Gynecologic Oncology 154 (2019) 565–570

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

Predictive factors for lymph node metastases in vulvar cancer. An analysis of the AGO-CaRE-1 multicenter study

Rüdiger Klapdor [a,*], Linn Wölber [b], Lars Hanker [c], Barbara Schmalfeldt [b], Ulrich Canzler [d], Tanja Fehm [e,f], Alexander Luyten [g], Martin Hellriegel [h], Jens Kosse [i], Christoph Heiss [j], Peer Hantschmann [k], Peter Mallmann [l], Berno Tanner [m], Jacobus Pfisterer [n], Julia Jückstock [o], Felix Hilpert [p], Nikolaus de Gregorio [q], Peter Hillemanns [a], Sophie Teresa Fürst [o], Sven Mahner [o]

[a] Department of Gynecology, Hannover Medical School, Hannover, Germany
[b] Department of Gynecology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany
[c] Department of Gynecology, UKSH Campus Lübeck, Lübeck, Germany
[d] Department of Gynecology and Obstetrics, Carl-Gustav-Carus University Dresden, TU Dresden, Dresden, Germany
[e] Department of Gynecology, Duesseldorf University Hospital, Duesseldorf, Germany
[f] Department of Gynecology and Obstetrics, University of Tübingen, Tübingen, Germany
[g] Department of Obstetrics and Gynecology, Klinikum Wolfsburg, Wolfsburg, Germany
[h] Department of Gynecology and Obstetrics, Georg-August-University, Göttingen, Germany
[i] Department of Gynaecology, Sana Klinikum Offenbach, Offenbach, Germany
[j] Department of Gynecology, Alb Fils Kliniken, Klinik am Eichert, Göppingen, Germany
[k] Department of Gynecology, Hospital Altoettingen, Altoettignen, Germany
[l] Department of Gynecology, University Hospital Cologne, Cologne, Germany
[m] Oberhavel Hospital, Oranienburg, Germany
[n] Gynecologic Oncology Center, Kiel, Germany
[o] Department of Obstetrics and Gynecology, University Hospital, Ludwig-Maximilians-University Munich, Munich, Germany
[p] Jerusalem Hospital, Hamburg, Germany
[q] Department of Gynecology, University of Ulm, Ulm, Germany

HIGHLIGHTS

- First large analysis on predictive factors for prevalence and extent of LN metastases in vulvar cancer
- Lymphvascular space invasion, tumor stage, age and depth of infiltration are associated with prevalence of LN metastases.
- Tumor stage or tumor diameter are associated with the number of LN metastases.

ARTICLE INFO

Article history:
Received 14 May 2019
Received in revised form 9 June 2019
Accepted 11 June 2019
Available online 18 June 2019

Keywords:
Vulvar cancer
Lymph node metastases
Sentinel lymph node
Predictive factors

ABSTRACT

Background. Lymph node (LN) metastasis is the most important prognostic factor in primary vulvar cancer. Assessing risk factors for the incidence and extent of LN metastases may help to select the optimal treatment strategy for each individual patient.

Methods. In a subgroup analysis of the large multicenter AGO-CaRE-1 study we included all patients treated with radical groin dissection. Univariate and multivariate regression analyses were performed in order to detect factors associated with the prevalence and extent of nodal involvement.

Results. In total, 1162 patients were analyzed. Univariate analyses detected age, ECOG as well as multiple tumor characteristics such as FIGO stage, grading, depth of invasion, tumor diameter, and (lymph)vascular space invasion to be related with the prevalence of LN metastases. Interestingly, only tumor stage, tumor diameter and depth of infiltration were found to be significantly associated with the number of LN metastases. In multivariate analysis, age (OR 1.03), lymphvascular space invasion (OR 4.97), tumor stage (OR 2.22) and depth of infiltration (OR 1.08) showed an association with the prevalence of LN metastases. Regarding the number of metastatic LNs, only tumor stage (OR 2.21) or, if excluded, tumor diameter (OR 1.02) were tested significant.

Conclusion. This large analysis of the multicenter AGO-CaRE-1-study identified lymphvascular space invasion, tumor stage, and depth of infiltration as factors with the strongest association regarding the prevalence of LN

* Corresponding author at: Department of Gynecology and Obstetrics, Hannover Medical School, Carl-Neuberg-Straße 1, 30625 Hannover, Germany.
E-mail address: Klapdor.ruediger@mh-hannover.de (R. Klapdor).

https://doi.org/10.1016/j.ygyno.2019.06.013

metastasis. Interestingly, tumor stage or, if excluded, tumor diameter were the only factors associated with the prevalence as well as the extent of LN metastases.

1. Introduction

Vulvar cancer is still a rare cancer with about 3300 cases per year in Germany [1]. Especially, HPV associated carcinomas among young woman show an increasing prevalence.

Lymph node metastases represent the most important prognostic marker in vulvar cancer [2,3]. The progression free survival drops from 75% to 35% if lymph nodes are affected [4]. Adequate lymph node staging does not only provide essential information regarding the prognosis of the patients, it also influences the treatment strategy [4]. Sentinel lymph node dissection (SLND) has been introduced into the primary surgical treatment of vulvar cancer with the aim to prevent severe morbidity like edema, wound breakdown or erysipelas by only dissecting the lymph nodes at highest risk [5–9]. Several studies found SLND to be a rational alternative to radical lymph node dissection (LND) [5–9]. However, groin recurrences after SLND or LND are associated with a high mortality and patients at high risk for metastatic disease should probably be treated and followed-up with special caution [5,10]. Only few studies evaluated predictive factors for LN metastases in vulvar cancer as reviewed by Oonk et al. [11]. Homesley et al. published the largest prospective study with 637 patients showing that clinical node status, lymphvascular space invasion, tumor thickness, age and GOG grading appear to be independent predictors of LN metastases in primary vulvar cancer [12]. More data is required to better understand the risk factors for lymph node metastases. Furthermore, we do not have information on predictive factors regarding the extent (size and number) of LN metastases. Therefore, we analyzed the patients of the AGO-CaRE-1-study. With this largest cohort so far we evaluated predictive factors for LN metastases in vulvar cancer in univariate and multivariate analyses.

2. Methods

2.1. Patients

This is an analysis investigating the large patient collective of the AGO-CaRE-1 study. The original study was performed to analyze treatment patterns and prognostic factors in vulvar cancer. Detailed information about the recruitment and data collection were published by Mahner et al. [4]. In short: 29 Arbeitsgemeinschaft Gynäkologische Onkologie (AGO) cancer centers included patients treated at their institution for invasive vulvar cancer between 1998 and 2008. In total, 1618 patients were documented. In 1254 patients information of LN staging was documented. Patients with isolated SLND (88) were excluded in order to prevent patients with false-negative SLN. Additionally, we did not have information about how SLND was performed and if stringent quality criteria were followed. Patient and tumor characteristics as well as treatment and follow-up data were collected in a centralized database by the AGO.

This study was approved by each local ethics committee and registered with clinicaltrials.gov (NCT01304667).

2.2. Statistical analysis

Data analysis was conducted using the statistical software R (http://www.cran.r-project.org). Linear and logistic regression analyses were performed to assess the influence of the clinical and pathological factors on prevalence, size and number of LN metastases. p-Values below 0.05 were considered as statistically significant and included in further multivariate analysis. Factors with p-values < 0.1 were also included. Multivariate linear or logistic regression using the general-to-specific modeling were applied to test for independently influencing variables. Independent variables together were confirmed to have significant influence by χ^2- or F-test.

3. Results

3.1. Univariate analysis

In total, 1162 patients were analyzed; all underwent a groin dissection. Patients with isolated SLN dissection were excluded. We performed a logistic regression analysis to select factors associated with the risk for LN metastasis. Table 1 shows the results and the included patients per analysis. Figs. 1 and 2 present the detailed results regarding the selected factors. In univariate analysis the prevalence of LN metastasis increased from 25.68% in patients younger than 40 years to 45.03% for those older than 80 years. Similarly, the rate of nodal metastases was >2-fold higher in tumors measuring 2-3 cm (37.97%) compared to those smaller than 1 cm in diameter (17.81%) or with a depth of infiltration of 4–5 mm (35.06%) compared to 1-2 mm (14.41%), respectively. Even higher attributed risks were detected regarding the variables grading (OR 2.09, 95%CI 1.69–2.60), tumor stage (OR 3.37, 95%CI 2.73–4.21) and (lymph)vascular space invasion (vascular: OR 6.10, 95%CI 3.07–13.22, lymphvascular: OR 11.26, 95%CI 7.15–18.41).

We were also interested in factors associated with the extent of LN metastasis. Therefore, we performed a univariate logistic regression analysis for the number of metastatic LN. Only the three factors tumor stage, depth of infiltration and tumor diameter showed significant association with the number of affected LNs. For example, in tumors larger than 4 cm the rate of patients with at least two metastatic LN was 69.59% compared to 15.38% in tumors measuring 0.5-1 cm and 34.64% in tumors with 1–2 cm diameter, respectively. Similar results were

Table 1
Univariate logistic regression analysis of factors regarding the prevalence and number of LN metastases.

	OR	95% CI		p-Value	N
LN+ prevalence					
Age (years)	1.02	1.01	1.03	<0.001	1162
BMI (kg/m^2)	1.01	0.98	1.04	0.388	626
History of cardiovascular disease	1.37	0.96	1.95	0.081	648
History of diabetes	1.04	0.74	1.46	0.831	646
Vascular space invasion	6.10	3.07	13.22	<0.001	806
Lymphvascular space invasion	11.26	7.15	18.41	<0.001	822
Tumor stage	3.37	2.73	4.21	<0.001	1161
Tumor diameter (mm)	1.03	1.02	1.03	<0.001	939
Depth of infiltration (mm)	1.05	1.04	1.08	<0.001	669
Grading	2.09	1.69	2.60	<0.001	1132
ECOG	1.40	1.20	1.63	<0.001	769
Number of metastastic LN					
Age (years)	1.00	0.99	1.02	0.775	419
BMI (kg/m^2)	0.98	0.94	1.02	0.348	231
History of cardiovascular disease	1.38	0.82	2.32	0.219	265
History of diabetes	1.25	0.77	2.03	0.368	266
Vascular space invasion	1.73	0.88	3.38	0.111	290
Lymphvascular space invasion	1.38	0.88	2.15	0.159	300
Tumor stage	2.21	1.63	3.00	0.00	419
Tumor diameter (mm)	1.02	1.01	1.03	0.00	351
Depth of infiltration (mm)	1.03	1.01	1.05	0.003	215
Grading	1.18	0.85	1.64	0.331	414
ECOG	1.09	0.87	1.36	0.454	267

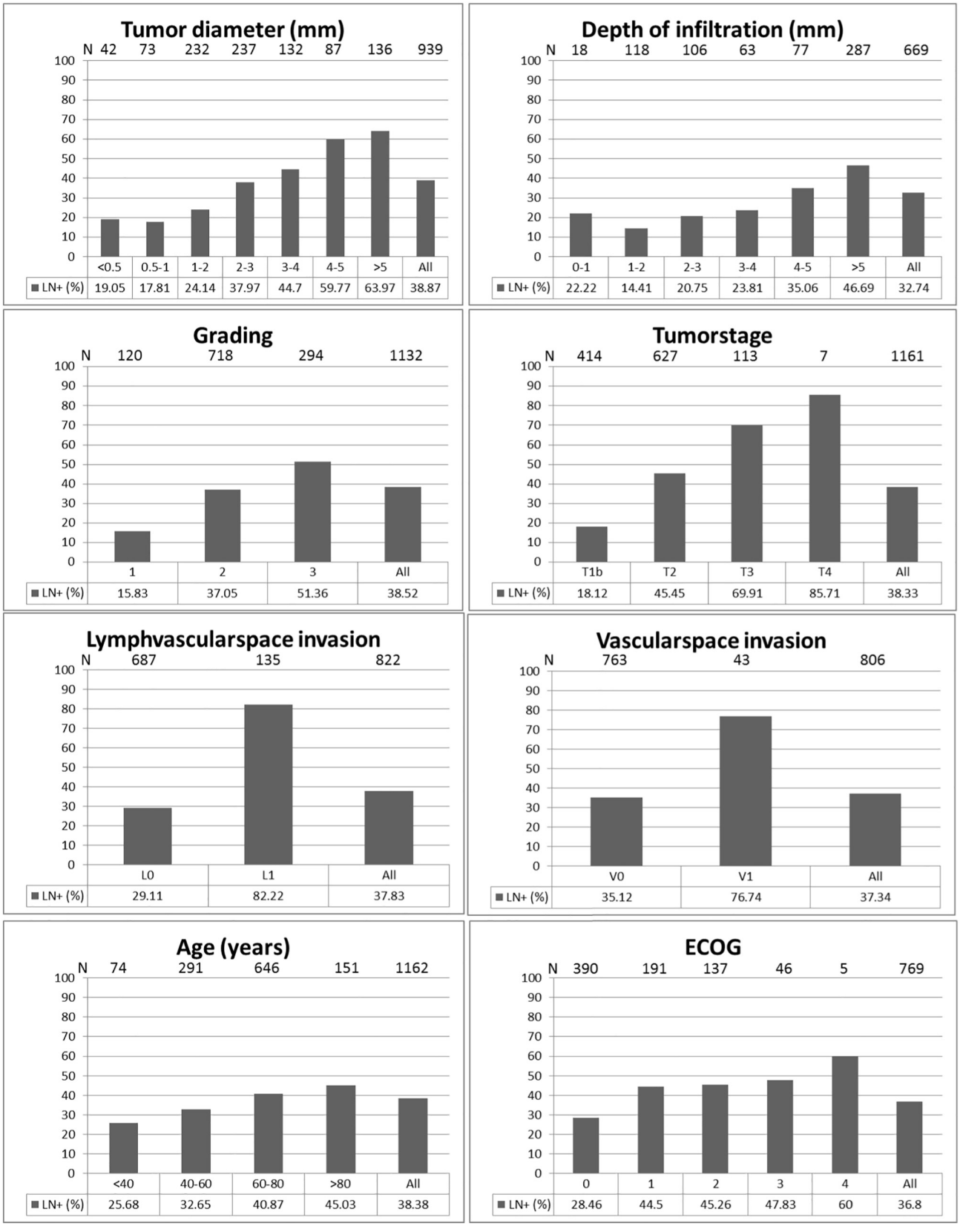

Fig. 1. Proportion of LN positive patients in relation to all patients depending on different tumor and patient characteristics.

also found for the maximal size of the LN metastasis (see supplement). Interestingly, (lymph-)vascular space invasion was not significantly associated with the number of affected LN in our cohort. Results are shown in Fig. 2.

3.2. Multivariate analysis

In order to find independent factors being associated with the risk and the number of LN metastases we conducted a multivariate analysis.

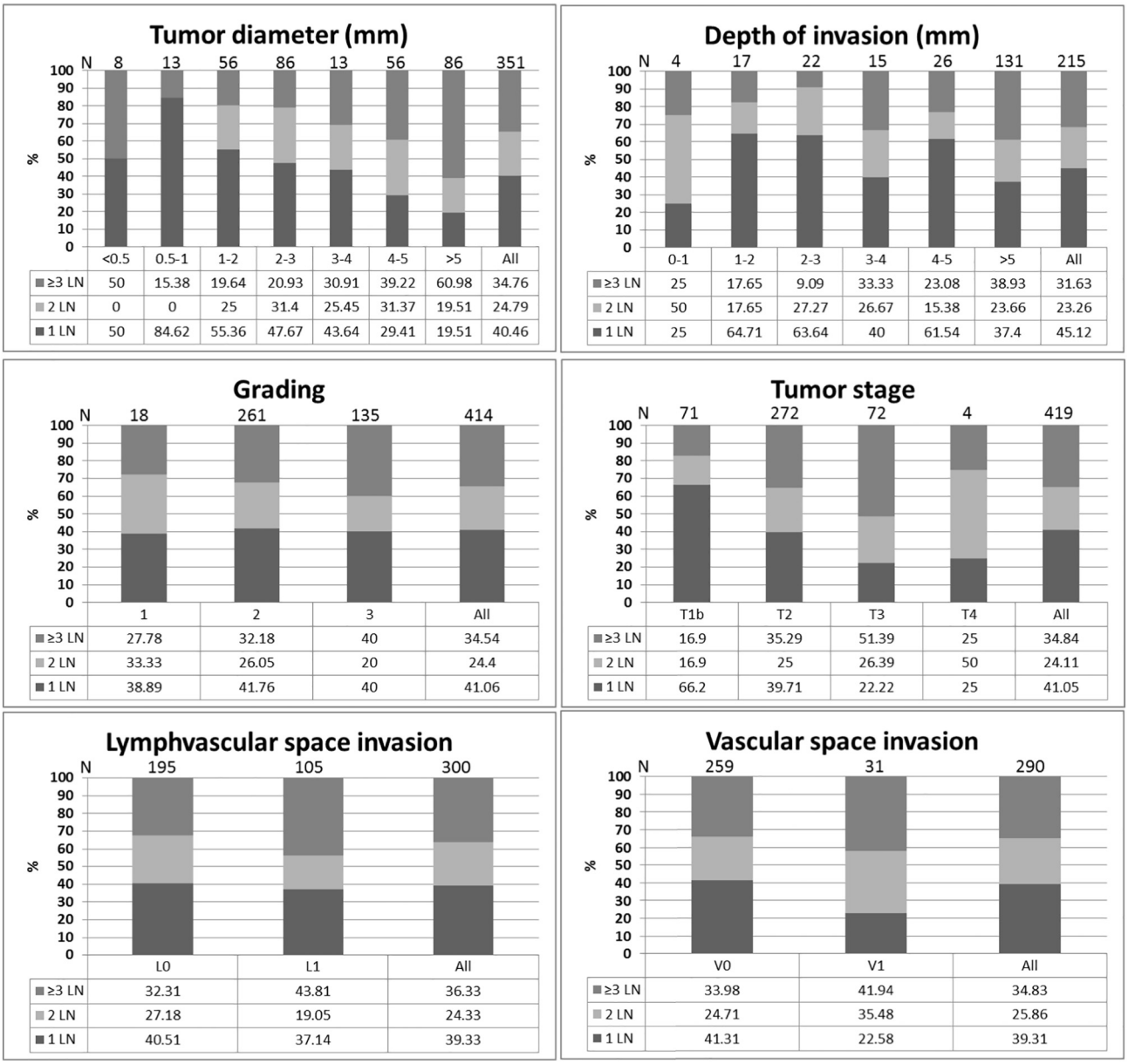

Fig. 2. Proportion of patients with 1, 2, or ≥3 LN metastases in relation to all LN-positive patients depending on different tumor characteristics.

In this multivariate logistic regression all variables were included which showed a *p*-value below 0.1 in univariate analysis. The results are listed in Table 2. As independent factors associated with a higher risk for LN metastases we identified the variables age (OR 1.03, 95%CI 1.01–1.04), depth of invasion (OR 1.08, 95%CI 1.03–1.13), tumor stage (OR 2.22, 95%CI 1.51–3.32) and lymphvascular space invasion which showed the strongest effect (OR 4.97, 95%CI 2.75–9.21). However, the maximal size of the LN metastasis was only associated with tumor stage and depth of infiltration (see supplement). And finally, multivariate analysis revealed that the tumor stage (OR 2.21, 95%CI 1.63–3.00) appeared to be the only factor strongly associated with the number of affected LN.

In addition, we performed a multivariate analysis excluding the composite variable tumor stage in order to better understand the influence of isolated tumor characteristics. Interestingly, instead of tumor stage the variable tumor diameter was now tested as a factor for the risk and number of LN metastases as shown in Table 3. Of note, tumor diameter was the only independent factor influencing the number of affected LN (OR 1.02, 95%CI 1.01–1.03).

4. Discussion

We present the largest study so far analyzing predictive factors for LN metastasis in vulvar cancer. In contrast to previous studies, we not

Table 2
Multivariate logistic regression analysis on prevalence and number of affected LN. The depicted variables are the results of a general-to-specific modeling including all variables which resulted in p-values below 0.1 in univariate analysis.

LN+ prevalence				
N = 494	OR	95% CI		p-Value
Age (years)	1.03	1.01	1.04	0.002
Lymphvascular space invasion	4.97	2.75	9.21	<0.001
Tumor stage	2.22	1.51	3.32	<0.001
Depth of invasion (mm)	1.08	1.03	1.13	0.001
Number of metastatic LN				
N = 419	OR	95% CI		p-Value
Tumor stage	2.21	1.63	3.00	<0.001

Table 3
Multivariate logistic regression analysis on prevalence and number of affected LN excluding tumor stage. The depicted variables are the results of a general-to-specific modeling including all variables which resulted in p-values below 0.1 in univariate analysis.

LN+ prevalence				
$N = 448$	OR	95% CI		p-Value
Lymphvascular space invasion	4.82	2.67	8.94	<0.001
Tumor diameter (mm)	1.02	1.01	1.03	0.004
Depth of infiltration (mm)	1.07	1.02	1.12	0.005
Number of metastatic LN				
$N = 351$	OR	95% CI		p-Value
Tumor diameter (mm)	1.02	1.01	1.03	<0.001

only evaluated the association of these factors with the prevalence but also with the extent of LN metastasis. We were able to show that, besides of age, only specific histologic tumor characteristics such as tumor stage, lymphvascular space invasion and depth of infiltration were associated with the risk for LN metastasis in our cohort of patients with primary vulvar cancer. Regarding the size or number of LN metastasis only tumor stage or tumor diameter and depth of infiltration were identified as independent factors in multivariate analysis, respectively.

LN metastasis represents the most important prognostic factor in vulvar cancer [2,4]. We learned from previous studies like the multicenter AGO-CaRE-1 study that patients with at least one affected LN appear to benefit from adjuvant radiotherapy [4]. Additionally, recent studies described a high mortality in patients experiencing groin recurrences [5,10]. Some of these cases might be explained by false-negative SLN. Previous studies indicated that patients with tumors larger than 4 cm or multifocal tumors are at higher risk for false-negative SLN and groin recurrences [6,8]. Reasons for false-negative SLN can be found in methodological limitations of the marking technique in larger tumors or by an increased risk for LN metastases in high risk tumors. Patients ask for individual counseling and individual risk estimations. There are patients seeking for maximal oncological safety and others refusing necessary therapies because they are afraid of therapy related morbidity. A systematic analysis and schematic presentation of risk factors will provide the necessary information for an individual patient counseling and a decision based on informed consent.

The only large prospective study evaluating predictive factors for the prevalence of LN metastasis was published by Homesley et al. almost three decades ago [12]. However, they did not assess factors influencing the size and number of affected LN. Interestingly, similar to our study they found age, tumor thickness and lymphvascular space invasion as significant independent factors in multivariate analysis. Additionally, they also revealed the GOG tumor grading as an independent factor. We, however, did not see conventional histologic grading as an independent factor in multivariate analysis but as a strong influencing factor in univariate analysis. This may be explained by the more exact differentiation of highly differentiated cancers with the GOG tumor grading. In their study, only 2.8% of patients in GOG grading 1 had LN metastasis whereas already 15.83% of our patients with conventional grading 1 suffered from affected LN. Of note, 51% of our patients with grade 3 tumors had positive LN. In the literature, the prognostic role of tumor grading in vulvar cancer is not clear. However, most studies could not detect an independent influence by tumor grading on prognosis and recurrence of vulvar cancer (reviewed in [13]).

In this study, we did not have information on HPV status and distinct tumor biology. HPV-status, for example, might be an explanation for the increasing rate of LN metastasis with higher age. In older women HPV-negative tumors are more frequent and these are associated with shorter disease free survival [14]. Previous results are conflicting and based on small studies [11].

Interestingly, we identified tumor stage as a predictive factor or if excluded in favor of its distinct composite variables, tumor diameter turned out to be associated with LN metastasis. Our results support earlier studies which indicated that tumor stage represents an independent predictor for survival [15,16]. Although the absolute effect size (OR 1.02) appears to be small, it is calculated on the basis of 1 mm increments and reached high statistical significance. According to our findings, the tumor diameter may be the best indicator for the extent of LN metastasis because it represents a reflection of the tumor biology and a result of speed and duration of tumor growth. Keeping in mind that the number of affected LN has been tested by several authors to be a negative predictor for survival [4,17–19], these results should sharpen the awareness for the groin treatment of larger tumors. In our cohort >60% of the patients with tumors larger than 4 cm suffered from at least 1 metastatic LN. This fact might explain one rationale behind the suggested restriction of SLND to tumors smaller than 4 cm [6,8]. International recommendations suggest restricting SLND to patients with unifocal tumors < 4 cm. Interestingly, tumor biological characteristics have not to be considered when counseling patients. In the univariate analysis of this study, vascular (OR 6.1) and lymphvascular (OR 11.3) space invasion are strongly associated with metastatic groin LN (V1 76.7% and L1 82.2%). Due to the severe impact on the patients' prognosis by false-negative SLN, we should be aware of the high risk for LN involvement in patients with (lymph-)vascular space invasion or grade 3. According to previous results, SLND appears to be also appropriate for these patients [5,6,8]. However, the groin staging of these patients should definitely be performed carefully analogue international guidelines.

There are some limitations to this study which have to be addressed. As subgroup analysis of a retrospective trial originally evaluating adjuvant therapy in advanced vulvar cancer it might be prone to selection and reporting bias. Only patients were included which underwent groin dissection. Thereby, factors influencing the risk for LN metastasis in very early vulvar cancer may be underestimated. However, the risk for LN metastasis in patients with tumor stage Ia is reported to be <2.6% [17]. So, it is not very probable that this group would significantly have changed the results. Interestingly, although original inclusion of the CaRE-1 study was restricted to tumor stages ≥ T1b, few patients with depth of infiltration of <1 mm were also documented in the database which had a surprisingly high rate of LN metastases (22%). Due to the multicenter retrospective design, single cases could not be validated. Most probable reasons for this finding are coding errors or a previous excision and histological examination of the main tumor in a different pathological institute. Due to the retrospective design, missing values could not be prevented. This led to a reduction of the analyzed study population in the multivariate analysis. We did also not have information on the localization (lateral, midline or multifocality) and tumor biology of the tumor. However, this is still by far the largest cohort in which multiple factors were analyzed and we were able to reach statistically significant results in multivariate analysis. Especially, in rare cancers like vulva cancer, such large cohorts are scarce and of particular value. Additionally, the multicenter design represents a potential strength of this study.

In summary, our results represent the first large study analyzing predictive factors on prevalence and extent of LN metastasis in vulvar cancer. We could show that tumor stage or, if excluded, tumor diameter appear to be independent factors associated with the number of affected LN. This may help to better assess the risk for LN metastasis and counsel patients with primary vulvar cancer.

Author contribution

All authors materially participated in the research. All authors were involved in article preparation and approved the final article. RK, PH, LW, SM were involved in study conception and design. RK, LW, LH, BS, UC, TF, AL, MH, JK, CH, PH, PM, BT, JP, JJ, FH, NG, PH, SF and SM were involved in acquisition of data. RK, PH, LW and SM were involved in analysis and interpretation of data. RK, PH, LW and SM wrote the initial draft

of the manuscript. RK, LW, LH, BS, UC, TF, AL, MH, JK, CH, PH, PM, BT, JP, JJ, FH, NG, PH, SF and SM were involved in critical revision.

Conflicts of interest and source of funding

All authors declare that there are no conflicts of interest involved with the presented data. The CaRE-1 study was supported by medac oncology without restriction in protocol or analysis.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ygyno.2019.06.013.

References

[1] Bericht zum Krebsgeschehen in Deutschland 2016. Zentrum für Krebsregisterdaten im Robert Koch-Institut (Hrsg). Berlin2016.
[2] M.P. Burger, H. Hollema, A.G. Emanuels, M. Krans, E. Pras, J. Bouma, The importance of the groin node status for the survival of T1 and T2 vulval carcinoma patients, Gynecol. Oncol. 57 (3) (1995) 327–334.
[3] L. Woelber, S. Mahner, K. Voelker, C.Z. Eulenburg, F. Gieseking, M. Choschzick, et al., Clinicopathological prognostic factors and patterns of recurrence in vulvar cancer, Anticancer Res. 29 (2) (2009) 545–552.
[4] S. Mahner, J. Jueckstock, F. Hilpert, P. Neuser, P. Harter, N. de Gregorio, et al., Adjuvant therapy in lymph node-positive vulvar cancer, the AGO-CaRE-1 study, JNCI 107 (3) (2015) (dju426-dju426).
[5] N.C. te Grootenhuis, A.G.J. van der Zee, H.C. van Doorn, J. van der Velden, I. Vergote, V. Zanagnolo, et al., Sentinel nodes in vulvar cancer, long-term follow-up of the GROningen INternational study on sentinel nodes in vulvar cancer (GROINSS-V) I, Gynecol. Oncol. 140 (1) (2016) 8–14.
[6] Van der Zee, G.J. Ate, M.H. Oonk, Hullu De, A. Joanne, A.C. Ansink, I. Vergote, R.H. Verheijen, et al., Sentinel node dissection is safe in the treatment of early-stage vulvar cancer, J. Clin. Oncol. 26 (6) (2008) 884–889.
[7] R. Klapdor, P. Hillemanns, L. Wölber, J. Jückstock, F. Hilpert, N. de Gregorio, et al., Outcome after sentinel lymph node dissection in vulvar cancer, a subgroup analysis of the AGO-CaRE-1 study, Ann. Surg. Oncol. 24 (5) (2017) 1314–1321.
[8] C.F. Levenback, S. Ali, R.L. Coleman, M.A. Gold, J.M. Fowler, P.L. Judson, et al., Lymphatic mapping and sentinel lymph node biopsy in women with squamous cell carcinoma of the vulva: a gynecologic oncology group study, J. Clin. Oncol. 30 (31) (2012) 3786–3791.
[9] J.A. de Hullu, H. Hollema, D.A. Piers, R.H. Verheijen, P.J. van Diest, M.J. Mourits, et al., Sentinel lymph node procedure is highly accurate in squamous cell carcinoma of the vulva, J. Clin. Oncol. 18 (15) (2000) 2811–2816.
[10] R. Klapdor, H. Hertel, P. Soergel, P. Hillemanns, Groin recurrences in node negative vulvar cancer patients after sole sentinel lymph node dissection, Int. J. Gynecol. Cancer 27 (1) (2017) 166–170.
[11] M.H.M. Oonk, H. Hollema, Hullu J.A. de, A.G.J. van der Zee, Prediction of lymph node metastases in vulvar cancer: a review, Int. J. Gynecol. Cancer 16 (3) (2006) 963–971.
[12] H.D. Homesley, B.N. Bundy, A. Sedlis, E. Yordan, J.S. Berek, A. Jahshan, et al., Prognostic factors for groin node metastasis in squamous cell carcinoma of the vulva (a Gynecologic Oncology Group study), Gynecolig Oncology 49 (3) (1993) 279–283.
[13] A. Gadducci, R. Tana, C. Barsotti, M.E. Guerrieri, A.R. Genazzani, Clinico-pathological and biological prognostic variables in squamous cell carcinoma of the vulva, Crit. Rev. Oncol. Hematol. 83 (1) (2012) 71–83.
[14] J. Zhang, Y. Zhang, Z. Zhang, Prevalence of human papillomavirus and its prognostic value in vulvar cancer, a systematic review and meta-analysis, PLoS One 13 (9) (2018), e0204162.
[15] B. Smyczek-Gargya, B. Volz, M. Geppert, J. Dietl, A multivariate analysis of clinical and morphological prognostic factors in squamous cell carcinoma of the vulva, Gynecol. Obstet. Investig. 43 (4) (1997) 261–267.
[16] T. Maggino, F. Landoni, E. Sartori, P. Zola, A. Gadducci, C. Alessi, et al., Patterns of recurrence in patients with squamous cell carcinoma of the vulva. A multicenter CTF Study, Cancer 89 (1) (2000) 116–122.
[17] H.D. Homesley, B.N. Bundy, A. Sedlis, E. Yordan, J.S. Berek, A. Jahshan, et al., Assessment of current International Federation of Gynecology and Obstetrics staging of vulvar carcinoma relative to prognostic factors for survival (a Gynecologic Oncology Group study), Am. J. Obstet. Gynecol. 164 (4) (1991) 997–1003 (discussion 1003-4).
[18] K.C. Podratz, R.E. Symmonds, W.F. Taylor, T.J. Williams, Carcinoma of the vulva, analysis of treatment and survival, Obstet. Gynecol. 61 (1) (1983) 63–74.
[19] L. Woelber, C. Eulenburg, M. Choschzick, A. Kruell, C. Petersen, F. Gieseking, et al., Prognostic role of lymph node metastases in vulvar cancer and implications for adjuvant treatment, Int. J. Gynecol. Cancer 22 (3) (2012) 503–508.