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Lymph node ratio in inguinal lymphadenectomy for squamous cell vulvar cancer: Results from the AGO-CaRE-1 study

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HIGHLIGHTS

- High LNR shows correlation with unfavorable tumor characteristics.
- High LNR is associated with unfavorable overall and progression-free survival.
- LNR allows more accurate prognostic stratification than number of affected lymph nodes.

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ABSTRACT

Objective. Lymph node ratio (LNR) can predict treatment outcome and prognosis in patients with solid tumors. Aim of the present analysis was to confirm the concept of using LNR for assessing outcome in patients with vulvar cancer after surgery with inguinal lymphadenectomy in a large multicenter project.

Methods. The AGO-CaRE-1 study multicenter database was used for analysis. LNR was defined as ratio of number of positive lymph nodes (LN) to the number of resected. Previously established LNR risk groups were used to stratify patients. LNR was investigated with respect to clinical parameters. Univariate and multivariable survival analyses were performed to assess the value of LNR in order to predict overall (OS) and progression-free (PFS) survival.

Results. In total, 1047 patients treated with surgery including inguinal lymph node resection for squamous cell carcinoma of the vulva were identified from the database. Of these, 370 (35.3%) were found to have positive inguinal LN. In total, 677 (64.7%) had a LNR of 0% (N0), 255 (24.4%) a LNR of >0% < 20%, and 115 (11%) a LNR of ≥20%. Patients with higher LNR were found to have larger tumor size ($P < .001$), advanced tumor stage ($P < .001$), high tumor grade ($P < .001$), and deep stromal invasion ($P < .001$), more frequently. Three-year PFS rates were 75.7%, 44.2%, and 23.1% and three-year OS rates were 89.7%, 65.4%, and 41.9%, in patients with LNRs 0%, >0%

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< 20%, and ≥20%, respectively (P < .001, P < .001). On multivariable analyses LNR (HR 7.75, 95%-CI 4.01–14.98, P < .001), FIGO stage (HR 1.41, 95%-CI 1.18–1.69, P < .001), and patient's performance status (HR 1.59, 95%-CI 1.39–1.82, P < .001), were associated with PFS. In addition, LNR (HR 12.74, 95%-CI 5.64–28.78, P < .001), and performance status (HR 1.72, 95%-CI 1.44–2.07, P < .001) were also the only two parameters independently associated with OS. LNR generally showed stronger correlation than number of affected LN when comparing the two different multivariable models.

Conclusions. In women with vulvar cancer LNR appears to be a consistent, independent prognostic parameter for both PFS and OS and allows patient stratification into three distinct risk groups. In survival analyses, LNR outperformed nodal status and number of positive nodes.

1. Introduction

Vulvar cancer is a rare gynecologic malignancy with an incidence rate of 5.8 cases in 100.000 women per year [1]. Investigating rare malignancies like vulvar cancer is exceptional difficult since even large gynecologic oncology centers treat only a handful of patients per year. In the case of vulvar cancer this is particularly challenging since the incidence rate has been rising [2]. To overcome the difficulties associated with a low incidence rate, the AGO Germany conducted the AGO Chemo and Radiotherapy in Epithelial Vulvar Cancer (CaRE-1) trial, a retrospective multicenter trial in order to get more profound data on vulvar cancer in Germany [3].

In patients with vulvar cancer, lymph node (LN) involvement is the most important prognostic factor for survival [4]. In patients without LN involvement 5-year overall survival (OS) rates of about 72% were reported whereas LN positive patients experience 5-year OS rates of 25–42% [4,5]. The wide range of variation in OS of LN positive patients is contributed to the extent of LN involvement. However, the amount of involved resected LN and the detection rate of lymph node metastases can depend on the extent of the surgical LN evaluation. Potentially some LN metastasis might be missed, if in LN positive patients only a small number of LN is surgically evaluated. Typically recommendations for adjuvant treatment are based on parameters from involved lymph nodes. However, the extent of resected LN is usually not taken into account when considering adjuvant treatment.

The lymph node ratio (LNR) is defined as the number of tumor infiltrated LN through the total number of resected LN. Thereby, the LNR combines the extent of LN involvement, with the extent of the surgical LN evaluation. LNR is an established prognostic parameter in a variety of solid tumors including cervical, endometrial, ovarian, and breast cancer [6–9]. In a retrospective analysis of the VULCAN trial dataset [10], LNR was reported as an independent prognostic parameter in patients with LN positive vulvar cancer [11]. LNR predicted survival of patients more accurately than the number of positive LN did and stratified patients into distinctive risk groups.

This study set out to validate LNR as a prognostic parameter in a large, independent cohort of patients, treated with surgery including lymph node assessment at multiple German centers with primary vulvar cancer.

2. Materials and methods

2.1. Patients

The AGO (Arbeitsgruppe Gynaekologische Onkologie) Germany performed a large retrospective multicenter cohort trial (AGO CaRE-1 trial). Twenty-nine study centers included 1618 patients with squamous cell carcinoma of the vulva. All patients included were diagnosed with and treated for vulvar cancer between 1998 and 2008. Data collection was performed in 2011 through a centralized database. Here, patients'

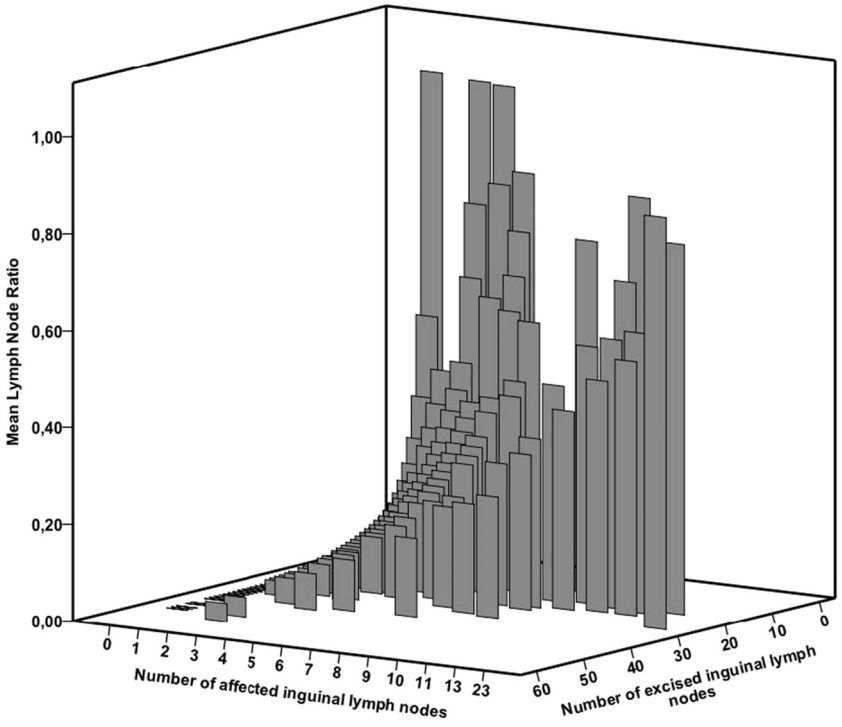

Fig. 1. Correlation between number of resected lymph nodes, number of affected lymph nodes and the lymph node ratio.

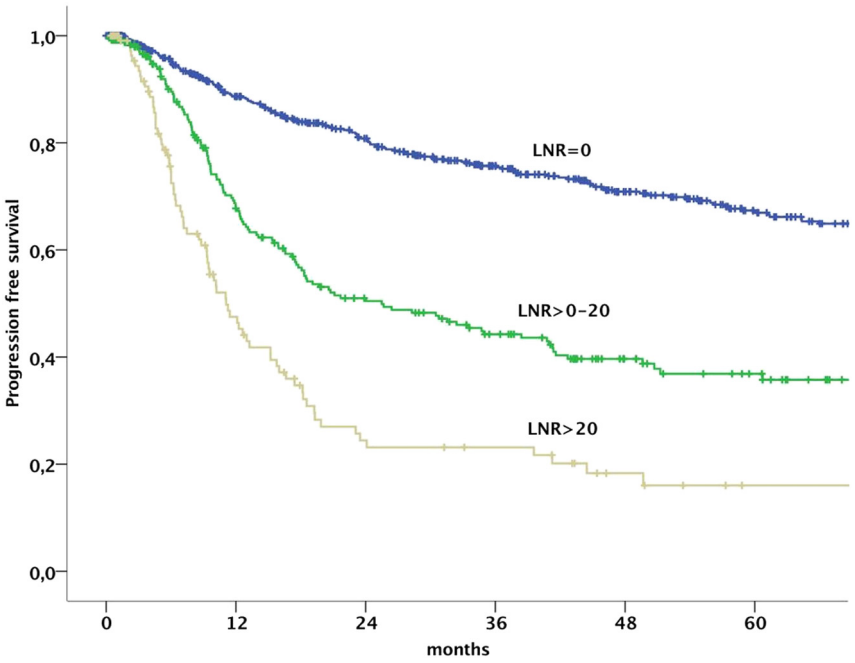

Fig. 2. Progression free survival of patients with squamous cell vulvar cancer categorized according to lymph node ratio.

demographics and medical history, information on the surgical as well as the non-surgical treatment, pathologic information of the surgical specimen, and follow up information were documented.

The AGO CaRE-1 trial evaluated the role of adjuvant treatment in patients with vulvar cancer. The study protocol was approved by each local ethic committee and the study is registered with clinicaltrials.gov (NCT01304667). The main results of this trial have been published elsewhere [3].

In the current analysis, only patients with primary vulvar cancer that were documented to have their inguinal lymph nodes surgically evaluated and had at least one lymph node resected, were included. Patients were excluded from the current analysis if metastatic disease was present at diagnosis or data regarding number of resected and/or metastatic LNs were missing. Analyses were conducted retrospectively, thus all result were of hypothesis generating nature.

2.2. Statistical analysis

Number of positive LNs was defined by the sum of positive LNs within both groins. Patients were stratified into 3 risk groups according to LNR as previously described [11]. The low risk group was defined as patients that had a lymph node ratio of 0% (N0), the intermediate risk group a lymph node ratio of >0% and <20%, and the high risk group a LNR of ≥20%. LNR was correlated with clinicopathologic parameters

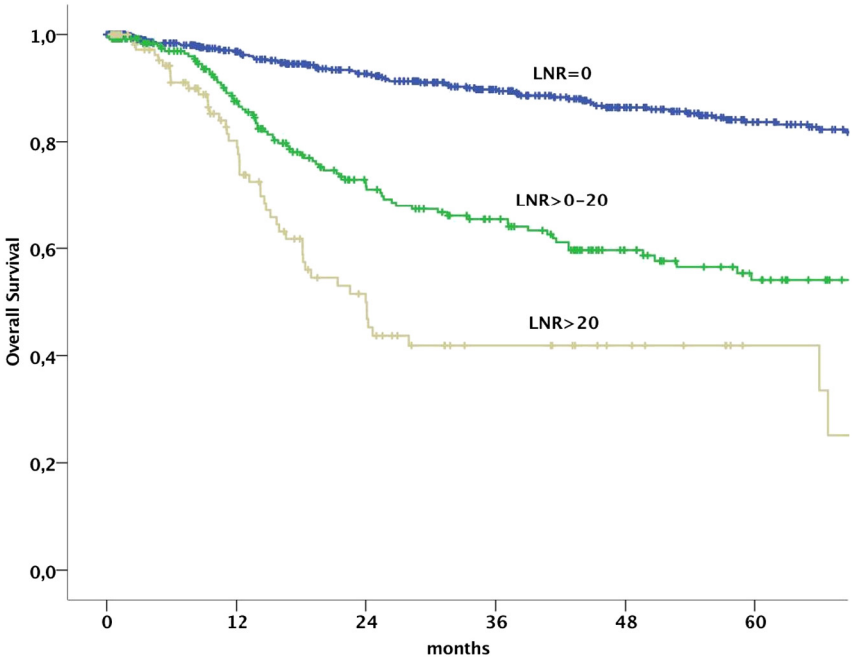

Fig. 3. Overall survival of patients with squamous cell vulvar cancer categorized according to lymph node ratio.

Table 1
Patients' demographics.

Parameter	N(%) or mean (SD)
Total number of patients enrolled	1047
Age at diagnosis (years)	64.5 (15.2)
Tumor stage	
T1	389 (37.2)
T2	567 (54.2)
T3	89 (8.5)
T4	1 (0.1)
Unknown	1 (0,1)
Histologic grade	
G1	113 (10.8)
G2	656 (62.7)
G3	258 (24.6)
Unknown	20 (1.9)
Type of lymphadenectomy	
Sentinel lymph node biopsy	261 (24.9)
Complete lymphadenectomy	768 (75.1)
Lymph node involvement	
N0	677 (64.7)
N1	370 (35.3)
Median number of resected lymph nodes (IQR)	15 (10–19)
Median number of positive lymph nodes (IQR)	2 (1–3)
Recurrence status	
Total number of recurrences	287 (27.4)
Local recurrence	208 (19.9)
Groin recurrence	90 (18.1)
Pelvic recurrence	21 (2.0)
Distant recurrence	58 (5.5)
Recurrence of unknown location	6 (0.6)
Median observational time (months, IQR)	26.4 (8.2–57.6)
Status at last observation	
Alive with no evidence of disease	622 (59.4)
Alive with disease	115 (11.0)
Alive with unknown status of disease	48 (4.6)
Deceased	221 (21.1)
Unknown	41 (3.9)

using chi-squared tests and One-way ANOVA tests. Clinico-pathologic parameters included the number of resected lymph nodes (continuous variable), tumor stage (T4 vs. T3 vs. T2 vs. T1), ECOG stage (4 vs. 3 vs. 2 vs. 1), histologic grading (G3 vs. G2 vs. G1), patients' age (continuous variable, years), tumor size (continuous variable, mm) and depth of tumor infiltration (continuous variable, mm). TNM-classification and stage-grouping version 6-2002 was used.

Univariate survival analysis for the endpoints PFS and OS were calculated using the Kaplan Meier product limit method. PFS was defined as the time from primary diagnosis to disease progression or death from any cause. Survivors without progression were censored on the last day they were known to be alive. OS was defined as the time from primary diagnosis to death from any cause. Survivors were censored on the last day they were known to be alive [3]. Survival differences between groups were calculated using log-rank tests and Cox Regression models. Multivariate survival analysis was performed by establishing cox-proportional hazard models for PFS and OS. Established prognostic parameters were analyzed within uni- and multivariate analyses irrespective of results within the univariate analyses. All values are given as mean (standard deviation) if not otherwise specified. P-values of <0.05 were considered statistically significant. SPSS 24.0 for MAC (IBM Inc., Armonk, NY) was used for statistical analysis.

3. Results

Of the complete cohort ($n = 1618$) analyzed previously, 1249 patients had surgical lymph node evaluation [3]. Of these 149 patients had information on the number of resected and/or metastatic LNs missing and 53 patients had metastatic disease and were therefore not eligible for analysis. Therefore 1047 patients who were documented to have undergone surgery including inguinal LN resection were included into the current analysis. Table 1 shows patients' demographics and follow-up data. While in 786 (75.9%) patients complete lymphadenectomy was performed, 261 (24.9%) had sentinel lymph node biopsy. Unilateral and bilateral inguinal lymphadenectomy was performed in 19.8% and 80.2% of patients. Unilateral and bilateral pelvic lymph node dissection was performed in 1.8% and 2.0% of patients. A total of 370 patients (35.3%) had positive inguinal LN (N1). Of these, 49.2% received postoperative adjuvant radiation therapy and 7.3% chemo-radiotherapy, 7% of patients had information of adjuvant treatment lacking. The median (range) number of resected LN per patient was 15 (1–81), and the median number of positive LN (of patients with at least one positive LN) was 2 (1−23). In total 677 (64.7%) patients had a LNR of 0% (N0), 255 (24.4%) patients a LNR of >0% < 20%, and 115 (11%) patients a LNR

Table 2
LNR in patients with vulvar cancer categorized according to clinico-pathologic parameters.

	LNR = 0	LNR > 0–20	LNR > 20	p-Value		Missing
	$n = 677$	n = 255	$n = 115$			
Parameter	64.7%	24.4%	11.0%			
Tumor stage				<0.001	a	1
T1	325 (48.0)	51 (20.0)	13 (11.3)			
T2	325 (48.0)	160 (62.7)	82 (71.3)			
T3	27 (4.0)	42 (16.5)	20 (17.4)			
T4	0 (0)	1 (0.4)	0 (0)			
ECOG				0.007	a	0
0	267 (57.7)	83 (48.5)	21 (29.6)			
1	105 (22.7)	45 (26.3)	27 (38.0)			
2	69 (14.9)	30 (17.5)	18 (25.4)			
3	21 (4.5)	12 (7.0)	4 (5.6)			
4	1 (0.2)	1 (0.6)	1 (1.4)			
Diabetes				0.026	a	470
Yes	98 (14.5)	42 (16.5)	29 (25.2)			
No	250 (36.9)	114 (44.7)	44 (38.3)			
Histologic grading				<0.001	a	20
G1	96 (14.2)	11 (4.3)	6 (5.2)			
G2	426 (62.9)	168 (65.9)	62 (53.9)			
G3	139 (20.5)	73 (28.6)	46 (40.0)			
Mean (SD) Age (years)	63.6 (14.5)	65.9 (13.4)	68.8 (12.5)	<0.001	b	2
Mean (SD) Tumor size (mm)	26.3 (22.7)	36.2 (23.3)	45.3 (29.6)	<0.001	b	168
Mean (SD) depth of invasion (mm)	6.4 (7.3)	10.1 (12.2)	13.3 (17.4)	<0.001	b	394
Number of resected LNs	14.8 (8.2)	18.5 (8.8)	11.8 (7.2)	<0.001	b	0
Number of affected LNs	0	1.6 (0.8)	4.2 (3.1)	<0.001	B	0

LNR lymph node ratio, ECOG European Cooperative Oncology Group, a) calculated with Chi-squared test, b) calculated with one-way ANOVA test.

Table 3a
Lymph Node Ratio in univariate and multivariable survival analyses of complete cohort.

	Progression-free survival			Overall survival		
	Univariat	Multivariat		Univariat	Multivariat	
	p-Value	p-Value	HR (95%-CI)	p-Value	p-Value	HR (95%-CI)
LNR	<0.001	<0.001	7.75(4.01–14.98)	<0.001	<0.001	12.74(5.64–28.78)
Tumor stage	<0.001	<0.001	1.41(1.18–1.69)	<0.001	0.051	1.23(0.99–1.51)
Hist. grading	0.018	0.22	0.89(0.73–1.07)	0.001	0.838	0.98(0.77–1.23)
ECOG	<0.001	<0.001	1.59(1.39–1.82)	<0.001	<0.001	1.72(1.44–2.07)
LVSI	<0.001	0.58	1.10(0.78–1.56)	0.001	0.549	0.87(0.54–1.39)

95%-CI = 95% confidence interval, LNR = lymph node ratio, ECOG = European Cooperative Oncology Group, LVSI = lymph vascular space invasion, LN = lymph node.

≥20%. Fig. 1 shows the correlation between number of resected LN and number of affected LN. Patients with higher LNR were more frequently found to have larger tumor size (P < .001), advanced tumor stage (P < .001), high tumor grade (P < .001), deep stromal invasion (P < .001) and a poorer ECOG performance status (P = .007). Table 2 shows clinico-pathological parameters categorized according to the LNR groups. Three-year PFS rates were 75.7%, 44.2%, and 23.1% and three-year OS rates were 89.7%, 65.4%, and 41.9%, in patients with LNRs 0%, >0% < 20%, and ≥20%, respectively (P < .001, P < .001). Figs. 2 and 3 show Kaplan-Meier curves for PFS and OS according to LNR groups. Tables 3a and 3b show multivariable cox proportional hazard models for PFS and OS including either LNR or number of affected LN as continuous variables in order to compare the HRs of both variables within the two models. On multivariable analyses LNR (HR 7.75, 95%-CI 4.01–14.98, P < .001), FIGO stage (HR 1.41, 95%-CI 1.18–1.69, P < .001), and patient's performance status (HR 1.59, 95%-CI 1.39–1.82, P < .001), were associated with PFS. In addition, LNR (HR 12.74, 95%-CI 5.64–28.78, P < .001), and performance status (HR 1.72, 95%-CI 1.44–2.07, P < .001) were also the only two parameters independently associated with OS. Table 4a and b shows multivariable survival models for PFS and OS in a subgroup of LN-positive patients including either LNR or number of affected LN as continuous variables in order to compare the HRs of both variables within the two models. On survival analyses HR for positive LN were lower when compared with HR for LNR (Tables 3a vs. 3b and Table 4a vs. b). Additionally we performed multivariable analyses for PFS and OS including both LNR and information on localization of groin lymph node metastases (uni- vs. bilateral). On multivariable analyses LNR (HR 3.01, 95%-CI 1.58–5.73, P = .001) and localization of groin lymph node metastases (HR 1.81, 95%-CI 1.33–2.46, P < .001) were associated with PFS and OS (HR 3.36, 95%-CI 1.48–7.65, P = .004), (HR 2.10, 95%-CI 1.44–3.06, P < .001). In the subgroup of patients with LNR 0–20% uni- and multivariate survival analyses were performed. Results are provided in Table 5 (Supplementary material).

4. Discussion

The present analysis showed that LNR is a strong and independent prognostic parameter in patients with squamous cell vulvar cancer after inguinal lymphadenectomy. Previously established risk groups were used to stratify patients based on LNR = 0%, LNR >0% < 20%, and LNR ≥ 20% into distinctive prognostic groups [11]. LNR outperformed the prognostic accuracy of number of positive LN in multivariable survival analyses for PFS and OS in patients with vulvar cancer.

The presence of lymph node metastases has consistently been shown to be an independent prognostic factor for PFS and OS in patients with vulvar cancer [4]. However, previous studies have reported variable prognostic significance depending on the number of positive lymph nodes, and size of lymph node metastasis [12,13]. Therefore, a wide range of 2-year PFS rates (29–60%), 3-year PFS rates (35%) 5-year PFS rates (39%) and 5-year OS rates (25–41%) in patients with positive nodes have been reported among different studies [3,5,14,15].

The extent of lymph node involvement is an important prognostic factor in most solid tumors [16,17]. The ratio of positive nodes to the total number of nodes removed - i.e. the LNR - has been found to be an independent predictor for survival in endometrial, cervical, and vulvar cancer [6,8,11]. Recently, there has been interest in using LNR as a prognostic tool that allows assessing the comprehensive nature of lymphadenectomy and the burden of nodal disease [6,8,11].

Studies investigating the prognostic value of LNR in patients with vulvar cancer are limited. Kunos and colleagues published the first study describing LNR for assessment of prognosis in an analysis of the Gynecologic Oncology Group (GOG) protocol #37 study [18]. Patients with LNR ≥20% were found to have an increased risk of contralateral lymph node metastases, pelvic node metastasis (non-significant trend), disease recurrence, cancer-related death, and all-cause death. Recently, the prognostic value of LNR was investigated within a cohort of 745 patients with vulvar cancer from a multi-institutional European registry (VULCAN study) [11]. In the current analysis LNR predicted the survival in LN-positive patients more accurately than the absolute number of positive lymph nodes did, similarly to the results of the analysis performed in the VULCAN trial cohort. These findings are plausible from a clinical point of view because important additional information is added when both parameters (positive and resected LN) are combined within the LNR. The number of metastatic nodes alone needs to be interpreted carefully. It has to be kept in mind that the extent and radicality of LN resection is not reflected. It is well known that examining an adequate number of lymph nodes improves staging accuracy and may reduce the risk of tumor recurrence.

When comparing VULCAN study with the present cohort several differences need to be kept in mind. First, only squamous cell cancers were included into the present analysis. TNM stage classification was used, whereas FIGO staging system was used within the VULCAN study.

Table 3b
Number of positive LN in univariate and multivariable survival analyses of complete cohort.

	Progression-free survival			Overall survival		
	Univariat	Multivariat		Univariat	Multivariat	
	p-Value	p-Value	HR (95%-CI)	p-Value	p-Value	HR (95%-CI)
No. of pos. LN	<0.001	<0.001	1.1(1.06–1.15)	<0.001	<0.001	1.14(1.09–1.20)
Tumor stage	<0.001	<0.001	1.43(1.19–1.71)	<0.001	0.038	1.25(1.01–1.53)
Hist. grading	0.018	0.43	0.93(0.78–1.11)	0.001	0.775	1.03(0.84–1.27)
ECOG	<0.001	<0.001	1.59(1.39–1.82)	<0.001	<0.001	1.69(1.41–2.03)
LVSI	<0.001	0.29	1.10(0.85–1.70)	0.001	0.819	0.95(0.58–1.53)

Patients within the present analysis were approximately five years younger and had less frequently lymph node metastases than in the VULCAN study. However, regarding the prognostic value of LNR, both independent cohorts showed a strong association of LNR with both PFS and OS.

In conclusion, LNR predicted the PFS and OS of patients with squamous cell vulvar cancer independently and more precisely than the number of positive nodes. Assessment of LNR should be incorporated into future clinical trials.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ygyno.2019.02.007.

Conflict of interest

All authors disclosed potential conflicts of interest within ICMJE Forms.

Author contribution

All authors materially participated in the research. All authors were involved in article preparation and approved the final article.

SP, RS, CG, PH, LW, SM were involved in study conception and design

CG, PH, JJ, FH, NG, AH, JS, STF, HGS, KB, FT, AM, PH, PW, HK, AR, LW, SM were involved in acquisition of data

SP, RS, CG, PH, LW, SM, were involved in analysis and interpretation of data.

SP, RS, CG, PH, JJ, FH, NG, AH, JS, STF, HGS, KB, FT, AM, PH, PW, HK, AR, LW, SM were involved in drafting of manuscript and critical revision.

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