Clinicopathological Prognostic Factors Influencing Survival Outcomes of Vulvar Cancer

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Research Article

Keywords: Clinico-pathological factors, survival outcome, vulva cancer

Posted Date: February 23rd, 2021

DOI: https://doi.org/10.21203/rs.3.rs-239195/v1

Abstract

Backgroud: Squamous cell carcinoma (SCCA) is the most common vulva cancer. This study purpose to evaluate the clinicopathological prognostic factors for survival outcomes of this disease after treated with surgery.

Methods: All SCCA vulva cancer patients who underwent surgery between January 2006 and December 2017 were reviewed. The clinicopathological factors were analyzed to identify the prognostic factors for the progression-free survival (PFS) and overall survival (OS) using the Kaplan- Meier method and Cox-Proportional Hazard model.

Results: One hundred twenty-five patients were recruited with a median age of 57 years. The recurrence rate was 35.2%. Patients with recurrence revealed a significant poorer five-year OS rate than those who did not recur (23.7% vs. 79.4%, $P < 0.001$). About 58.1% of palpable groin nodes revealed metastasis. The independent poor prognostic factors for PFS were groin node-positive and a tumor diameter more than 25 mm. whereas postmenopausal status, preoperative tumor area more than 11 $cm^{2,}$ and groin node enlargement were independent poor prognostic factors for OS.

Conclusion: Groin node-positive and tumor diameter longer than 25 mm. were independent poor prognostic factors for PFS whereas postmenopausal status, large tumor area than 11 $cm^{2,}$ and enlargement of groin nodes were independent poor prognostic factors for OS. Patients with these factors should be closely followed.

Backgound

Vulva cancer is a rare gynecologic cancer. The latest data from Globocan 2018 showed a crude rate of 1.2 per 100,000 women-year [1]. The most common histology is squamous cell carcinoma (SCCA) classified into two types. The first one is the human papillomavirus (HPV) related. This type typically is found with a high-grade squamous cell intraepithelial lesion (HSIL) and is associated with the immunosuppressive state, smoking and usually occurs in younger age population. The other type is non-HPV related. The precursor lesion of this type is differentiated vulvar intraepithelial neoplasia (dVIN) usually occurring in postmenopausal women [2].

The standard treatment for early-stage SCCA vulva cancer is composed of the wide local or radical vulvectomy with or without groin node dissection depended on the depth of the primary lesion. If the tumor revealed an invasion of more than one mm., groin node dissection is warranted. Adjuvant treatment with pelvic and/or vulvar radiation is given when the groin node or surgical margins were involved [3]. Despite radical treatment, the recurrence rates still occurred in a range of 16–40% [4–7]. It has been shown that the patients who developed recurrence revealed poor survival outcomes [6, 7]. We recently reported the series of 145 SCCA vulva cancer patients and found the common recurrent sites were groin and vulva regions with unfavorable survival outcomes [6]. Previous publications identified some clinicopathologic factors such as tumor size, depth of invasion, margin –status, tumor grade, lymph vascular space invasion (LVSI), groin node involvement, and age were affect the recurrence and survival outcomes [4, 7–9]. However, with the small numbers in previous studies and limited data in the Asian population, we conducted this retrospective study to analyze the clinicopathological factors influencing the survival outcomes.

Methods

After the protocol was approved by the local ethics committee, the medical records of the vulva cancer patients with SCCA treated at Chiang Mai University Hospital from January 2006 through December 2017 were reviewed. The patients who underwent vulvectomy and/or groin node dissection with at least one postoperative follow-up were included in the study. The adjuvant treatment either concurrent chemo-radiation or radiation alone was given when the groin node was positive. The patients whose vulvar specimen revealed a tumor-free margin less than 8 mm. were given radiation at the vulva site. Neoadjuvant chemotherapy was given in some patients whose primary lesions were too large. After treatment, the patients were scheduled for follow up with history taking and pelvic examination by gynecologic oncologists every three months in

the first year, every four months in the second year, every six months in the third to fifth years and annually following. The CT-scan was performed when clinically indicated.

The FIGO 2009 staging, the sites and time of recurrence or death, the clinicopathological data including body-mass index (BMI), age, menstruation status, parity, treatment type, postoperative wound complication, underlying disease, pre-operative tumor area, groin node enlargement, groin node involvement, number of nodes removed in each side, pathologic tumor longest diameter, tumor grade, surgical margin, LVSI, and the presence of identifiable vulvar intraepithelial neoplasia or high-grade squamous intraepithelial lesion (VIN or HSIL) were searched from the medical record and pathology reports for further analysis. Regarding the pathological information, all surgical pathology specimens were examined and reported by a group of gynecologic pathologists. In cases where the data was incomplete, a gynecologic pathologist (S.K.) reexamined the available histologic slides. Progression-free survival (PFS) defined as the time from the initial treatment to the time of recurrence or progression of the disease or the time of last contact and overall survival (OS) defined as the same starting time as PFS to the time of patient death or the time that the patients were still alive at the end of the study. This time was sought from the Thai Civil Registration.

Statistical analysis of the data was carried out using IBM SPSS Statistics for Windows program (version 22; IBM Corporation, Armonk, NY, USA). A receiver operating characteristic curve (ROC) was used to assess the discriminative value and the best cut-off value of the possible clinicopathologic factors was determined to predict the recurrence or progression. The PFS and OS were estimated by the Kaplan-Meier method. Clinicopathological factors influencing survival as mentioned above were analyzed using log-rank test analysis. Cox proportional hazard models were applied to explore predictors of survival outcomes through univariate and further multivariate analysis if the P-value from the log-rank test less than 0.1. A p-value of < 0.05 was considered statistically significant.

Results

One hundred seventy-three SCCA vulva patients were treated at our institute in the study period. Of those patients, 48 cases were excluded from the study due to non-surgical treatment in 36 cases and not followed up postoperatively in 12 cases. Therefore, 125 cases were recruited in this study. The median age of them was 57 years with a range of 32–82 years. For the median follow up time as 15.03 months (range 1-128 months), 44 patients developed recurrence. Thus, the recurrence rate was 35.2%. These data were summarized in Fig. 1. At the time of analysis, 59 patients (47.2%) had died and the five-year PFS was 70%. The five-year OS rate was significantly different in patients with and without recurrence as showed in Fig. 2. The patients without recurrence revealed a better five-year OS rate as 79.4% while the patients with recurrence had a five- year OS rate only 23.7%, $P < 0.001$.

Figure 3 displayed the ROC curve of age, preoperative tumor area, and the longest pathological tumor diameter to find the optimal cut- off point value for predicting the recurrence state. The results revealed the cut -off point level as follows; for age was 55-year-old, for tumor preoperative tumor area was 11 cm^2 and for longest pathological tumor diameter was 25 mm.

The clinicopathological data were divided into two groups for each item and compared to find the influence of PFS and OS outcomes as noted in Table 1. For PFS, we found patients older than 55 years, postmenopausal status, advanced stage, pre-operative tumor area larger than 11 cm^2, groin node-positive, and pathological longest tumor diameter more than 25 mm. were significant for poorer PFS in univariate analysis. However, only the groin node-positive and pathological longest tumor diameter more than 25 mm. were significant in multivariate analysis with a hazard ratio of 2.231 and 2.811, respectively.

Table 1
Comparison of the PFS and OS Divided by Prognostic Factors

Factors	Total	5-Year PFS (%)	Univariate Analysis		Cox-Regression Analysis†		5-year OS (%)	Univariate Analysis		Cox-Regression Analysis†	
			HR†	P-Value*	HR!	P-Value		HR†	P-Value*	HR!	P-Value
BMI (kg/m2)			1.032 (0.284-4.300)	0.966	-	-		1.478 (0.456–4.798)	0.512	-	-
<=30	108	55.4					61.2				
> 30	6	62.5					50.0				
No data	11										
Age(years)			1.781 (0.942–3.365)	0.072	1.147 (0.501–2.625)	0.745		2.246 (1.289–3.914)	0.003	1.710 (0.750–3.896)	0.202
<=55	54	69.9					74.9				
> 55	71	45.0					47.6				
Menstruation			2.580 (1.143–5.826)	0.018	2.780 (0.953–8.110)	0.061		2.470 (1.249–4.888)	0.007	3.172 (1.319–7.633)	0.010
Pre-menstruation	36	70.9					76.9				
Post-menstruation	89	44.5					52.5				
Parity			1.574 (0.486–5.096)	0.445	-	-		1.878 (0.680–5.189)	0.216	-	-
Nulliparity	12	59.3					78.6				
Multiparity	113	51.2					55.9				
Treatment			1.588 (0.705–3.574)	0.260	-	-		1.223 (0.646–2.317)	0.536	-	-
Surgery	25	60.5					70.3				

*log rank test

† Cox Proportional Hazard model

! adjusted Hazard ratio

$ adjuvant treatment: surgery followed by radiation (75 cases), surgery followed by concurrent chemoradiation (18 cases), surgery followed by chemotherapy (1), concurrent chemoradiation followed by surgery (1 case), neoadjuvant followed by surgery (4 cases)

PFS = progression free survival, OS overall survival, HR = hazard ratio, BMI = body mass index, VIN = vulva epithelial neoplasia, LVSI = lymphovascular space invasion

Factors	Total	5-Year PFS (%)	Univariate Analysis		Cox-Regression Analysis†		5-year OS (%)	Univariate Analysis		Cox-Regression Analysis†	
			HR†	P-Value*	HR!	P-Value		HR†	P-Value*	HR!	P-Value
Surgery + adjuvant treatment[$]	100	49.0					56.8				
Stage			3.105 (1.687–5.714)	< 0.001	0.370 (0.049–2.804)	0.336		2.674 (1.595–4.483)	< 0.001	0.963 (0.084–11.075)	0.976
I&II	79	66.3					71.9				
III&IV	46	25.8					37.7				
Table 1 **Comparison of the PFS and OS Divided by Prognostic Factors (continued)**											
Wound complication			1.317 (0.709–2.448)	0.382	-	-		1.002 (0569-1.764)	0.996	-	-
Not Present	87	56.9					57.2				
Present	38	48.5					64.8				
Underlying disease			1.121 (0.618–2.031)	0.707	-	-		1.513 (0.899–2.548)	0.116	-	-
Not present	60	55.0					66.4				
Present	65	48.7					53.5				
Tumor area (mm2)			2.678 (1.413–5.076)	0.002	1.175 (0.510–2.707)	0.704		2.344 (1.362–4.034)	0.002	2.182 (1.155–4.122)	0.016
<=11	58	67.6					75.7				
> 11	67	34.8					44.4				
Groin node enlargement			1.463 (0.798–2.684)	0.216	-	-		2.481 (1.424–4.323)	0.001	2.920 (1.484–5.745)	0.002
Not present	58	61.8					76.0				

*log rank test

† Cox Proportional Hazard model

! adjusted Hazard ratio

$ adjuvant treatment: surgery followed by radiation (75 cases), surgery followed by concurrent chemoradiation (18 cases), surgery followed by chemotherapy (1), concurrent chemoradiation followed by surgery (1 case), neoadjuvant followed by surgery (4 cases)

PFS = progression free survival, OS overall survival, HR = hazard ratio, BMI = body mass index, VIN = vulva epithelial neoplasia, LVSI = lymphovascular space invasion

Factors	Total	5-Year PFS (%)	Univariate Analysis		Cox-Regression Analysis†		5-year OS (%)	Univariate Analysis		Cox-Regression Analysis†	
			HR†	P-Value*	HR!	P-Value		HR†	P-Value*	HR!	P-Value
Present	67	48.2					45.0				
Groin node positive			2.790 (1.494–5.212)	0.001	2.231 (1.071–4.646)	0.032		2.526 (1.481–4.308)	< 0.001	1.734 (0.896–3.355)	0.102
Not present	66	65.0					72.8				
Present	44	27.2					35.1				
No data	15										
Number of nodes removal (right)			0.565 (0.201–1.590)	0.273	-	-		0.605 (0258-1.415)	0.241	-	-
>=5	93	51.9					58.3				
< 5	17	50.3					57.7				
No data	15										
Table 1 **Comparison of the PFS and OS Divided by Prognostic Factors (continued)**											
Number of nodes removal (left)			1.115 (0.574–2.166)	0.951	-	-		0.992 (0.531–1.852)	0.980	-	-
>=5	81	51.4					51.6				
< 5	28	54.1					62.6				
No data	16										
Pathologic longest tumor diameter (mm)			3.565 (1.649–7.704)	0.001	2.811 (1237 – 6.391)	0.014		2.142 (1.152–3.980)	0.014	1.221 (0.552–2.699)	0.622
<=25	47	72.5					77.8				
> 25	58	40.4					48.5				
No data	20										

*log rank test

† Cox Proportional Hazard model

! adjusted Hazard ratio

$ adjuvant treatment: surgery followed by radiation (75 cases), surgery followed by concurrent chemoradiation (18 cases), surgery followed by chemotherapy (1), concurrent chemoradiation followed by surgery (1 case), neoadjuvant followed by surgery (4 cases)

PFS = progression free survival, OS overall survival, HR = hazard ratio, BMI = body mass index, VIN = vulva epithelial neoplasia, LVSI = lymphovascular space invasion

Factors	Total	5-Year PFS (%)	Univariate Analysis		Cox-Regression Analysis†		5-year OS (%)	Univariate Analysis		Cox-Regression Analysis†	
			HR†	P-Value*	HR!	P-Value		HR†	P-Value*	HR!	P-Value
Tumor grade			1.301 (0.680–2.490)	0.425	-	-		0.694 (0.367–1.311)	0.258	-	-
Grade 1	90	60.4					57.4				
Grade 2&3	32	39.9					61.2				
No data	3										
Surgical margin			1.065 (0.553–2.050)	0.851	-	-		1.008 (0.569–1.787)	0.979	-	-
Negative	64	58.7					69.2				
Positive	49	37.6					58.3				
No data	12										
Nearest margin(mm)			1.360 (0.501–3.690)	0.544	-	-		0.832 (0.367–1.887)	0.659	-	-
>=8	17	60.3					72.1				
< 8	47	58.0					65.0				

*log rank test

† Cox Proportional Hazard model

! adjusted Hazard ratio

$ adjuvant treatment: surgery followed by radiation (75 cases), surgery followed by concurrent chemoradiation (18 cases), surgery followed by chemotherapy (1), concurrent chemoradiation followed by surgery (1 case), neoadjuvant followed by surgery (4 cases)

PFS = progression free survival, OS overall survival, HR = hazard ratio, BMI = body mass index, VIN = vulva epithelial neoplasia, LVSI = lymphovascular space invasion

Factors	Total	5-Year PFS (%)	Univariate Analysis		Cox-Regression Analysis†		5-year OS (%)	Univariate Analysis		Cox-Regression Analysis†	
			HR†	P-Value*	HR!	P-Value		HR†	P-Value*	HR!	P-Value
Total	64										
Table 1 **Comparison of the PFS and OS Divided by Prognostic Factors (continued)**											
VIN related			1.830 (0.921–3.635)	0.080	1.497 (0.656–3.416)	0.338		2.270 (1.223–4.214)	0.008	1.991 (0.913–4.344)	0.084
Present	45	51.5					74.8				
Not Present	79	47.7					51.6				
No data	1										

*log rank test

† Cox Proportional Hazard model

! adjusted Hazard ratio

$ adjuvant treatment: surgery followed by radiation (75 cases), surgery followed by concurrent chemoradiation (18 cases), surgery followed by chemotherapy (1), concurrent chemoradiation followed by surgery (1 case), neoadjuvant followed by surgery (4 cases)

PFS = progression free survival, OS overall survival, HR = hazard ratio, BMI = body mass index, VIN = vulva epithelial neoplasia, LVSI = lymphovascular space invasion

Factors	Total	5-Year PFS (%)	Univariate Analysis		Cox-Regression Analysis†		5-year OS (%)	Univariate Analysis		Cox-Regression Analysis†	
			HR†	P-Value*	HR!	P-Value		HR†	P-Value*	HR!	P-Value
LVSI			1.639 (0.873–3.079)	0.120	-	-		1.389 (0.795–2.428)	0.246	-	-
Not present	87	57.3					61.8				
Present	34	33.0					53.7				
No data	4										
*log rank test											
† Cox Proportional Hazard model											
! adjusted Hazard ratio											
$ adjuvant treatment: surgery followed by radiation (75 cases), surgery followed by concurrent chemoradiation (18 cases), surgery followed by chemotherapy (1), concurrent chemoradiation followed by surgery (1 case), neoadjuvant followed by surgery (4 cases)											
PFS = progression free survival, OS overall survival, HR = hazard ratio, BMI = body mass index, VIN = vulva epithelial neoplasia, LVSI = lymphovascular space invasion											

Regarding overall survival, the factors including age older than 55 years, postmenopausal status, advanced stage, preoperative tumor area larger than 11 cm^2, groin node enlargement, groin node-positive, pathological longest tumor diameter longer than 25 mm. and tumor without VIN were significant poor prognostic factors in univariate analysis. However, only postmenopausal status, preoperative tumor area lager than 11$cm^{2,}$ and groin node enlargement were significant poor prognostic factors in multivariate analysis.

The relation of enlargement groin nodes from physical examination and groin node-positive were noted in Table 2. About 58.1% of enlargement groin node revealed metastasis while 16.7% of metastatic groin node did not palpate. In the group of patients with groin node enlargement. The five-year OS was a significant difference in patients whose groin nodes were negative and positive (67.8% vs. 26.1%, P = 0.027). However, in the group of patients without groin node enlargement, the 5-year OS was not significantly different neither in patients whose groin node was negative nor positive (76.2% vs. 75.0%, P = 0.356).

Table 2
Relationship between Palpation and Pathology of Groin Nodes

Groin node	Pathology		Total
	Negative (%)	Positive (%)	
Not palpable	40(83.3)	8(16.7)	48
Palpable	26(41.9)	36(58.1)	62
Total	66	44	110

Regarding 44 patients with metastatic groin nodes, 15 cases (34.1%)revealed extracapsular invasion. The five-year PFS of patients with extracapsular node invasion was significantly poorer than patients without extracapsular node invasion (9.6%

vs 38.2%, P-0.014). Also, the five-year OS of patients with and without extracapsular node invasion was 21.4% and 42.2%, respectively. However, this survival did not reach statistical difference (P = 0.265)

Discussion

The present study found the recurrence rate as 35.2% in patients with SCCA of the vulva who were treated with surgery and those recurrent patients showed a very poor survival outcome with the five-year OS only 23.7%. This recurrence rate corresponded to previous studies. Singareddy et al [10] revealed 76 patients diagnosed as SCCA vulva cancer. Of those patients, 59 cases were treated with radical surgery with or without radiation while the rest were treated with radiation alone. They found a recurrence rate of 24.5% in the surgery group, 12% in surgery plus radiation, and 47% in the radiation group. Another small series from India recruited 18 SCCA of the vulva and treated with radical surgery with a recurrence rate of 27.7% [9].

Regarding the prognostic factors for the survival outcome, the present study found positive groin nodes and tumor with a pathological diameter longer than 25 mm. were independent poor prognostic factors for PFS while postmenopausal status, preoperative tumor area larger than 11 cm^2 and groin node enlargement were the independent poor prognostic factors for OS. These prognostic factors agreed with the previous studies. Li et al. [11] revealed 184 SCCA of the vulva in Chinese patients treated with radical surgery. They reported that tumor diameter longer than two cm., lymph node metastasis, number of positive nodes, extranodal growth, and bilateral positive nodes were significant prognostic factors for PFS, cancer-specific survival, and OS while an age older than 60 years was a significant prognostic factor for OS. However, the authors did not report the data of multivariate analysis for these factors. Woelber et al. [8] performed a subset analysis of AGO (Arbeitsgemeinschaft Gynäkologische Onkologie)-CaRE (Chemo and Radiotherapy in Epithelial Vulvar Cancer)-1 study [12]. The AGO-care study is a large retrospective study from 29 gynecologic cancer centers in Germany aimed to evaluate the benefit of adjuvant therapy in lymph node-positive vulvar cancer. This subset analysis recruited 1,249 patients who received groin node dissection. Of those patients, 360 (28.8%) patients developed disease recurrence within the median follow up time of 27.5 months. The authors found the independent clinicopathological factors for vulvar recurrence were nodal involvement, presence of a residual tumor, older age, and advanced tumor stage. However, this study did not show the prognostic factors for PFS or OS. Woelber et al. [13] reviewed 157 primary SCCA of vulva patients treated with primary surgery and found the positive lymph nodes and increasing age per year were independent prognostic factors for PFS. This data corresponded to our results with the factor of positive nodes. We did not find age to be an independent prognostic factor for PFS. The different outcomes might be from the non-similar recruited patients. Woelber et al. [13] recruited only patients who received radical local resection with a surgical margin of 10 mm. and BGND while our study recruited all patients who underwent all operations.

Notably, our study found the enlargement of groin nodes and large preoperative tumor areas greater than 11 cm^2 were the independent prognostic factors for the poor OS but not for PFS. The inconsistent results might be explained because the OS data were obtained from patients who died from the Thai Civil Registration whereas the PFS data was obtained from medical records that probably missed tumor progression data if the patients did not come back for follow up. Also, our results showed 40% of enlarged groin nodes revealed no metastasis This may raise a possibility for false negative result due to the missing of small metastatic foci in at least some of these cases by the the routine method in processing lymph node specimen. Recently, the pathology laboratory in our institution has adopted the protocol for serial sectioning of enlarged lymph nodes perpendicular axis to the long axis, which should allow a more thorough examination of the subcapsular areas than the traditional bisection method [14].

Regarding the characteristic of groin node involvement, the present study found the poor survival outcome in both PFS and OS in patients with extracapsular node involvement. This result corresponded to previous studies [2, 11]]. However, with the low number of patients who had positive groin nodes in our study, the difference in OS did not reach statistical significance despite the five-year OS. Patients with extracapsular node involvement were very poor as 21.4% compared to those patients with intracapsular node involvement revealed from five- year OS of 42.2%.

Concerning age group, advanced age was also an independent prognostic factor for survival outcomes in previous publications with various cut-off points. Landrum et al. [15] reviewed 63 patients with stage III and IV squamous cell carcinoma of the vulva treated by primary surgery or primary chemoradiation and found advanced age older than 74 years was the only independent poor prognostic factors for PFS and OS. Stroup et al. [16] recruited 523 vulvar cancer patients from the National Cancer Institute's (NCI) Patterns of Care Study using the Surveillance, Epidemiology, and End-Results (SEER) Program. They found 11% of the patients had died and the risk of cancer-related mortality increased 6.8-fold in patients diagnosed at age 50–74, and 13.8-fold at age > 75 years old, relative to patients < 50-years-old. Gaulin et al. [17] recently reported survival outcomes in 18,207 vulvar cancer patients in all stages obtained data from the National Cancer Database (NCDB) of America. The median age at diagnosis was 64 years and about one-third of the patients were older than 75 years and were classified as the elderly group. They found that survival was 3.5 times worse in the elderly than the non-elderly. However, Hami et al. [18] retrospectively analyzed 300 vulvar cancer patients treated with primary surgery from four specialized hospitals in Germany. They found an advanced stage and lymph node metastasis had a higher risk of recurrence and survival outcomes while the age older than 50 years were not related. This contrasted with our study that did not find advanced age as an independent prognostic factor for survival outcomes. The different results might be from various factors such as ethnicity, type of treatment, and the number of studied patients.

Regarding tumor size, a pathological tumor diameter longer than 25 mm was the independent poor prognostic factor for PFS not for OS in our study while preoperative tumor area larger than 11 cm2 was an independent poor prognostic factor for overall survival outcome. However, both have similar prognostic trend, but the effect in multivariate is not strong enough for tumor diameter. Also, the finding in this study is not against the previous study. Aragona et al. study [19] reviewed 194 patients with SCCA of the vulva and reported that the tumor size of more than 8 cm was the independent prognostic poor prognostic factor for OS. This size was larger than our result. The different values might be from the non-similar inclusion criteria. Aragona et al. Study [19] included only patients with a pathological tumor-free margin of at least 8 mm while our study included all patients who underwent surgery.

The OS in the pateints with identifiable VIN was better than those without, but the difference did not significant in multivariate analysis. VIN is related to HPV-associated vulvar cancer, which showed a better survival outcome and more commonly occurred in premenopausal women compared to non-HPV-associtaed vulvar cancer [2, 20]. Unfortunately, p16 immunohistochemistry to confirm the HPV-related vulvar cancer was not performed in this study. However, our study found that post-menopausal status was an independent poor prognostic factor for OS. This is probably from the non-HPV vulvar cancer type that often develops in postmenopausal women [2].

Regarding the pathological tumor-free margin, the present study did not find the pathological tumor-free margin less than 8 mm. was the independent prognostic factor for survival outcomes. Our results correspond to a study by Grootenhis et al [21]. They reviewed 287 SCCA vulvar patients treated in two Dutch centers and reported the ten-year local recurrence rate as 42.5%. They summarized that pathological tumor-free margin distance did not affect the risk of local recurrence either using a cutoff of eight, five, or three mm.

Furthermore, our study did not find an advanced stage to be an independent poor prognostic factor as in previous reports [7]. This might be explained from our study recruiting only advanced-stage patients who underwent surgery. Therefore, both PFS and OS in early and advanced stages were not significantly different in multivariate analysis.

Due to various results of these prognostic factors, Grootenhuis et al. [7] recently published a systematic review regarding the prognostic factors for local recurrence of SCCA of the vulva from 22 studies. They summarized that these prognostic factors as follows: pathologically tumor-free margin distance less than 8 mm., presence of lichen sclerosis, groin node metastases, tumor grade, tumor size, depth of tumor invasion, LVSI, tumor localization and presence of HPV remain equivocal due to the inconsistent outcome of these publications.

The strength of our study was that all data came from one institute with many patients. Thus, the variety of treatment pattern was similar and all pathology was reported by gynecologic pathologists. However, with the nature of a retrospective study and some patients did not continue regular follow up, the recurrence data might be missed. Also, we could not identify cancer-specific survival. Possibly some patients died from other causes.

Conclusion

Groin node-positive and tumor diameter longer than 25 mm. were independent poor prognostic factors for PFS while postmenopausal status, groin node enlargement, and large tumor area than 11 cm^2 were independent prognostic factors for OS. Patients with these factors should be given adequate treatment and careful follow up.

Abbreviations

SCCA: squamous cell carcinoma; PFS: progression-free survival; OS: overall survival; HPV: human papilloma virus; HSIL: high-grade squamous cell intraepithelial lesion; dVIN: differentiated vulvar intraepithelial neoplasia; LVSI: lymph vascular space invasion; BMI: body-mass index; VIN: vulvar intraepithelial neoplasia; ROC: receiver operating characteristic curve; AGO: Arbeitsgemeinschaft Gynäkologische Onkologie; CaRE: Chemo and Radiotherapy in Epithelial Vulvar Cancer; NCDB: National Cancer Database

Declarations

Ethics approval and consent to participate

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study, **formal consent is not required**. This article does not contain any studies with animals performed by any of the authors. The Faculty of Medicine, Chiang Mai University Ethical Committee approved the study (number 475/2018), with **waiver of informed consent** due to the retrospective and observational design of the study.

Consent for publication

Not applicable.

Availability of data and materials

The datasets generated and/or analyzed during the current study are not publicly available due to **patient privacy but are available from the corresponding author on reasonable request.**

Competing interests

The authors declare that they have no competing interests

Funding

This project was supported by the National Research University Project under Thailand's Office of Higher Education Commission and Chiang Mai University. The funding did not involve in any part of this manuscript

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Acknoweledgements

Not applicable

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Figures

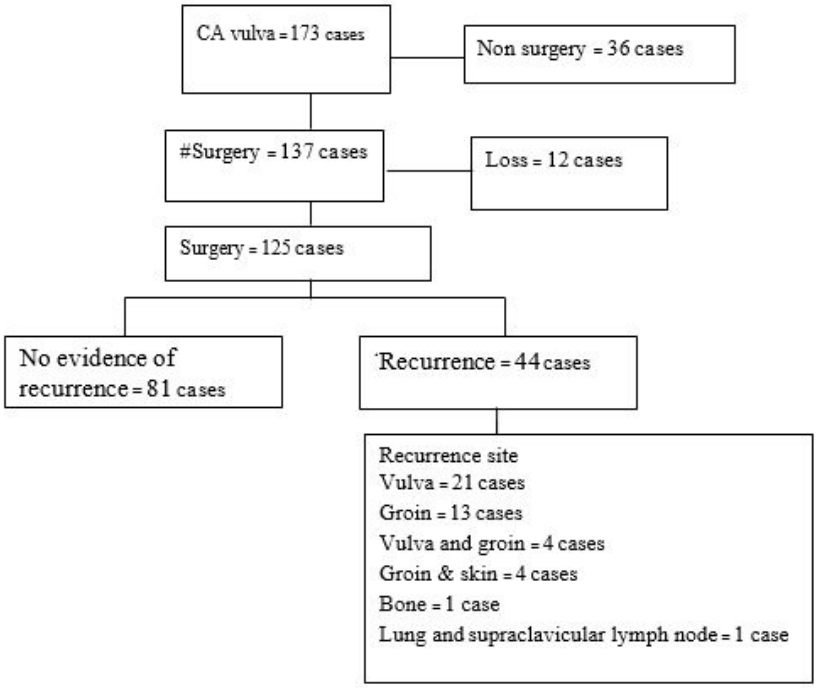


Figure 1

Consort of the Patients Studied # surgery: RLE+BGND (68 cases), RLE+UGND(6 cases), RLE+BGND+BPND(6 cases),WLE(9 cases),WLE+BGND(13 cases), WLE+ UGND(3 cases) ,groin node biopsy+biosy at left upper labia minora(1 case), BGND(13), BGND+BPND(3 cases), anterior vulvectomy+ fasciocutaneous flap with rectus sheath (1 case),left hemivulvectomy + debulking tumor (1 case), TAH+BSO(due to dermoid cyst)+anterior vulvectomy+BGND(1 case) RLE=radical local excision, BGND=bilateral groin node dissection , UGND=unilateral groin node dissection, BPND= bilateral pelvic node dissection, WLE = wide local excision, TAH=trans- abdominal hysterectomy, BSO=bilateral salpingo-oophorectomy

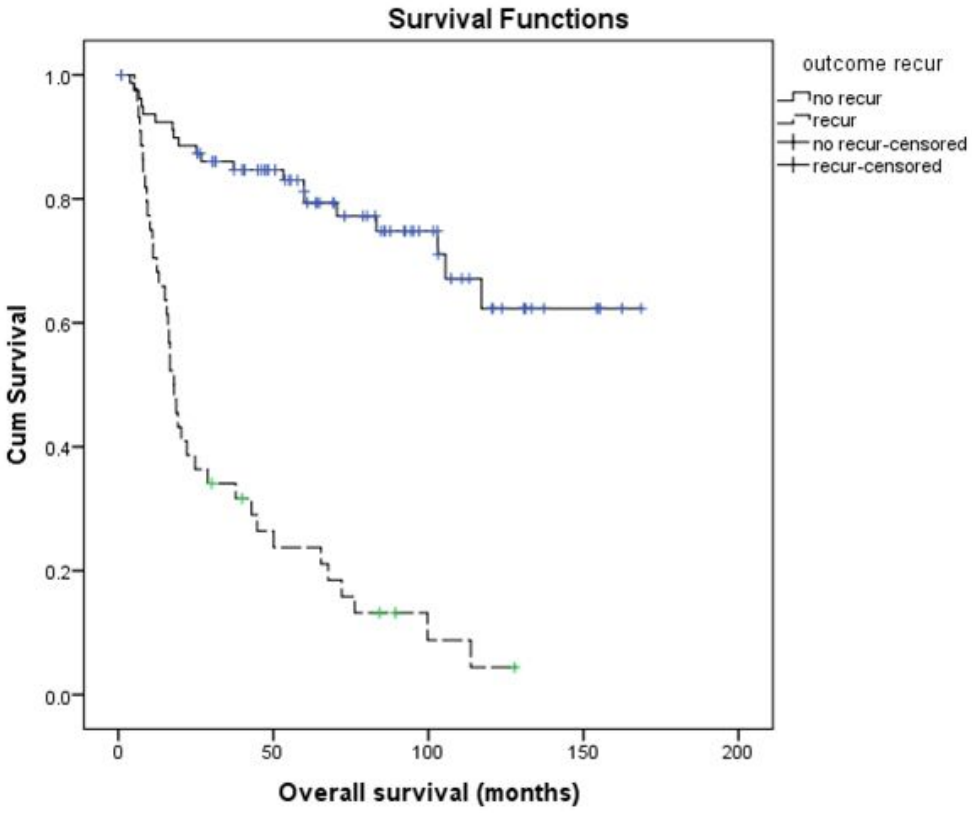
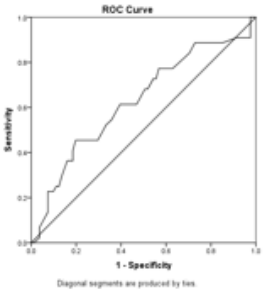


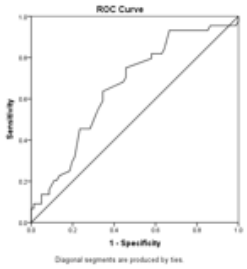
Figure 2

Overall Survival Divided by Recurrence Status 5 year overall survival in no recurrence group = 79.4% 5 year overall survival in recurrence group = 23.7% P value < 0.001 Median FU time = 48.40 months (1-169 months)

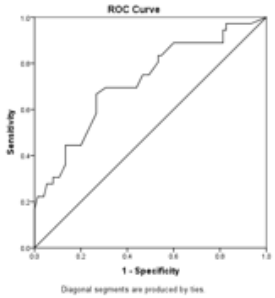
3A : Age (years)



3B: Preoperative tumor area



3C: Longest diameter of tumor specimen



Test	AUC	95%CI	Cut point	Sensitivity	Specificity	P value
Age (years)	0.627	0.522-0.732	55	68.2%	49.4%	0.019
Tumor area (cm2)	0.658	0.559-0.757	11	68.2%	55.6%	0.004
longest diameter of tumor specimen (mm)	0.719	0.615-0.823	25	69.4%	56.0%	<0.001

Figure 3

Receiver-Operating-Characteristic (ROC) and Area Under the Curve (AUC) for Clinicopathologic Parameters to Recurrence