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# Predicting the course of disease in recurrent vulvar cancer – A subset analysis of the AGO-CaRE-1 study

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## HIGHLIGHTS

- N+ pts have a higher risk for isolated vulvar recurrences than N-pts (2-y recurrence rate 19% vs. 13.5%, p = 0.001).
- Nodal involvement and R1 resection were the most relevant prognostic factors for an increased risk of vulvar recurrence.
- 58 (30.1%) of the pts with local recurrence developed second recurrence. 2-year mortality after any recurrence was 56.3%.
- Pts with isolated local recurrence had a 2-and 5-year OS of 82.2% and 66.9%, respectively

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## ABSTRACT

*Objective.* In vulvar cancer (VSCC), the course of disease with regard to localization of recurrence and relation of different recurrence sites is poorly described.

*Methods.* The AGO CaRE-1 study is a retrospective survey of treatment patterns and prognostic factors in vulvar cancer. Patients (pts) with primary VSCC, FIGO stage ≥1B treated in Germany from 1998 to 2008 were included in a centralized database (n = 1618). In the current subgroup analysis, different sites of primary recurrence and their impact on disease course and survival were analyzed using multistate and competing risks methods.

*Results.* 1249 pts with surgical groin staging and known lymph-node status (35.8% N+) were included in the analysis. 360 pts (28.8%) developed disease recurrence; thereof 193 (53.6%) at the vulva only, with a cumulative incidence of 12.6% after 2 years. Generally, prognosis after disease depended on recurrence site: Hazard ratios

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(HRs) (95% confidence interval) to die for pts with compared to without recurrence at the same time: vulvar only: 5.9 (4.3–8.2); groins only: 6.0 (3.0–10.2); vulvar and groins: 14.1 (7.6–26.4); pelvic/distant: 21.2 (15.3–29.4). Fifty-eight (30.1%) pts with local recurrence developed second recurrence. 2-year mortality after any recurrence was 56.3%. After vulvar recurrence pts had a 2-year and 5-year overall survival rate of 82.2% and 66.9%.

*Conclusions.* Prognosis after recurrence is highly depending on recurrence site. Pts with isolated vulvar recurrence have an impaired prognosis as many affected pts develop second recurrences.



## 1. Introduction

Incidence of vulvar cancer has been rising over the past decades and the disease has increasingly been diagnosed in younger women [1]. Standard therapy for locally restricted disease comprises local wide excision and staging of the groin lymph nodes. Lymph node involvement is the major prognostic factor for survival [2] and still requires radical inguino-femoral lymphadenectomy (if-LAE) with considerable morbidity for the patient (pts). With publication of the *GROningen INternational Study on Sentinel Nodes in Vulvar cancer* (GROINSS-VI) ten years ago [3] it was shown, that it is safe to omit if-LAE in case of a negative sentinel node and under strict consideration of contraindications.

Local surgical treatment has been de-escalated from complete vulvectomy to a tumor free pathological margin of ≥8 mm, which was regarded standard of care for years. However, a pathological margin of 8 mm can easily result in mutilation, especially when the primary tumor is located close to the clitoris as it is in up to 25–37% and data supporting a wider margin are questionable [1]. Therefore, many guidelines now recommend a tumor-free resection margin (R0 resection) instead [4,5].

With regard to recurrent disease, approximately 12–37% of pts will suffer from local recurrence [6–8]. After recent publications the risk is approximately 4%/year without a clear decrease even several years after initial diagnosis [9]. Isolated local recurrence is deemed to be of minor influence on overall survival (OS) and therefore treated with curative intention [10]. However, recently this believe has been challenged by Grootenhuis et al. showing a 21.7% decrease in OS after local recurrence of vulvar cancer. Contrary, groin recurrence has repeatedly been reported, as almost always lethal with a median OS of only 6–10 months [3,11]. Distant recurrences are rare with 5–8% [12–14] and have a severely limited median survival of 4–7 months [12,15,16]. Unfortunately, most retrospective analyses reporting on recurrence are based on small and heterogeneous pts cohorts leading to limited interpretation of results.

Furthermore, little information is available on further prognostic factors for various sites of recurrence, their timely appearance and the influence different sites of recurrence might have on OS.

The aim of this subgroups analysis was therefore, to investigate prognosis and potential prognostic factors of isolated local recurrence in pts with known lymph node status in the large and homogenous CaRE-1 cohort. Also, prognosis and timely appearance with regard to other localization of recurrent disease were analyzed.

## 2. Methods

The current analysis is investigating a subgroup of the AGO (Arbeitsgemeinschaft Gynäkologische Onkologie)-CaRE (Chemo and Radiotherapy in Epithelial Vulvar Cancer)-1 study [2]. The AGO-CaRE study is a large retrospective study, evaluating treatment patterns and prognostic factors in vulvar cancer. Participating institutions could include all pts with the diagnosis of invasive vulvar cancer stage >pT1a independent of the mode and initial place of treatment [Union for International Cancer Control (UICC) version 6]. Pts data collection was performed retrospectively between February and December 2011. Documentation and analysis was done through a specifically designed centralized database by the AGO-study-group. The study was approved by each local Ethics Committee (leading vote: Hamburg (reference number PV3658)) and registered with ClinicalTrials.gov (NCT01304667).

This subgroup analysis focuses on recurrence with a particular aspect on prognostic factors for local recurrence and subsequent course of disease. Distinctions were made between recurrence at the vulva only, at the groins only, vulva and groins, as well as pelvic and distant metastases and unknown recurrence site. As it has been reported that most pts experience groin recurrence early in the course of disease with a median of 12 months (range 5–16 months) [3], two-year recurrence rates were calculated. Cancer-specific survival was not indicated as too many missing concerning cause of death occurred.

### 2.1. Statistical analysis

Analysis was performed using Stata (StataCorp LP, Version 14.2). For the determination of significance, we calculated *p*-values using two-sided tests with a 5% level for significance. Progression-free survival (PFS) was calculated as the time interval between primary diagnosis and disease progression or death of any cause, and OS was the period resulting from primary diagnosis to death of any cause. Prognosis after recurrence was calculated as the period between primary recurrence and second recurrence or death, respectively. Cox regression analysis was conducted to determine prognostic factors in (multivariate) regression analysis.

Different sites of primary recurrence and their impact on further recurrence-free survival and OS were analyzed simultaneously using multistate analysis techniques, to consider the competition between primary recurrence sites and also the secondary recurrences. Cumulative incidence curves were computed to display the recurrence probabilities (primary and secondary) at different sites, considering the aspect of competing risks.

## 3. Results

### 3.1. Primary therapy

Of 1618 adult pts with stage IB-IV vulvar squamous cell carcinoma, being treated between 1998 and 2008 at one of 29 AGO cancer centers in Germany, 1249 pts with surgical groin staging and known lymph-node status (n = 447 N+, n = 802 N-) were included in this subgroup analysis (Fig. 1). Median age was 67 years (range: 20–94 years). Pts characteristics with regard to nodal status are displayed in Table 1. Median FU was 27.5 months. Most pts had locally restricted tumors [1124/1249 (90.0%), pT1b/pT2] and received R0 resection [1022/1249 (81.8%)]. 447/1249 pts (35.8%) were node-positive (N+). 324 pts (25.9%) of the total cohort received adjuvant treatment. Radiation to the vulvar field was performed in 274 pts (21.9%).

### 3.2. Recurrence

A total of 28.8% (360/1249) pts developed disease recurrence (Table 2); 53.6% (193/360) of these at the vulva only as the most frequent site for first recurrence, after a median of 17.1 months. 38 of

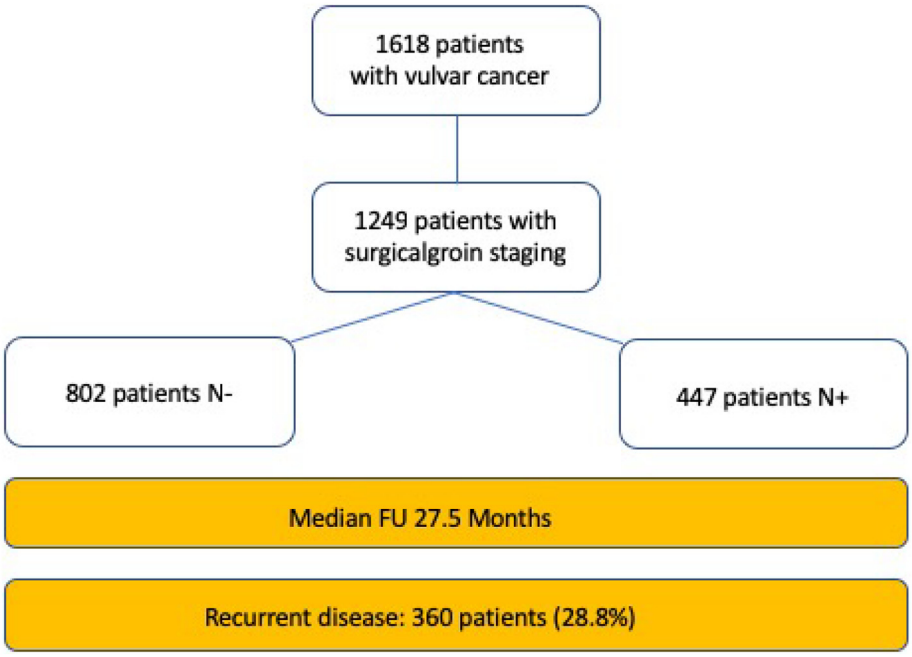


**Fig. 1.** Pts that were included for subgroup analysis of the total CaRE cohort (N+ with nodal involvement, N-without nodal involvement, FU follow up, pts patients).

these pts (19.7%) had initially received adjuvant radiotherapy to the vulva, thereof only 26.3% (10/38) because of R1 resection.

Two years after primary surgery, 12.6% of the pts had experienced a vulvar recurrence. Isolated groin recurrences (2-y recurrence rate: 3.8%) or relapses to vulva and groins (2-y recurrence rate: 2.2%) were significantly less frequent. 7.8% of pts suffered from pelvic or distant recurrences after two years. Death before recurrence occurred in 8.3% after two years, in 0.4% the cause of death was unknown. Pts with nodal involvement (N+) did not only have a significantly higher overall risk for disease recurrence than N- pts (2-y recurrence rate 42.7% vs. 21.1%, $p < 0.001$), but also isolated vulvar recurrences (2-y recurrence rate 19% vs. 13.5%, $p < 0.001$) occurred significantly more often in these pts.

In multivariate analysis, nodal involvement [N+ vs. N-: HR 2.16, 95% CI (1.55–2.99)], residual tumor status [R1 vs R0: HR 1.64, 95%CI (1.03–2.63)], age [age per year: HR 1.01, 95%CI (1.00–1.02)] and tumor stage [pT2 vs pT1b: HR 1.7, 95%CI (1.21–2.39)] were identified as prognostic factors for an increased risk of vulvar recurrence (Table 3). Grading, invasion depth, resection margin and also adjuvant radiation to the vulva had no influence on local recurrence in these pts.

Treatment of vulvar recurrences comprised surgery alone in 104 (53.9%) cases. Surgery in combination with radiotherapy was applied in 40 (20.7%) and radio(chemo)therapy without surgery in 14 (7.3%) pts. 19 pts (9.8%) did not receive any treatment and in 16 (8.3%) cases the treatment was unknown.

### *3.3. Prognosis after recurrence*

After vulvar recurrence, pts had 2-year and 5-year overall survival rates of 82.2% and 66.9%. As expected, pts with nodal involvement and vulva recurrence displayed the poorest OS (2-year OS 65.6%, and 5-year OS after vulva recurrence 54,6%, respectively). Fig. 2 shows the cumulative incidence of recurrence at different sites over time. It was shown that vulvar recurrence can still occur years after primary diagnosis while recurrence at the groins occurs early in the course of the disease (Fig. 2a). Prognosis after recurrence changes with recurrence site (Fig. 2a and b). Local recurrence at the vulva only increases mortality 5.9 fold [HR for OS: 5.9 (CI: 4.3–8.2)] in comparison to patients who are recurrence-free at the same time, isolated groin recurrence 6.0 fold [HR for OS: 6.0 (CI: 3.0–10.2)]. However, as groin recurrences occur earlier in the course of disease after a median of 9.67 months, prognosis is inferior to isolated local recurrence (median time to recurrence 17.14 months).

Simultaneous recurrence at groins and vulva increases mortality 14-fold [HR for OS: 14.1 (CI: 7.6–26.4)]. The highest risk for death was calculated for pelvic/distant sites recurrences, that increase mortality to the 20-fold [HR for OS: 21.2 (CI: 15.3–29.4)]. 2-year mortality after any recurrence was 56.3%. Median overall (disease-free) survival from primary diagnosis was 141.1 (69.3) months.

Pts that had suffered from local recurrence once, consequently had a risk for further recurrences. Median FU after diagnosis of a local recurrence was 11.5 months. 1-year disease-free survival rate after vulvar recurrence was 58.5%. Of 193 pts with isolated local recurrence, 58 (30.1%) developed second recurrences at the following sites: 40 (20.7%) vulva (thereof 30 (15.5%) vulva only), 15 (7.8%) groin, 7 (3.6%) pelvis, 12 (6.2%) distant, 2 (1.0%) unknown (multiple locations possible) with influence on OS (Supplementary Fig. 1).

## 4. Discussion

The findings of this large subgroup analysis of the CaRE-1 trial reveal that the localization of recurrence has a major impact on prognosis. Against common belief that isolated local recurrences should be judged to be of minor relevance for OS, this subgroup analysis shows that vulvar recurrence considerably impairs prognosis. PFS and OS are significantly decreased, with a lower 2-year and 5-year OS rate compared to pts without recurrence because these pts developed second recurrences not only at the vulva, but also to the groins, pelvis and distant sites. In contrast to earlier retrospective and mostly unicentric and heterogeneous analyses [10] with 5-year OS of up to 97%, the long-term FU data of the prospective GROINSS-V-I study showed similar evidence with local recurrences occurring frequently, and also long time after initial treatment [7]. Grootenhuis and colleagues showed, that the risk of local recurrence is still present after a long recurrence free time of 5 and 10 years. The rate of local recurrence at 10 years was 39.5% for all pts in comparison to 27.2% at 5 years. In case of local recurrence, median 10-year disease specific survival (DSS) decreased significantly from

**Table 1**
Patients characteristics with regard to nodal status for isolated vulvar recurrence and no recurrence (*6th edition of UICC TNM staging system, N+ with nodal involvement, N- no nodal involvement, ECOG performance status, R0 free margin, R1 cancer cells present at resection margin, Rx unknown, SLN sentinel node, LN lymph-node).

| | | Isolated vulvar recurrence | | | Recurrence free | | |
|---|---|---|---|---|---|---|---|
| | | Total (n = 193) | N+ (n = 85) | N- (n = 108) | Total (n = 889) | N+ (n = 256) | N- (n = 633) |
| | | n (%) | n (%) | n (%) | n (%) | n (%) | n (%) |
| Age, years (median, range) | | 68.3 (20–91) | 66.6 (20–91) | 66.5 (31–91) | 66.7 (20–94) | 67.5 (26–94) | 62.8 (20–94) |
| Tumor stage* | pT1b | 56 (29.0) | 10 (11.8) | 46 (42.6) | 376 (42.3) | 48 (18.8) | 328 (51.8) |
| | pT2 | 117 (60.6) | 62 (72.9) | 55 (50.9) | 435 (48.9) | 156 (60.9) | 279 (44.1) |
| | pT3 | 16 (8.3) | 10 (11.8) | 6 (5.6) | 74 (8.3) | 48 (18.8) | 26 (4.1) |
| | pT4 | 2 (1.0) | 2 (2.4) | 0 | 4 (0.5) | 4 (1.6) | 0 |
| | Unknown | 2 (1.0) | 1 (1.8) | 1 (0.9) | 0 | 0 | 0 |
| Nodal status | pN0 | 108 (55.9) | n.a. | 108 (100) | 633 (71.2) | n.a. | 633 (100) |
| | pN1 | 85 (44.0) | 85 (100) | n.a. | 256 (28.8) | 256 (100) | n.a. |
| Number nodes affected | | | | | | | |
| 0 | | 108 (55.9) | 0 | 108 (100) | 633 (71.2) | 0 | 633 (100) |
| 1 | | 36 (18.7) | 36 (42.4) | n.a. | 103 (11.6) | 103 (40.2) | n.a. |
| 2 | | 22 (11.4) | 22 (25.9) | n.a. | 58 (6.2) | 58 (22.7) | n.a. |
| 3 | | 10 (5.2) | 10 (11.8) | n.a. | 36 (4.0) | 36 (14.1) | n.a. |
| >3 | | 11 (5.7) | 6 (7.1) | n.a. | 49 (5.5) | 10 (3.9) | n.a. |
| Unknown | | 6 (3.1) | 11 (12.9) | n.a. | 0 | 49 (19.1) | n.a. |
| Tumor diameter mm (median, range) | | 28 (2−200) | 40 (2–200) | 26 (2–200) | 24 (1–345) | 42.6 (2.8–240) | 25.3 (1–345) |
| Depth of invasion mm (median, range) | | 5 (0.25–90) | 12.4 (0.6–70) | 5.7 (1−30) | 4 (0.25–90) | 11 (0.25–90) | 6.2 (0.75–60) |
| Grading | G1 | 28 (14.5) | 6 (7.1) | 22 (20.4) | 104 (11.7) | 10 (3.9) | 94 (14.8) |
| | G2 | 115 (59.6) | 53 (62.4) | 62 (57.4) | 553 (62.2) | 159 (62.1) | 394 (55.1) |
| | G3 | 44 (22.8) | 25 | 19 (17.6) | 211 (23.7) | 82 (32.0) | 129 (20.4) |
| | Unknown | 6 (3.2) | 1 (1.8) | 5 (4.6) | 21 (2.4) | 5 (2.0) | 16 (2.5) |
| ECOG | 0 | 46 (23.8) | 15 (17.6) | 31 (28.7) | 371 (41.7) | 79 (30.9) | 292 (46.1) |
| | 1 | 30 (15.5) | 16 (18.8) | 14 (13.0) | 128 (14.4) | 42 (16.4) | 86 (13.6) |
| | 2 | 34 (17.6) | 14 (16.5) | 20 (18.5) | 89 (10.0) | 33 (12.9) | 56 (8.8) |
| | 3 | 12 (6.2) | 5 (17.6) | 7 (6.5) | 26 (2.9) | 12 (4.7) | 14 (2.2) |
| | 4 | 0 | 0 | 0 | 5 (0.6) | 3 (1.2) | 2 (0.3) |
| | Unknown | 71 (36.8) | 35 (41.2) | 36 (33.3) | 270 (30.4) | 87 (34.0) | 183 (28.9) |
| Surgical therapy vulva | | | | | | | |
| Wide excision | | 20 (10.4) | 9 (10.6) | 11 (10.2) | 93 (10.5) | 13 (5.1) | 80 (12.6) |
| Partial vulvectomy | | 65 (33.7) | 20 (23.5) | 45 (41.7) | 330 (37.1) | 74 (28.9) | 256 (40.4) |
| Complete vulvectomy | | 105 (54.4) | 54 (63.5) | 51 (47.2) | 456 (51.3) | 166 (64.8) | 290 (45.8) |
| Exenteration | | 2 (1.0) | 2 (2.4) | 0 | 9 (1.0) | 3 (1.2) | 6 (0.9) |
| Surgery type unknown | | 1 (0.5) | 0 | 1 (0.9) | 1 (0.1) | 0 | 1 (0.2) |
| Resection margin mm (median, range) | | 4 (1–25) | 6.0 (1–25) | 5.5 (1−10) | 5 (0.2–33) | 5.2 (0.25–25) | 6.2 (0.2–33) |
| Resection status | R0 | 145 (75.1) | 62 (72.9) | 83 (76.9) | 753 (84.7) | 183 (71.5) | 570 (90.0) |
| | R1 | 26 (13.5) | 14 (16.5) | 12 (11.1) | 74 (8.3) | 44 (17.2) | 30 (4.7) |
| | Rx | 22 (11.4) | 9 (10.6) | 13 (12.0) | 62 (6.9) | 29 (11.3) | 33 (5.2) |
| Type of groin surgery | | | | | | | |
| Complete groin dissection | | 183 (94.8) | 85 (100) | 98 (90.7) | 818 (92.0) | 256 (100) | 562 (88.8) |
| After initial SNL dissection | | 38 (19.7) | 17 (20.0) | 21 (19.4) | 211 (23.7) | 64 (25) | 147 (23.2) |
| Primary complete dissection | | 128 (66.3) | 58 (86.2) | 70 (64.8) | 582 (65.5) | 176 (68.8) | 406 (64.1) |
| Unknown if primary or secondary | | 17 (8.8) | 10 (11.8) | 7 (6.5) | 25 (2.8) | 16 (6.25) | 9 (1.4) |
| SNL procedure only | | 10 (5.2) | 0 | 10 (9.3) | 71 (8.0) | 0 | 71 (11.2) |
| Pelvic node dissection | | 14 (7.3) | 12 (14.1) | 2 (2.4) | 38 (4.3) | 26 (10.2) | 14 (2.2) |
| Number of dissected LNs (groin) per patient (median, range) | | 15 (1–81) | 15.5 (2–81) | 14 (1–49) | 15 (0–62) | 16 (1–62) | 14 (0–48) |
| Radiotherapy during primary treatment | | | | | | | |
| No | | 133 | 39 (45.9) | 94 (87.0) | 643 (72.3) | 82 (32.0) | 561 (88.6) |
| Yes | | 56 (29.0) | 43 (50.6) | 13 (12.0) | 218 (24.5) | 150 (58.6) | 68 (10.7) |
| Yes, including vulva | | 38 (19.7) | 27 (31.8) | 11 (10.2) | 170 (19.1) | 105 (41.0) | 65 (10.3) |
| Thereof R1 | | 10 (26.3) | 6 (22.2) | 4 (36.4) | 39 (22.9) | 25 (23.8) | 14 |
| Thereof R0 | | 21 (55.3) | 17 (63.0) | 4 (36.4) | 119 (70.0) | 70 (66.7) | 49 |
| Unknown | | 7 (18.4) | 4 (14.8) | 3 (27.3) | 12 (7.1) | 10 (9.5) | 2 |
| Unknown | | 4 (2.1) | 3 (3.5) | 1 (0.9) | 28 (3.1) | 24 (9.4) | 4 (0.63) |

96.1% to 80.8% ($p < 0.0001$) as pts often experienced further disease recurrences.

Nodal involvement is generally known to be the strongest factor for PFS (3-year PFS: 35.2% vs. 75.2% in N- pts.), and poor OS (3-year OS: 56.2% vs. 90.2% in N- pts.) [2]. Interestingly, N+ pts are also at particular risk for isolated local recurrence vs. N- pts (2-y recurrence rate 19% vs. 13.5%, $p = 0.001$) in our cohort. In fact, in our analysis nodal involvement was the most important factor for local disease recurrence in multivariate analysis [N+ vs. N-: HR 2.47, 95%CI (1.52–4.03)], whereas other factors like grading, invasion depth, resection margin and most importantly adjuvant radiation to the vulva had no influence on local recurrence in the large cohort of the CaRE study. As the tumor classification for vulvar cancer has been adjusted and cannot simply be converted to the new classification the higher risk for local recurrence in pts with pT2 vs. pT1b tumors does not apply any more [pT2+ vs. pT1b-: HR 1.70, 95%CI (1.21–2.39)]. Unfortunately, decisive factors

**Table 2**
Site of disease recurrence during follow-up period (multiple sites reported).

| Localization of disease recurrence | Total (n = 1249 pts) 360 recurrences (%) | N- (n = 802 pts) 169 recurrences (%) | N+ (n = 447 pts) 191 recurrences (%) |
|---|---|---|---|
| Vulva (±other localizations) | 266 (21.3) | 132 (16.5) | 134 (30.0) |
| Thereof vulva only | 193 (15.5) | 108 (13.5) | 85 (19.0) |
| Groins (±other localizations) | 103 (8.3) | 39 (4.9) | 64 (14.3) |
| Thereof groins only | 41 (3.3) | 22 (2.7) | 19 (4.3) |
| Pelvis (±other localizations) | 31 (2.5) | 10 (1.3) | 21 (4.7) |
| Thereof pelvis only | 5 (0.4) | 2 (0.3) | 3 (0.7) |
| Distant (±other localizations) | 68 (5.4) | 16 (2.0) | 52 (11.6) |
| Thereof distant only | 17 (1.4) | 1 (0.1) | 16 (3.6) |
| Unknown | 8 (0.6) | 5 (0.6) | 3 (0.7) |

that might have affected local recurrence as well, like Human Papillomavirus (HPV) infection or pre-existing chronic inflammatory disease (e.g. lichen sclerosus) have not been documented in these pts.

The long-term FU of the large GROINNS-VI dataset has shown before, that node positive pts have a considerably higher local recurrence rate of 33.2% 46.4%, after 5- and 10 years in comparison to node-negative pts where local recurrence rates of 24.6% and 36.4% were reported. While the biology behind this fact is insufficiently understood, lifelong FU is recommended by local and European guidelines for vulvar cancer pts and our data corroborate this approach. Considering the different routes of tumorgenesis with HPV and lichen sclerosus induced vulvar cancer, pts with lichen sclerosus have a higher risk of local recurrence and should be monitored more intensively.

In this respect, Grootenhuiss and colleagues were able to show a difference in DSS for pts that developed local recurrence early vs. late in the course of their disease (5-year DSS ≤2 years 53.1% vs. 5-year DSS >2 years 76.1% p = 0.05). An improved prognosis with occurrence of a late recurrence supports the presumption of pts with lichen sclerosus being at risk for 'de novo' carcinomas, that however, are frequently being mistaken as disease recurrence.

Groin recurrences on the other side are reported to occur early in the course of disease. In our cohort, the isolated groin recurrence rate after 2 years was relatively low with 3.3% for the total population (N+: 4.3%; N-: 2.7%). After radical surgical therapy with if-LAE and adjuvant (chemo)-radiation to groins and pelvis, groin recurrences are regarded to be almost always lethal [3]. Interestingly, one recently published large multicenter retrospective analysis identified 30 pts that presented with groin and/or pelvic recurrences from vulvar cancer within the observational period between 2000 and 2014 [17]. Initially, 15 of these pts were node positive. Median time to groin recurrence was very similar to the GROINSS-VI trial with 10 vs. 12 months, but overall survival was greatly improved with 50% at 7 years. In our cohort the HR for vulvar, as compared to groin recurrence was almost identical with a 6-fold increased risk for recurrence or death (vulvar recurrence [HR for OS: 5.9 (CI: 4.3–8.2)], isolated groin recurrence [HR for OS: 6.0 (CI: 3.0–10.2)]). However, as groin recurrences occur earlier in the course of disease after a median of 9.67 months in comparison to vulvar recurrence that occurred after a median of 17.14 months, prognosis is inferior to isolated local recurrence (Fig. 2a/b). Ultrasound has been suggested as an excellent tool for preoperative detection of lymph node metastases [18] and might be useful in early detection of recurrence as well. Unfortunately, no evidence based recommendation for early detection of

**Table 3**
Multivariate Cox analysis of prognostic factors for vulvar recurrence only as first recurrence (n = 1240, events 193).

| Local recurrence | HR | P-value | 95% CI | |
|---|---|---|---|---|
| Age (per year) | **1.01** | **0.018** | **1.00** | **1.02** |
| pT2 vs. pT1b | **1.70** | **0.002** | **1.21** | **2.39** |
| pT3/pT4 vs. pT1b | 1.05 | 0.888 | 0.56 | 1.94 |
| pT unknown vs. pT1b | 3.09 | 0.082 | 0.87 | 11.05 |
| Depth of invasion in mm | 0.99 | 0.117 | 0.97 | 1.00 |
| Grade 2 vs. Grade 1 | 0.90 | 0.593 | 0.58 | 1.36 |
| Grade 3 vs. Grade 1 | 1.00 | 0.659 | 0.55 | 1.46 |
| Grade unknown vs. Grade 1 | 0.50 | 0.195 | 0.18 | 1.42 |
| Resection margin in mm | 0.97 | 0.089 | 0.94 | 1.00 |
| R1 vs. R0 | **1.64** | **0.037** | **1.03** | **2.63** |
| Rx vs. R1 | 0.64 | 0.142 | 0.35 | 1.16 |
| Adjuvant radiotherapy vulva yes vs. no | 0.75 | 0.149 | 0.51 | 1.11 |
| Adjuvant radiotherapy vulva unknown vs. no | 1.22 | 0.658 | 0.51 | 2.92 |
| Nodal involvement (N+ vs. N-) | **2.16** | **<0.001** | **1.55** | **2.99** |

(n = 1240, number of events = 193; HR hazard ratio; CI confidence interval).

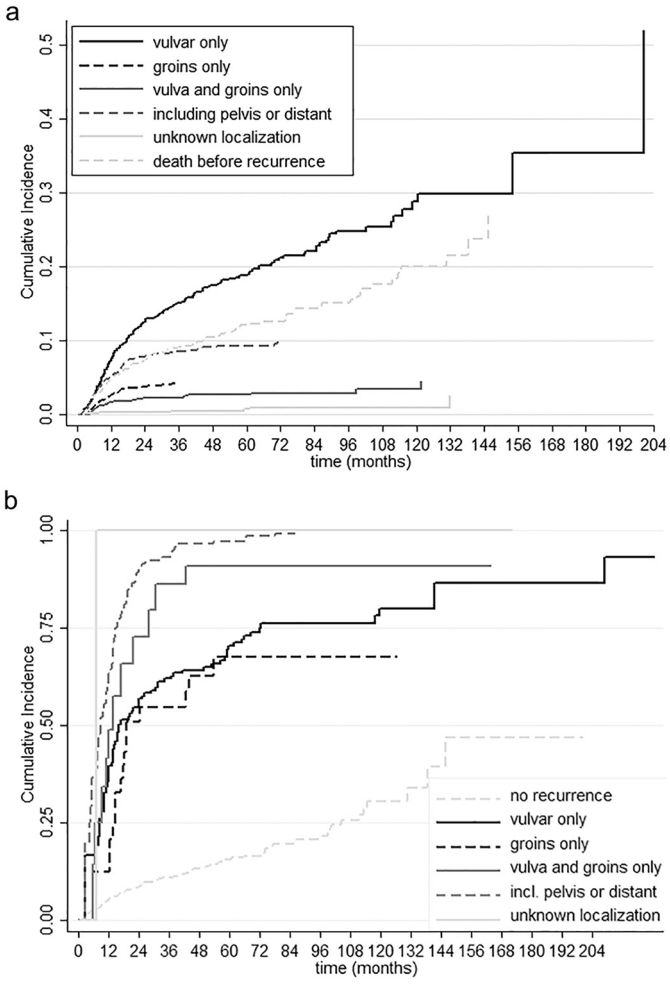


**Fig. 2.** a: Cumulative incidence curves for primary recurrence at different sites and death before recurrence. b: Kaplan-Meier failure curves for death after primary recurrence at different sites.

groin recurrence exists and guidelines merely recommend clinical examination.

The highest risk for death was calculated for pelvic/distant sites recurrences in our cohort. Despite a low cumulative incidence of 7.8% in 24 months, mortality was increased to the 20-fold [HR for OS: 21.2 (CI: 15.3–29.4)]. This supports earlier data from unicentric analysis of our group, with distant metastasis being rare with 5.1% [12] but prognosis highly impaired, reflecting in a median survival of 5.6 months at 33 months median FU.

The relatively short FU of 27.5 months is a major weakness of our study, as well as the limitations of any retrospective setting and the absence of a disease specific survival. Especially more local recurrences might have been detected with a longer FU time. To our knowledge, this is the largest published homogenous pts collective in a multicentric setting, outside a prospective trial with highly selected pts population, looking at different types of events during the course of disease in vulvar cancer. This accounts for a unique strength of our study.

In summary our analysis shows, that more than every second vulvar cancer patient suffering from recurrence, develops first recurrence at the vulvar. Prognosis is significantly declined after recurrence that can occur many years after primary diagnosis. Prognosis after recurrence changes with recurrence site, as vulvar or groins only recurrence increase mortality to the 6-fold, pelvic/distant recurrence increase mortality to the 20-fold.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ygyno.2019.07.009.

## Author contribution

All authors have made substantive intellectual contributions to the study and given final approval for the final manuscript to be published. L.W. initial design and coordination of the AGO-CaRE Study and multiple subprojects, data acquisition, statistically analyzed and interpreted the data, drafted the manuscript. C.E.: statistically analyzed and interpreted the data, helped to draft the manuscript. S.M. initial design and coordination of the AGO-CaRE Study and multiple subprojects, participated in the design and coordination of the study and the interpretation of the results, revised the manuscript critically. K.P. designed the subproject of the AGO-CaRE study, statistically analyzed and interpreted the data and drafted the manuscript. J.K., P.N., C.H., P.H., P.M., B.T. J.P., B.R., J.J., F.H., N.G., S.I., J.S., A.H., P.H., S.P., H-G.S., participated in the study design, was involved in data acquisition and revised the manuscript critically.

## Declaration of Competing Interest

L. Woelber reports grants from Medac Oncology, during the conduct of the CaRE-1 study. All other authors declare that there are no conflicts of interest involved with the presented data.

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