysis pubis
All patients with greater than Stage IA disease should have inguinofemoral node dissection
Ipsilateral inguinofemoral node dissection is required for labia majora tumors <2 cm in diameter, with subsequent contralateral inguinofemoral node dissection in node-positive cases
Bilateral inguinofemoral groin node dissection is required in tumors of the labia minora, central tumors within 1 cm of or crossing the midline or large lateral lesions of >2 cm
No nodal dissection is required for depth of invasion of <1 mm
Pelvic lymphadenectomy is not required

FIGO – International Federation of Obstetrics and Gynecology

Table 2: Royal college of pathologists minimum dataset vulval cancer

Tumor type, according to the WHO classification
Tumor differentiation
Tumor size (in at least two dimensions)
Thickness/depth of invasion
Presence or absence of lymphovascular invasion
Status of all resection margins
Minimum tumor-free margins
Presence of associated VIN or Paget's disease
Status of resection margins for VIN or Paget's disease
Minimum distance to margins for VIN or Paget's disease
Presence or absence of nonneoplastic epithelial disease
Presence or absence of LN metastases
Presence of extranodal spread
Whether nodal metastasis is larger than 5 mm

VIN – Vulvar intraepithelial neoplasia; LN – Lymph node

nodes (<5 mm) or evidence of extracapsular spread in any inguinal node. Concomitant chemotherapy was also given in a few selected cases. All demographic, histological, and clinical data were collected on a spreadsheet and retrospective data analysis was performed using IBM SPSS Statistics for Windows, Version 22.0. (Armonk, NY: IBM Corp.) and JMP®, Version 14.0. (SAS Institute Inc., Cary, NC). The logistic regression model was constructed to assess the effects of the selected characteristics of patients on the recurrence of vulval cancer. Both univariable and multivariable logistic regression analyses were performed. No imputation was made for the missing values.

Results

The retrospective analysis identified 72 patients with a new diagnosis of vulval squamous cell carcinoma between January 1, 2007 and December 31, 2013. The average age was 75 years (range 28–99 years, median 78 years). Full demographics are detailed in Table 3.

The majority of the cases (53/72) were Federation of Obstetrics and Gynecology Stage 1 and 2 tumors, with 15 classified as stage 3 and four unclassified. Two cases were excluded from the final analysis as their initial biopsy did not provide enough information to complete the minimal dataset and also they did not have definitive surgery: one proceeded straight to palliative radiotherapy and the other declined treatment. In four cases (5.7%), the minimum dataset was not complete, with full details of the resection margins not available in the pathology report. However, these cases were included in the analysis as factors including lesion size, depth, LVSI, background skin status, and stage were available. The 70 patients included in analysis all had primary surgery to excise the tumor.

Table 3: Clinical and patient characteristics

	n	Mean	Range	Median
Total patients	72			
Age (years)		74.91	28-99	77.79
FIGO stage				
1A	8			
1B	33			
2A	11			
2B	0			
2C	1			
3A	3			
3B	2			
3C	10			
Grade				
Poorly differentiated	13			
Moderately differentiated	33			
Well differentiated	25			
Not reported	1			
Depth of invasion	70	6.85 mm	0.4-35 mm	5 mm
Lesion size	68	30.96 mm	1-100 mm	25 mm
LVSI				
Present	10			
None	55			
Not reported	7			
Background				
VIN	39			
LS	9			

FIGO – International Federation of Obstetrics and Gynecology; LVSI – Lymphovascular space invasion; LS – Lichen sclerosis

In total, 70 patients were analyzed and 62 had wide local excision of the vulval tumor, seven had radical vulvectomy, and one patient needed posterior exenteration as primary treatment. Bilateral groin node dissection was performed in 26 (37.1%) cases; unilateral groin node dissection in nine (12.9%) cases and one case had a lymph node excision biopsy (full groin node dissection not performed due to extent of nodal disease and potential for neurovascular complications).

Groin node excision was not performed in 21 cases where the clinical details suggest that it was indicated. In 16 cases it was documented that groin node dissection was not performed despite tumor depth being >1 mm due to a combination of patient comorbidities and informed choice. One case had an isolated groin node removed, while another had previously had groin surgery for other pathology. In the remaining cases, the decision-making was not recorded, although it is worth noting that 3/21 cases were also documented as unfit for adjuvant radiotherapy, so these comorbidities may have precluded the patients from groin surgery too. Some centers advocate follow-up of patients who have not had groin node dissection with 3-monthly groin ultrasound and fine-needle cytology where nodes are suspicious, although this practice is not currently performed locally.[13]

Of those patients without any recorded explanation for not undergoing groin node dissection or adjuvant groin radiotherapy, the only evident clinical patterns are that they were all stage 1 tumors with negative skin margins.

The margin status of all vulval resections was recorded: 13 (18%) had positive margins and 57 (82%) had negative margins. Of those patients who had positive margins, eight were predictable as excision was limited due to proximity of the bowel, urethra, clitoris, anal sphincter. Five were unexpected – one had further excision, two were unfit for further excision and RT, and two had adjuvant RT. Histological margins below 8 mm were found in 38 cases (67%). The background skin status was also recorded to assess whether vulvar intraepithelial neoplasia (VIN) or Lichen sclerosis was present, and also if it was present at the excision margin. Background VIN was reported in 40 (57%) patients, and 12 (17%) of these had involved skin excision margins with VIN 3 in all but one case. Background Lichen sclerosis was found in 10 (14%) patients, with only 1 (1%) extending to the excision margin.

Following surgery, 13/70 patients had adjuvant treatment: Palliative chemoradiotherapy was given to one patient, three had groin radiotherapy, and nine patients received pelvic external beam radiotherapy. There was one postoperative death, one declined any adjuvant therapy, and three were unfit for adjuvant treatment.

Positive groin nodes were found in 15 (21%), of which 11 had adjuvant radiotherapy, two were unfit to proceed with adjuvant treatment and two were observed under routine follow-up following discussion of pros and cons treatment. Negative groin nodes were reported in 25 (36%) patients, of which 23 were observed, two had adjuvant vulval radiotherapy due to margin status.

The recurrence rate in this study was found to be 21/70 (30%). The site of recurrence is detailed in Table 4. Clinical notes were reviewed and those patients who had confirmed recurrence on histology were identified. Local vulval recurrences were seen in 14 (20%), while seven (10%) recurred in the groin nodes. Of note, only two of the recurrences at the groin were "true" recurrences as 4/5 cases had not originally had groin node dissection at primary treatment, and 1/5 had only had groin node dissection on the opposite side to the site of groin recurrence as the original lesion had not been central or large enough to warrant bilateral lymphadenectomy. The intervention for each recurrence was also recorded. Groin recurrences were treated with either external beam radiotherapy (3/7) or a combination of both surgery and external beam radiation therapy (RT) (3/7), although one case had no apparent treatment. None of the cases of vulval recurrence had received radiotherapy to the vulva; however, three cases had received groin radiotherapy. Vulval recurrences were treated with repeat excision in 7/14 cases, vulval RT in 4/14 cases and a combination of surgery and RT in 3/14 cases.

Adjuvant treatment after primary surgery was originally indicated in 18 of those cases that recurred but was only given in three cases, as eight patients were documented as unfit or declined treatment. In the remaining cases, groin nodes were clear although vulval excision margin status was below 8 mm.

For all patients, total follow-up time was recorded. All patients continued to attend for follow-up and the latest date for follow-up was February 2016. The follow-up times are equivalent to the survival times, as indicated in Table 5 by the Kaplan–Meier curve.

The median survival for this patient group was 84.2 months, with a mean of 65.9 months. In those patients where disease recurrence occurred, the median disease-free interval was 19.1 months, with a mean of 24.7 months [Table 6, Figures 1 and 2].

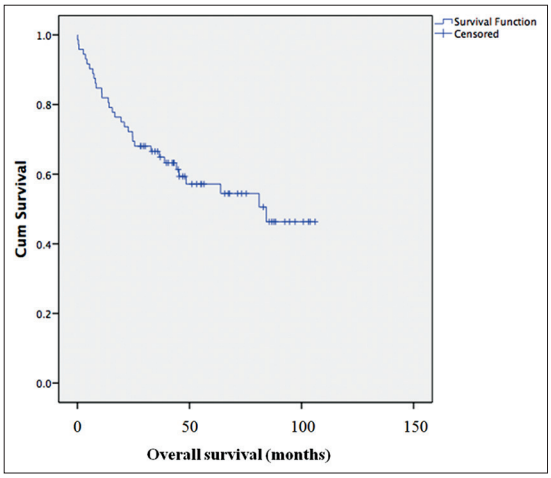

Figure 1: Overall survival in patients treated for vulval cancer

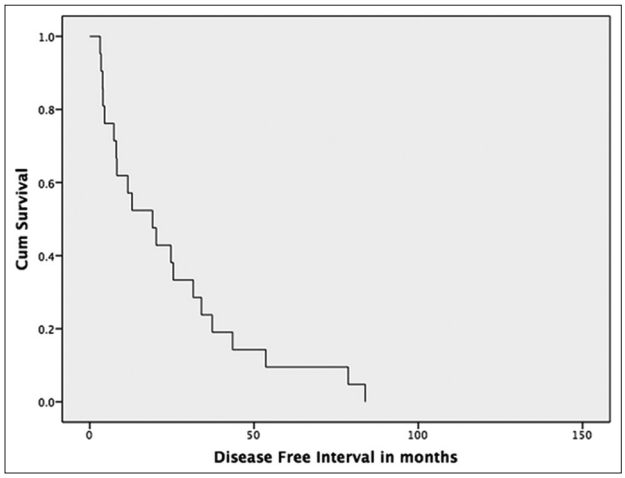

Figure 2: Disease-free interval in patients treated for vulval cancer

Table 4: The sites of recurrence among the 22 cases

Site of recurrence	*n*	Percentage recurrence (*n*=21) (%)	Percentage of patients (*n*=72) (%)	Groin node excision?	Adjuvant treatment?
Local recurrence	15	71.4	19.4		
Vulval	12	57.1	15.3	8-1 positive, 7 negative	1
Buttock	1	4.8	1.4	Positive	No
Peri-anal	1	4.8	1.4	Negative	No
Peri-urethral	1	4.8	1.4	Negative	Yes
Groin recurrence	6	28.6	9.7		
Right groin	5	23.8	6.9	2-1 positive, 1 negative	1
Left groin	1	4.8	2.8	0	0

Logistic regression analysis was performed to predict recurrence. The most significant factors in predicting recurrence were found to be LVSI, positive groin histology, and stage of disease. Cox-regression analysis was also used to predict recurrence, using the disease-free interval as the outcome measure, but none of the factors were found to be statistically significant.

Discussion and Conclusions

Falconer *et al*. carried out a prospective audit between 1997 and 2002 and found that the proportion of cases with a tumor-free margin >8 mm reduced from 54% to 35% during the study period. This pattern appears to have continued within our cohort, with 18/70 (26%) cases having tumor-free margins >8 mm [Figure 3]. The reasons for the reduction in adequate histological margin are multifactorial: seemingly adequate skin margins at surgery but clinically occult involvement of apparently healthy skin, reduced skin margins for the preservation of urethral and anal function, and more conservative surgery on older patients who are less likely to tolerate extensive morbidity-inducing surgery.

Table 5: Predictors of recurrence

Source	Nparm	DF	L-R ChiSq	Prob>ChiSq
Grade	2	2	1.72	0.42
Lesion size (mm)	1	1	0.02	0.88
Depth (mm)	1	1	1.43	0.23
Cancer margin status	1	1	2.01	0.15
Lateral margin	1	1	0.90	0.34
Deep margin	1	1	2.80	0.09
Background skin	2	2	2.98	0.22
LVSI	1	1	5.84	0.015*
LN positivity	3	3	12.65	0.005*
Stage	2	2	6.26	0.043*
Adjuvant treatment	4	4	0.65	0.95

*Significant <0.05. LVSI – Lymphovascular space invasion; L-R: Likelihood ratio; LN – Lymph node

Table 6: Predictors of overall survival

Characteristic	Significance	95.0% CI
Grade	0.504	0.013
Lesion size (mm)	0.008	1.028
Depth (mm)	0.724	0.700
Cancer margin status	0.000	0.000
Lateral margin	0.613	0.825
Deep margin	0.569	0.937
Margin status of background skin	0.050	0.010
Background skin	0.009	7.007
LVSI	0.737	0.190
Neural invasion	0.988	0.000
Groin histology	0.003	5103.528
Stage	0.845	0.107
Adjuvant treatment	0.001	0.000
Age	0.004	1.047

CI – Confidence interval; LVSI – Lymphovascular space invasion

Within our cohort, 68% (49/72) patients were aged 70 or over at diagnosis, which is much higher than the overall UK average. The Cancer Research UK Statistics report that 55% of vulval cancer cases in the UK each year are diagnosed in females aged 70 and over (2012–2014).[1]

Counseling patients for groin dissection surgery, more extensive vulval excision and radiotherapy will undoubtedly include discussion of the impact of treatment on survival, prognosis, and risk of recurrence. It could be argued that patients at the upper end of the age range are less likely to opt for more aggressive treatments that will impact significantly on their quality of life at a time when other comorbidities are likely to be more influential in their life expectancy.

In this study, there were several cases where groin dissection was not performed due to patient comorbidities, despite being clinically indicated. It is possible that with the introduction of more sentinel lymph node surgery in vulval cancer, those patients who would have previously been deemed unfit for full groin node dissection or were not willing to pursue such surgery could opt for this less invasive and less complicated procedure. This in turn would enable more effective triage of patients who are likely to benefit from more justified adjuvant treatment or a full lymphadenectomy.

The recurrence rate in this study was 30% of cases, which is within the range of reported recurrence rates in the literature (15%–33%).[14] The mean time for recurrence was at 24 months, and 14/21 (67%) recurrences occurred locally at the vulva. One of the statistically significant factors for recurrence was found to be the involvement of the lateral skin margin, so more conservative surgery may account for a recurrence rate which is at the higher end of reported rates. However, LVSI, stage, and positive groin histology were also statistically significant in predicting recurrence, so these factors also need to be considered carefully in decision-making about adjuvant treatment and repeat surgery.

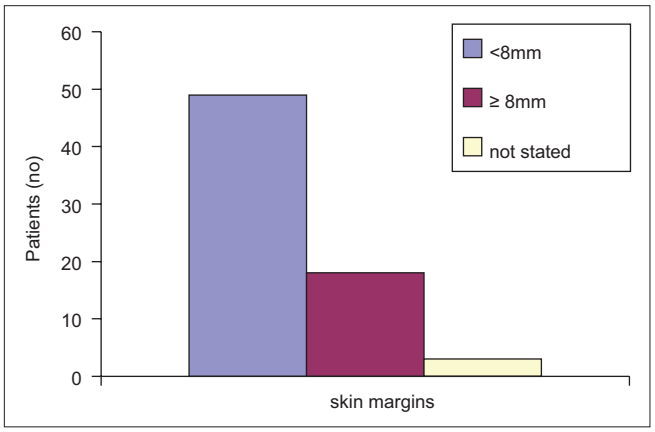

Figure 3: Tumor-free skin margins

There were seven cases of groin recurrence, which accounted for one-third of all recurrences. However, only two of these cases were true recurrences since the remainder did not have any prior groin surgery at the site of recurrence: One case had previously negative groin histology and so did not have adjuvant radiotherapy, while the other case had positive groin histology and received external beam radiotherapy. It is difficult to draw conclusions about these two cases, but one consideration is whether initial groin dissection was extensive enough to remove all of the inguinofemoral lymph nodes. Previous research has debated over the extent of inguinofemoral lymphadenectomy and whether the saphenous vein should be preserved to reduce complications such as wound breakdown, cellulitis, and lymphedema, although this could leave residual lymph node tissue with microscopic disease. Thomas *et al*. reported a similar incidence of recurrent disease with and without saphenous vein sparing in their study.[15]

The question of this study was whether surgical techniques have become too conservative and are adversely affecting recurrence rates. The main factors that contribute to recurrence were identified as LVSI, lateral margin involvement, positive groin histology, and increasing stage of tumor. It appears that margin involvement is a significant contributor, and in fact, the proportion of margins <8 mm has increased over the last decade. It is important that we continue to carefully mark skin margins and aim for a 2-cm surgical excision margin. It is likely that more careful counseling will be required so that patients are aware that a more conservative excision (sparing the anal sphincter or urethra) may result in an increased risk of recurrence at an average of 2-year postsurgery, and likely repeat surgery. Alternatively, if patients have close margins at primary excision and they would prefer to avoid more extensive surgery, they should be counseled about the greater need for groin lymph node assessment as if positive this will be influential in guiding adjuvant treatment. With the increased use of sentinel lymph node assessment, it should be easier and more acceptable for patients to have this procedure in combination with a more conservative vulval excision.

In terms of influencing factors regarding disease-free interval, there was not a clear significant factor identified within this study. It, therefore, seems that our current surveillance program is acceptable and there is no indication to tailor the follow-up interval according to the particular patient or tumor factors.

Resection margins will contribute to recurrence rates, but decision-making regarding primary treatment and adjuvant treatment should also incorporate other significant factors such as presence of LVSI, tumor stage, and groin node status. These factors can be incorporated into a recurrence prediction model, and this will be the next stage of our research.

In addition, it is very clear from this study that many patients who were eligible for adjuvant treatment or groin node dissection did not always opt for these interventions. There can often be a multidisciplinary team decision that such treatments are not suitable for older patients with significant comorbidities, particularly if a recurrence is not likely to occur within their life expectancy. However, with increased tumor stage and groin involvement being predictive of recurrence, we should aim to deliver either sentinel or full groin node dissection and adjuvant radiotherapy for the majority of our patients if it is indicated. Patients may choose to decline these interventions, but this should be following a detailed discussion of the risks and benefits and should then be fully documented. The role of groin ultrasound scanning in disease surveillance should be considered for patients who decline groin surgery and adjuvant treatment despite clinical indications.

Acknowledgment

The authors would like to thank Mr. Amit Patel for assistance with statistical analysis support and Dr. Jo Bailey for general support of the project

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Cancer Research. Information Originally Obtained from Office National Statistics. Available from: http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/vulval-cancer#heading-Two. [Last accessed on 2017 Jul 16].
2. Royal College of Obstetricians and Gynaecologists/British Gynaecological Cancer Society. Guidelines for the Diagnosis and Management of Vulval Carcinoma. London, UK: Royal College of Obstetricians and Gynaecologists/British Gynaecological Cancer Society; 2014.
3. Royal College of Pathologists. Datasets for the Histopathological Reporting of Vulval Neoplasms. 3rd ed. London, UK: Royal College of Pathologists; 2010.
4. Yap J, O'Neill D, Nagenthiran S, Dawson CW, Luesley DM. Current insights into the aetiology, pathobiology, and management of local disease recurrence in squamous cell carcinoma of the vulva. BJOG 2017;124:946-54.
5. Heaps JM, Fu YS, Montz FJ, Hacker NF, Berek JS. Surgical-pathologic variables predictive of local recurrence in squamous cell carcinoma of the vulva. Gynecol Oncol 1990;38:309-14.
6. De Hullu JA, Hollema H, Lolkema S, Boezen M, Boonstra H, Burger MP, *et al*. Vulvar carcinoma. The price of less radical surgery. Cancer 2002;95:2331-8.
7. Van der Velden J. Surgical interventions for early squamous cell carcinoma of the vulva. Cochrane Database of Systematic Reviews 2000;(2) Art. No.: CD002036. DOI: 10.1002/14651858.CD002036.
8. Burke TW, Levenback C, Coleman RL, Morris M, Silva EG, Gershenson DM, *et al*. Surgical therapy of T1 and T2 vulvar

carcinoma: Further experience with radical wide excision and selective inguinal lymphadenectomy. Gynecol Oncol 1995;57:215-20.

9. DiSaia PJ, Creasman WT, Rich WM. An alternate approach to early cancer of the vulva. Am J Obstet Gynecol 1979;133:825-32.
10. Woelber L, Griebel LF, Eulenburg C, Sehouli J, Jueckstock J, Hilpert F, *et al.* Role of tumour-free margin distance for loco-regional control in vulvar cancer-a subset analysis of the Arbeitsgemeinschaft Gynäkologische Onkologie CaRE-1 multicenter study. Eur J Cancer 2016;69:180-8.
11. Hacker NF, Van der Velden J. Conservative management of early vulvar cancer. Cancer 1993;71:1673-7.
12. Falconer AD, Hirschowitz L, Weeks J, Murdoch J; South West Gynaecology Tumour Panel. The impact of improving outcomes guidance on surgical management of vulval squamous cell cancer in Southwest England (1997-2002). BJOG 2007;114:391-7.
13. Moskovic EC, Shepherd JH, Barton DP, Trott PA, Nasiri N, Thomas JM, *et al.* The role of high resolution ultrasound with guided cytology of groin lymph nodes in the management of squamous cell carcinoma of the vulva: A pilot study. Br J Obstet Gynaecol 1999;106:863-7.
14. Piura B, Masotina A, Murdoch J, Lopes A, Morgan P, Monaghan J, *et al.* Recurrent squamous cell carcinoma of the vulva: A study of 73 cases. Gynecol Oncol 1993;48:189-95.
15. Dardarian TS, Gray HJ, Morgan MA, Rubin SC, Randall TC. Saphenous vein sparing during inguinal lymphadenectomy to reduce morbidity in patients with vulvar carcinoma. Gynecol Oncol 2006;101:140-2.