ORIGINAL ARTICLE

A Study of Patients Treated for Primary Squamous Cell Carcinoma of the Vulva in the Regional Cancer Centre in Cardiff, UK

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ABSTRACT

Objective: Review of patients operated for primary squamous cell carcinoma (SCC) of the vulva in the Department of Gynaecological Oncology, University Hospital of Wales in Cardiff, to determine factors related to recurrence as well as survival of disease.

Material/Methods: A retrospective review using details obtained from patients' records. Hazard ratio estimation was carried out with Cox Regression analysis and survival plots were determined using Kaplan-Meier plots.

Results: 144 women with primary vulval SCC were operated from 2002-2010. Commonly, radical wide local excision (49.3%) and radical vulvectomy (46.5%) were carried out, apart from ano-vulvectomy (1.4%) and local excision biopsies (2.8%). In 77.1% lympnode dissection was performed and inguinal metastasis was diagnosed in 28.8%, bilaterally in 68.8%. Histologically, 64.4% were moderate/poor differentiation and 30.9% were advanced disease (FIGO III and IVA). The 5-year survival rate (OS) was 61.1%. Stratified by FIGO classification, the 5-year OS for stages IA, IB, II, III and IVA were 72.7%, 86.0%, 50%, 34.4% and 45.5% respectively. Age >70 years was an important prognostic factor (51.9% OS) compared to 71.6% in patients 70 years. Patients with grade 1 disease survived in 72.5%, grade 2 in 58.8% and poorly differentiated cancer in 41.7%. Presence of inguinal metastasis was associated with a 40.6% 5-year OS, absence with 74.7%.

Conclusions: Cox regression analysis confirms that age, presence/bilaterality of inguinal lymphnode metastasis, high-grade tumour differentiation, tumour size, FIGO stage and adjuvant therapy are important prognostic factors for 5-year survival.

INTRODUCTION

Being a generally rare disease, vulval cancer causes about 8% (~27,000 women annually worldwide) of gynaecological cancers in the United Kingdom (UK). An increasing incidence to about 1% per annum was published recently[1,2] giving it a lifetime risk for cancer development of about 1:293 in the UK. This equates to over 370 deaths from vulval cancer each year. Compared to a younger generation (1:1,000,000 in 25-44 years), this carries a sixty-fold increase in risk for middle aged women (6:100,000 in 45-64 years) and a 120-fold increase for the older generation (12:100,000 in 80 years).[3] However, overall mortality continuously improved in the recent past, which is likely a result of greater understanding of the disease, and improvements in general healthcare. It is presumed that vulval and vaginal cancers' incidence will continually rise, in particular because of our aging population and an increased ubiquity of oncogenic HPV infections.[3]

Scrutinising UK cancer services, the Calman-Hine "Policy Framework for Commissioning Cancer Services"[4] promotes reorganisation of local and regional services to establish a higher quality in care and to grant patients access to experts in the field, wherever they live in the country. In the NHS, it is essential since 2015 to collect data on gynaecological cancers and to publish outcome measures for public inspection. The provision of information on cancer incidence, clinical staging, histopathology, recurrence and survival, treatments

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provided, treatment-related morbidity, co-morbidities and trial recruitment has become mandatory.

Following the previous reviews of outcomes of cervical and endometrial carcinoma treatment carried out in our South Wales Cancer Centre in Cardiff, the authors intended to present a service evaluation of the follow-up of women undergoing vulval cancer treatment in this unit.[5,6] Notably, this study constitutes the first attempt at surveying vulval cancer treatment in South Wales over a time period of over 10 years. This shall establish a basis for future reference and provide a benchmark for comparative studies, when monitoring the quality of service.

METHODS

The study represents a retrospective investigation of women in South East Wales, having undergone surgical treatment for primary squamous vulval cancer between 2002 and 2010. Until May 2015, data was collected on patients referred to our regional cancer centre in Cardiff from patients' records and computerised NHS (Wales) data systems, containing details on their gynaecological cancer treatment. From this material, we determined morbidity and mortality information. The local audit and ethics department reviewed our study and being a retrospective service evaluation, ethical approval was deemed unnecessary.

SPSS, version 20, was used to carry out statistical calculations. As the data's variables were often skewed or categorical, non-parametric tests were used for evaluation, including χ^2, Mann-Whitney, Kruskal Wallis tests where appropriate. To meet requirements of statistical tests, some variables were transformed into binary variables. Age was ranked into and ≤ 70 and > 70 years old, lymphnode dissection into bi- and unilateral, FIGO stage into early (stage 0, IA/B and II) and advanced disease (stage III, IVA), number of lymphnodes dissected into and ≤ 17 and > 17 (according to its mean), tumour size into and ≤ 30 mm >30 mm (according to its mean), surgical excision margins into ≤ 8 mm or more and depth of invasion (DOI) into ≤ 1 mm or more. The analysis of categorical data was carried out with a χ^2 test. Kaplan-Meier procedures and Cox hazard regression explored relationships of the various variables on progression free survival (PFS) and overall survival (OS), allowing comparison of all variables. To test survival in groups, a Log Rank test was computed. A *P* value of <0.05 was deemed significant.

The 2007 FIGO staging was applied, as histopathological reporting has only recently changed with the issue of latest staging guidance. The operation date and the last contact with the patient in clinic were used as starting point and censor parameter in order to analyse recurrence and survival. For vulval cancer, Welsh cancer guidelines recommend conventional three monthly appointments in the first year, then twice in the second year, followed by one appointment per annum from then onwards.[7] At each of these visits patients would be examined and biopsies were taken of suspicious or symptomatic vulval skin areas. OS was determined as months from operation to demise and PFS as the period following treatment until disease relapse.

RESULTS

From 2002 to 2010, one hundred and forty-four women were treated surgically in South East Wales for primary SCC of the vulva. The median age of these women was 72 (mean 68, range 22-98). The mean survival at 5 years was 97.0 months (95%CI: 86.9-107.1) with an OS rate of 61.1%. The mean PFS at 5 years was 110.6 months (95%CI: 100.6-120.5), while 65.3% of patients had relapsed (Figure 1).

Table 1 depicts further details of our cohort's clinical details and demographics. Most patients were diagnosed in stage I and II (69%), 84% had grade I or II disease, and either underwent a radical wide local excision (WLE, 49.3%) or radical vulvectomy (RV, 46.5%). Inguinal lymphnode dissection was carried out in 111 patients (77.1%), mostly bilateral (98.2%). Adjuvant therapy in the form of radiotherapy was carried out in 54 (37.8%) women.

Fifty patients (35%) in toto developed a recurrence during the time of our analysis, of which 43 (29.9%) relapsed within 5 years after the primary operation and the majority occurred within the first two years (52%, 26/50). Women developing disease recurrence within 5 years had a 5-year OS of 46.5%. Their mean survival interval was 82.7 months, compared to 67.3% 5-year OS and 111.8 months in patients without recurrence. The 5-year PFS was 84.0% in patients with cancer relapse and 1.1% for patients free from disease. All these women were diagnosed during a routine clinical examination in a gynaecological oncology clinic during a scheduled appointment.

Statistical significance was established for survival and age, surgical stage, histological grade, tumour size, presence and laterality of inguinal lymphnode metastasis (IM), recurrence and adjuvant treatment, as well as between PFS and age, surgical stage, tumour size, inguinal lymphnode status, recurrent disease and adjuvant therapy. These are demonstrated in the Cox regression analysis in Table 1. On univariate Cox regression analysis no association was established, neither for OS nor PFS, with type of surgery performed, number of lymphnodes (LN) removed, depth of invasion (DOI), surgical margin, and vascular invasion (LVSI). Furthermore, for PFS, histological differentiation had no influence. The multivariate Cox regression demonstrates

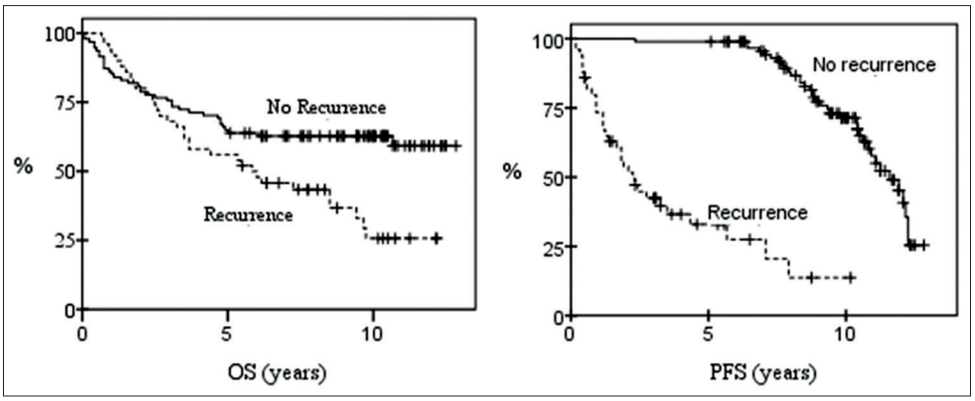

Figure 1: Kaplan-Meier graphs depicting overall survival and progression free survival in women with primary SCC of the vulva

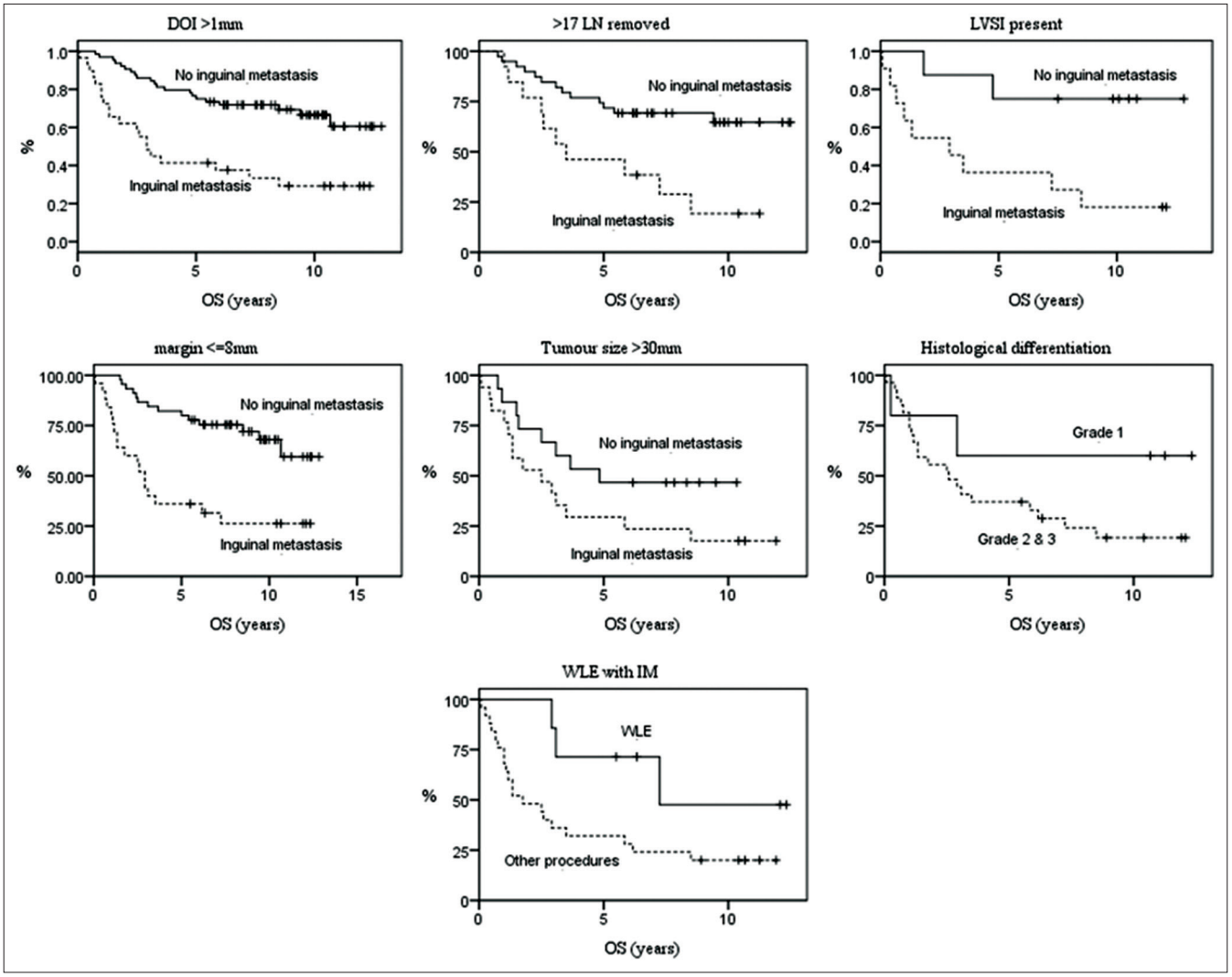

Figure 2: Kaplan-Meier graphs depicting 5-year OS in women with inguinal metastasis compared to DOI, number of LN removed, histological grade of tumour, type of operation, LVSI and surgical margins

that age <70 years, WLE, stage I, grade 1 disease and no recurrence have a significant 5-year survival benefit (Table 2).

The most important factors affecting IM (Table 3) in order of importance were DOI, number of LN removed during surgery, histological grade, surgical margin, LVSI, WLE and tumour size. Twenty-nine (31.2%) tumours with DOI > 1 mm developed IM, opposed to 16.7% in a DOI. Amongst well differentiated tumours, 13.5% (5/37) metastasised in comparison to 30.2% (16/53) in moderate

Table 1: Cox regression analysis of patient demographics and treatment characteristics in patients with primary squamous cell carcinoma of the vulva, *n*=144

	n (%)	Overall survival			Progression free survival		
		HR	*P*	95% CI	HR	*P*	95% CI
Age							
≤70	77 (54)	1.00			1.00		
>70	67 (46)	2.30	0.001	1.38-3.81	1.81	0.022	1.09-3.01
Total	144						
Operation							
WLE	71 (49)	1.00			1.00		
RV	67 (47)	1.51	0.097	0.93-2.47	1.29	0.305	0.79-2.11
RAV	2 (1)	1.07	0.945	0.15-7.88	0.49	0.491	0.06-3.67
Biopsy	4 (3)	4.69	0.011	1.42-15.47	1.01	0.984	0.31-3.35
Total	144						
Surgical stage							
I	61 (44)	1.00			1.00		
II	34 (25)	2.60	0.004	1.34-5.03	2.37	0.010	1.23-4.57
III	32 (23)	3.94	<0.001	2.11-7.38	2.26	0.011	1.21-4.24
IV A	11 (8)	3.99	0.001	1.79-8.89	3.31	0.004	1.47-7.43
Total	138						
Histological grade							
1	51 (36)	1.00			1.00		
2	68 (48)	1.55	0.130	0.88-2.73	1.09	0.775	0.61-1.93
3	24 (17)	2.76	0.003	1.43-5.43	1.73	0.121	0.87-3.46
Total	143						
Lymphnode status							
Negative nodes	79 (71)	1.00			1.00		
Positive nodes	32 (29)	3.49	<0.001		2.29	0.004	1.30-4.03
Unilateral	22 (20)	3.48	<0.001	1.84-6.60	2.22	0.015	1.17-4.23
Bilateral	10 (9)	3.51	0.002	1.59-7.76	2.41	0.030	1.09-5.34
Total	111						
Number lymphnodes removed							
≤17	58 (53)	1.00			1.00		
>17	52 (47)	1.05	0.859	0.60-1.86	1.52	0.153	0.86-2.70
Total	110						
Tumour size in mm							
≤30	65 (60)	1.00			1.00		
>30	43 (40)	2.57	0.002	1.43-4.61	2.88	0.001	1.55-5.35
Total	108						
Surgical margin >8 mm							
Yes	31 (25)	1.00					
No	94 (75)	0.82	0.543	0.44-1.52	0.83	0.543	0.45-1.53
Total	125						
DOI >1 mm							
No	10 (13)	1.00			1.00		
Yes	122 (87)	1.27	0.643	0.46-3.50	1.06	0.917	0.38-2.92
Total	132						
LVSI							
No	96 (79)	1.00			1.00		
Yes	25 (21)	1.32	0.347	0.74-2.37	1.25	0.460	0.70-2.23
Total	121						
Adjuvant therapy							
No	89 (62)	1.00					
Yes	54 (38)	4.01	<0.001	2.32-6.92	2.76	<0.001	1.60-4.77
Total	143						
Recurrence							
No	94 (65)	1.00			1.00		
Yes	50 (35)	1.91	0.008	1.19-3.06	14.15	<0.001	7.53-26.59
Total	144						

DOI: Depth of invasion; LVSI: Lymphovascular space invasion; RAV: Radical ano-vulvectomy; RV: Radical vulvectomy; WLE: Wide local excision

Table 2: Multivariate cox regression analysis of patients with primary squamous cell carcinoma of the vulva

	5-year overall survival			5-year progression free survival		
	HR	*P*	95% CI	HR	*P*	95% CI
Age	1.99	0.012	1.14-3.46	0.61	0.084	0.35-1.07
WLE vs other procedures	1.86	0.025	1.08-3.20	1.45	0.184	0.84-2.49
RV vs other procedures	0.65	0.104	0.38-1.09	0.67	0.138	0.40-1.14
Stage I vs II-IV	4.92	<0.001	2.47-9.79	3.96	<0.001	1.99-7.88
Grade 1 vs 2/3	1.93	0.033	1.05-3.53	1.71	0.081	0.94-3.14
No recurrence vs. Recurrence	1.82	0.028	1.07-3.10	8.59	<0.001	4.22-17.47

HR: Hazard ratio; RV: Radical vulvectomy; WLE: Wide local excision

Table 3: Multivariate cox regression analysis of patients with inguinal metastasis

Inguinal metastasis	5-year overall survival			5-year progression free survival		
	HR	*P*	95% CI	HR	*P*	95% CI
DOI>1 mm vs ≤1 mm	3.63	<0.001	1.84-7.14	2.56	0.007	1.30-5.05
>17 LN removed vs ≤17 LN	3.35	<0.001	1.77-6.37	2.53	0.005	1.32-4.84
Grade 1 vs 2/3	3.35	0.001	1.61-5.97	2.30	0.012	1.20-4.43
Surgical margin>8 mm vs <8 mm	3.30	0.001	1.64-6.64	2.38	0.016	1.18-4.83
LVSI vs no LVSI	2.94	0.003	1.46-5.93	2.15	0.033	1.06-4.35
WLE vs other procedures	2.89	0.001	1.52-5.51	2.12	0.027	1.09-4.12
Tumour size≤30 mm vs >30 mm	2.13	0.042	1.03-4.40	1.50	0.287	0.71-3.14

DOI: Depth of invasion; HR: Hazard ratio; LN: Lymphnode; LVSI: Lymphovascular space invasion; WLE: Wide local excision

and 55% (11/20) in poor differentiation. Whenever more than 17 LN were removed during inguinal groin node dissection, 25.0% (13/52) developed metastasis compared to 31.0% (18/58) if < 17 LN were found. If the surgical margin was less than 8mm, 35.7% (25/70) patients had inguinal spread, while 20.8% (5/24) did with better margins. In eleven (57.9%) of 19 tumours with LVSI inguinal metastasis was evident, while without LVSI only 25.7% (18/70) metastasised. Women undergoing WLE had a lower chance of developing IM (14.3%; 7/49), than following RV, RAV and local excisions combined (40.3%; 25/62). Lastly, tumour size of >30mm had a risk of 53.1% (17/32) for groin node metastasis in comparison to 25.0% (12/48) if the tumour was smaller (Figure 2).

DISCUSSION

Our patients' demographical and clinical features are comparable to recently published studies. The cohort size of 144, median age of 68 and follow-up period of over 10 years correlates to other publications. Amongst these, study sizes ranged from 16 to 588 patients (median 146), age at diagnosis from 46 to 74 and patients were followed up over 3 to 50 years.[8-41,45] In terms of surgical staging, our study composition of clinical stages I-IV of 44%, 25%, 23% and 8% respectively, matches the demographics of other studies ranging for stage I disease from 35% to 55%, stage II (26-37%), stage III (13-29%) and stage IV (5-13%).[14,20,21,42] Furthermore, histological differentiation amongst our cohort is as well analogous to the literature - grade 1 was found in approx. one third of patients, moderate differentiation in half and poorly differentiated cancer in every 6th patient.[14]

Survival in vulval cancer has been linked to tumour size, clinical stage, age, presence of pelvic and inguinal lymphnode metastasis, LVSI, positive surgical margins, DOI, poor histological differentiation, multifocal tumour and treatment in hospitals operating on less than 20 cases per year.[8,12,14,16,20,22,27] Our study supports most of these important prognostic factors for 5-year survival. The 5-year OS of 61.1% is well within the range of described survival rates ranging from 44.4-76.1%.[13,20,22-24,28-30]

Akin to El Afandy's review,[19] the majority of patients in our cohort recurred within the first 2 years following diagnosis. Published recurrence rates vary from 14 to 78.6% and our outcome (34.7% overall recurrence; 93% local) is situated within this spectrum.[9,11,13,15,18,24,25,28,32,35,42] Amongst our patients, the 5-year PFS at stage I (47.4%), stage II (22.7%), stage III (21.6%) and stage IVA (8.2%) correlates with currently published data. Significant predictors for PFS include tumour size, clinical stage, pelvic or inguinal lymphnode metastasis, DOI and positive surgical margins, which our study supports by and large (recurrence independent from surgical margin in our cohort).[12,13,19,21,42] Likewise, we can confirm that recurrence itself is a strong predictor for cancer related mortality.

Surgical stage of disease is as described a vital prognostic marker for vulval carcinoma. For stage I, 5-year OS ranges from 40% to 100% in previous studies, for stage II from 54.9% to 91%, for stage III from 36% to 77% and for stage IV from 7.1% to 31%.[14,15,17,20,25-29,31-33] This matches our own patients, having a 5-year OS at stage I of 83.6% and at stage II 50%. However, the comparatively lower survival rate of 12.9% at stage III and the high survival rate in stage IV is likely explicable by a low cell count (Stage III 11/32; stage IV 5/11) and would probably be adjusted by a larger number of study participants. This is as well represented in the mean survival times of 80 months in stage II, 65 months in stage III and 73 months in stage IV.

Age is an accepted independent prognostic factor for survival.[14,20,21,24,25,29,38] Blecharz et al.[29] describe a 5-year OS if patients were younger than 70 of 47.1% and if older 30.5%, which corresponds to our study with 51.9% 5-year OS in patients younger than 70 and 45.5% if older.

Histological differentiation has been suggested as having a good prognostic value in survival in several studies.[20,21,27,38] Mean survival rates according to histological grade were 120 months for grade 1, 99 months for moderate and 75 months for poor differentiation, being very similar to times reported by Rosen et al. (152, 114 and 74 months respectively).[14] Overall survival according to histopathological grade (G1 - 72.5%, G2 - 58.8%, G3 - 41.7%) correlate to other reported outcomes (78%, 70% and 22% respectively).[29]

Tumour size is a relevant factor for clinical staging, but the impact on OS and PFS are reported with varying results.[11,12,20,28,32,39,43] Amongst our patients, 5-year survival of tumours greater than 3cm was 39.5% compared to 69.2% if smaller. Rodolakis et al.[23] report a similar outcome with 79.5% 5-year OS for tumours smaller than 3cm and 52.6% if greater.

Our study confirms that lymphnode metastasis is one of the greatest impact factors on survival and recurrence.[8,15,20,21,23,30,31,40,42,44] Five-year overall survival ranging from 85% to 98% in negative nodal status and from 18% to 54% if IM was present are comparable to our data.[9,15,23,30,31,44] The presence of IM is heavily influenced by age, tumour size, DOI, poor histological differentiation, LVSI and clinical stage.[9,38-40] Homesley et al.[37] report groin metastasis in 18.9% if tumour lesions were 2cm or under and 41.6% if more, which correlates with our study (25.0% IM if tumour 3 cm; 53.1% IM if >3 cm).

Being a retrospective study, the authors feel that part of the limitations of our paper is that the comprehensiveness of data collection compared to a prospective study could not be achieved. However, this paper constitutes the largest review of vulval cancer treatment undertaken so far in Wales. Study group uniformity may sometimes not have been ideal, in particular due to occasional low cell counts and because of facing challenges whilst obtaining follow-up data for some patients. However, our reported outcomes were comparable to current literature as described above. As well, histopathological reporting has only in recent years reached an exhaustive quality, making it challenging to thoroughly comment on specimen specificities retrospectively.

In conclusion, uni- and multivariate analysis of our data support that strong predictors for OS are age, presence or bilaterality of inguinal lymphnode metastasis, high-grade tumour differentiation, tumour size, FIGO stage and adjuvant therapy. Compared to the previous reviews on cervical and endometrial cancer in our cancer centre,[5,6] given the high recurrence rates and impaired OS amongst women with vulval cancer, we support a hospital based follow-up to ensure timely interventions for early diagnosis of recurrence. Nonetheless, at a time of decreasing financial funding, a specialised nurse-led follow-up clinic may help in reducing the workload of a dedicated gynaecological oncology outpatient department.

CONCLUSIONS

Cox regression analysis confirms that age, presence/bilaterality of inguinal lymphnode metastasis, high-grade tumour differentiation, tumour size, FIGO stage and adjuvant therapy are important prognostic factors for 5-year survival.

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