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# Pelvic Lymphadenectomy in Vulvar Cancer – Does it make sense?

## Pelvine Lymphonodektomie beim Vulvakarzinom – Wohl oder Übel?

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## ABSTRACT

Since the publication of the updated German guideline in 2015, the recommendations for performing pelvic lymphadenectomy (LAE) in patients with vulvar cancer (VSCC) have changed considerably. The guideline recommends surgical lymph node staging in all patients with a higher risk of pelvic lymph node involvement. However, the current data do not allow the population at risk to be clearly defined, therefore, the indication for pelvic lymphadenectomy is still not clear. There are currently two published German patient populations who had pelvic LAE which can be used to investigate both the prognostic effect of histologically verified pelvic lymph node metastasis and the relation between inguinal and pelvic lymph node involvement. A total of 1618 patients with primary FIGO stage ≥ IB VSCC were included in the multicenter AGO CaRE-1 study (1998–2008), 70 of whom underwent pelvic LAE. During a retrospective single-center evaluation carried out at the University Medical Center Hamburg-Eppendorf (UKE), a total of 514 patients with primary VSCC treated between 1996–2018 were evaluated, 21 of whom underwent pelvic LAE. In both cohorts, around 80 % of the patients who underwent pelvic LAE were inguinally node-positive, with a median number of three affected groin lymph nodes. There were no cases of pelvic lymph node metastasis without inguinal lymph node metastasis in either of the two cohorts. Between 33–35 % of the inguinal node-positive patients also had pelvic lymph node metastasis; the median number of affected groin lymph nodes in these patients was high (> 4), and the maximum median diameter of the largest inguinal metastasis was > 40 mm in both cohorts. Pelvic lymph node staging and pelvic radiotherapy is therefore probably not necessary for the majority of node-positive patients with VSCC, as the relevant risk of pelvic lymph node involvement was primarily found in node-positive patients with high-grade disease. More, ideally prospective data collections are necessary to validate the relation between inguinal and pelvic lymph node involvement.

## ZUSAMMENFASSUNG

Seit der Veröffentlichung der aktualisierten deutschen Leitlinie 2015 hat sich die Empfehlung zur pelvinen Lymphonodektomie (LNE) bei Patientinnen mit Vulvakarzinom (VSCC) grundlegend verändert – die Durchführung eines operativen Lymphknoten-Stagings wird darin bei allen Patientinnen mit erhöhtem Risiko für eine pelvine Lymphknotenbeteiligung empfohlen. Allerdings ist die Risikopopulation anhand der aktuellen Datenlage unscharf definiert und daher die Indikation zum Eingriff in der Praxis weiterhin unklar. Um sowohl den prognostischen Einfluss einer histologisch gesicherten pelvinen Lymphknotenmetastasierung als auch den Zusammenhang zwischen inguinaler und pelviner Lymphknotenbeteiligung zu beleuchten, stehen aktuell 2 deutsche Kollektive von Patientinnen mit pelviner LNE zur Verfügung: in der multizentrischen AGO-CaRE-1-Studie wurden insgesamt 1618 Patientinnen mit primärem VSCC FIGO-Stadium ≥ IB (1998–2008) dokumentiert, davon erhielten 70 eine pelvine LNE; im Zuge einer retrospektiven monozentrischen Auswertung am UKE wurden von 1996–2018 insgesamt 514 Patientinnen mit primärem VSCC ausgewertet, hiervon 21 mit pelviner LNE. In beiden Kollektiven waren ca. 80 % der Patientinnen mit durchgeführter pelviner LNE inguinal nodal positiv mit einer medianen Anzahl von 3 betroffenen Leistenlymphknoten. Pelvine Lymphknotenmetastasen ohne inguinale Lymphknotenmetastasen wurde in beiden Kollektiven nicht beobachtet. Zwischen 33–35 % der inguinal nodal positiven Patientinnen waren pelvin ebenfalls nodal positiv, bei diesen war die mediane Anzahl betroffener Leistenlymphknoten hoch mit > 4 und einem medianen Maximaldurchmesser der größten inguinalen Metastase von > 40 mm in beiden Kohorten. Für die Mehrheit nodal positiver Patientinnen mit VSCC ist damit vermutlich weder ein pelvines Lymphknoten-Staging noch eine pelvine Radiotherapie notwendig, da ein relevantes Risiko für eine pelvine Lymphknotenbeteiligung vor allem in hochgradig nodal positiven Fällen besteht. Für eine valide Vorhersage des Zusammenhangs zwischen inguinaler und pelviner Lymphknotenbeteiligung bedarf es weiterführender prospektiver Datenerhebungen.

## Introduction

Despite its increased incidence (currently 5.5/100 000 women/year) and the decreased age at onset of disease, vulvar cancer is still a rare tumor entity which mostly affects older women (median age at onset of disease: 72 years) [1, 2]. The treatment of choice in the early stages of disease (cT1, cN0) consists of radical local tumor excision combined with surgical staging of the inguinal lymph nodes in patients (pts.) with FIGO stage IB (> 20 mm diameter und > 1 mm depth of invasion) disease and above. Groin lymph node status remains the most important prognostic factor for progression-free survival (PFS) and overall survival (OS) of affected patients (3-year PFS rate of 35.2% and OS rate of 56.2% for N+ patients vs. 75.2% and 90.2% for N− pts.) [3 – 7]. In this context, the number of affected inguinal lymph nodes (LNs) was found to be significantly correlated with prognosis (27% 2-year OS for patients with ≥ 4+ inguinal LNs, 66% 2-year OS for patients with 2 or 3+ inguinal LNs and 88% 2-year OS for pts. with only one positive inguinal LN, $p < 0.0001$) [4].

Data on pelvic metastasis and the treatment of pelvic LNs in patients with vulvar cancer is limited. It has been estimated that fewer than 10% of all cases with primary vulvar squamous cell carcinoma and fewer than 2% of cases with early-stage vulvar carcinoma (T1, cN0) present with lymphogenic metastatic spread extending beyond the inguinal region into the pelvis [3, 8 – 10]. The overall risk of pelvic lymph node involvement in patients with node-positive vulvar cancer is estimated to be between 20% and 35%. Despite this, adjuvant radiotherapy of the groins AND the pelvis in patients with > 1 lymph node metastasis to the groin has been performed for decades. Pelvic irradiation is associated with significant levels of morbidity, especially as patient populations with vulvar carcinoma tend to be older. The current German guideline therefore now recommends to perform surgical pelvic lymph node staging in the form of systematic pelvic lymphadenectomy in all patients with a higher risk of pelvic lymph node metastasis. Sentinel lymph nodes should be completely embedded and sliced into consecutive tissue sections for detailed examination. In addition, sentinel lymph nodes with a negative H & E morphology should be investigated further using immunohistochemistry (ultra-staging) [11]. But, depending on the chosen approach, these additional investigations may require a second surgery using a transperitoneal approach (laparoscopic or open pelvic LAE). This will also have a relevant impact on morbidity, and the affected population at risk has not yet been sufficiently defined. In principle, the risk of pelvic metastasis appears to increase as the number of affected inguinal lymph nodes increases [12, 13]. According to the current German guideline, the following patients are considered to be particularly at risk [11]:

- patients with an inguinal LN metastasis larger than 5 mm,
- patients with > 1 inguinal LN metastases (including bilateral involvement) and/or metastasis with extracapsular growth.

While these characteristics are associated with an unfavorable prognosis, it is not currently clear whether this is due to pelvic lymph node metastasis. In a pilot study in Berlin carried out in 2005, 12 patients with node-positive vulvar carcinoma (8 of whom were primary cases with 1–7 positive inguinal lymph nodes) underwent pelvic LAE, but ultimately only two patients in the group were found to have pelvic metastasis (17%) [3].

The question of whether to carry out pelvic LAE in patients with VSCC has been a topic of clinical scientific discussion since the 1980s. The American Gynecologic Oncology Group (GOG) attempted to answer the question based on the findings of a randomized study published in 1986 by Homesley et al. [4]. In the study, patients who were found to be node-positive after inguinal LAE were either treated with inguinal and pelvic irradiation at 45–50 Gy or underwent pelvic LAE without adjuvant radiotherapy. Pelvic lymph node metastases were diagnosed in in 15/53 patients (28.3%) in the "pelvic LAE group". The study was terminated ahead of schedule because of the statistically significantly higher survival rate in the "radiotherapy group". Since the study results were published, adjuvant irradiation of the inguinal and pelvic regions has been the standard therapy to treat patients with vulvar carcinoma and more than 1 inguinal lymph node metastasis. However, because of the study design, interpreting the findings was, and is, difficult. The aim of the study was not to determine which patients should receive pelvic treatment (either LAE or radiotherapy). The 2-year OS rate in the "radiotherapy group" was better than that of the "pelvic LAE group" (68 vs. 54%); however, the radiotherapy group also had a higher rate of pelvic recurrence compared to the LAE group (6 vs. 2%). The comparatively poor results of the "pelvic LAE group" were mainly due to a lack of any adjuvant irradiation of the inguinal region, which ultimately resulted in an inguinal recurrence rate of 23.6% and a corresponding deterioration in prognosis compared to just 5.1% in the "radiotherapy group".

The question which patients with inguinal LN metastasis should undergo pelvic staging to exclude pelvic involvement or receive pelvic radiotherapy thus remains unanswered. Ideally, it should be possible to define the connection between inguinal and pelvic LN involvement, which would mean that at least some affected patients would be spared having to undergo either of these treatment approaches.

## Review

Two German patient cohorts with prior pelvic LAE are being reviewed to obtain a better understanding of both the prognostic impact of histologically verified pelvic lymph node metastasis and the connection between inguinal and pelvic lymph node involvement. The multicenter AGO CaRE-1 study [5] was carried out between 1998–2008 in 29 German centers and included a total of 1618 patients with primary VSCC (FIGO stage ≥ IB); 70 of these patients underwent pelvic LAE (DGGG 2020 abstract number: A-1107-0001-00146, unpublished manuscript, under review). During a retrospective single-center evaluation at the University Medical Center Hamburg-Eppendorf (UKE), a total of 514 patients with primary VSCC were treated between 1996–2018, 21 of whom underwent pelvic LAE (IGCS 2020 abstract number 35930; unpublished manuscript, under review). The patient characteristics of all pelvic node-positive patients in both cohorts are summarized in ▶ **Table 1**. Because of the respective survey periods, tumor staging in both cohorts was done using the TNM classification of the Union internationale contre le cancer

▶ **Table 1** Comparison of pelvic node-positive patients in the CaRE-1 and UKE cohorts.

| | Status unknown | pelvic N+, UKE n = 6 | pelvic N+, CaRE-1 n = 14 | Total n = 20 |
|---|---|---|---|---|
| Patient age, median (range) | | 56.5 (37.0–70.0) | 71.5 (31.5–82.8) | 64.0 (34.3–74.4) |
| Tumor stage | | | | |
| ▪ pT1b | | 3 | 3 | 6 (80%) |
| ▪ pT2 | | 1 | 6 | 7 (35%) |
| ▪ pT3/4* | | 1 | 0 | 1 (2%) |
| ▪ unknown | | 1 | 5 | 6 (30%) |
| Node status (inguinal) | | | | |
| ▪ pN− | | 0 | 0 | 0 |
| ▪ pN+ | | 6 | 14 | 20 (100%) |
| No. of affected inguinal LNs, median (range) | 4 | 4.5 (2.0–9.0) | 7 (1.0–30.0) | 5.8 (1.5–19.5) |
| Maximum diameter of inguinal LN metastasis in mm, median (range) | 5 | 45.0 (23.0–54.0) | 42.5 (12.0–50.0) | 43.75 (17.5–52) |
| No. of affected pelvic LNs, median (range) | | 2.5 (1.0–8.0) | 2.5 (1.0–12.0) | 2.5 (1.0–10.0) |
| No. of resected LNs per pt., median (range) | | 19 (12–24) | 15 (6–36) | 17 (9–30) |
| No. of resected pelvic LNs per pt., median (range) | | 16 (6–27) | 10 (1–28) | 13 (3–28) |
| Depth of invasion in mm, median (range) | 9 | 11.5 (7.0–16.0) | 5.3 (5.0–6.0) | 8.4 (6.0–11.0) |
| Grading | | | | |
| ▪ G 1 | | 0 | 0 | 0 |
| ▪ G 2 | | 4 | 4 | 8 (40%) |
| ▪ G 3 | | 2 | 10 | 12 (60%) |
| Vulvar surgery | | | | |
| ▪ partial vulvectomy | | 3 | 3 | 6 (30%) |
| ▪ complete vulvectomy | | 1 | 10 | 11 (55%) |
| ▪ no surgery/unknown | | 2 | 1 | 3 (15%) |
| Resection margin in mm, median (range) | 11 | 2.4 (0.9–4.0) | 3.0 (2.0–4.0) | 2.7 (1.5–4.0) |
| Inguinofemoral LAE | | 6 | 14 | 20 (100%) |
| ▪ unilateral | | 1 (16.7%) | n. a. | n. a. |
| ▪ bilateral | | 5 (83.3%) | n. a. | n. a. |
| Pelvic LAE | | 6 | 14 | 20 (100%) |
| ▪ unilateral | | 2 (33.3%) | n. a. | n. a. |
| ▪ bilateral | | 4 (66.7%) | n. a. | n. a. |
| Radiotherapy | | | | |
| ▪ radiotherapy | 4 | 1 (16.7%) | 10 | 11 (55%) |
| ▪ radiochemotherapy (RCTX) | | 4 (66.7%) | n. a. | n. a. |
| ▪ neoadjuvant RCTX | | 1 (16.7%) | n. a. | n. a. |
| Areas treated with radiotherapy | 5 | | | |
| ▪ groin ± vulva | | 0 | 2 | 2 (10%) |
| ▪ groin and pelvis ± vulva | | 6 | 6 | 12 (60%) |
| ▪ pelvis ± vulva | | 0 | 1 | 1 (2%) |
| Median PFS (months) | 1 | 9.9 | 12.5 | 11.7 |
| Median OS (months) | 1 | 31.1 | 30.8 | 31.0 |

LN: lymph node; LAE: lymphadenectomy; No.: number; OS: overall survival; PFS: progression-free survival; pt.: patient

* TNM classification, version 6

(UICC), version 6 [14]. During the subgroup analysis of the CaRE-1 study [5, 15], 70 patients with known inguinal lymph node status who underwent surgical pelvic staging (pelvic LAE) were identified [15]. The median patient age was 63 years (range: 20–85 years) and the median follow-up (FU) was 31 months. The majority (n = 47; 67.1%) had local tumors (T1b/T2) which could be completely resected (41/57 R0; 71%). Interestingly, 16/70 patients (22.8%) had no inguinal lymph node metastasis (inguinal node-negative), while 54/70 patients (77.1%) were inguinal node-positive with a median of 3 affected inguinal lymph nodes. Data on the number of affected inguinal and pelvic lymph nodes were available for 42 patients. Pelvic lymph node metastases were detected in 14/42 (33.3%) of inguinal node-positive patients (median number of affected pelvic lymph nodes: 2.5 [range: 1–12]). The median number of affected inguinal lymph nodes in the 14 pelvic node-positive patients was 7 (range 1–30). Ten of them had ≥ 6 positive inguinal lymph nodes; one patient only had a single inguinal lymph node metastasis. Unfortunately, the diameter of the inguinal lymph node metastasis was not documented for this specific patient. ROC analysis showed an AUC of 0.85 with a sensitivity of 83.3% and a specificity of 92.6% for the prediction of pelvic lymph node involvement in case of ≥ 6 positive inguinal lymph nodes [15].

In the UKE cohort, 21 patients with pelvic LAE and known inguinal lymph node status were analyzed. The patient cohort was 10 years younger compared to the subgroup from the CaRE-1 study (median age: 53 years, range: 28–71); the majority (n = 15; 78.9%) also had local tumors (pT1b/2). What was particularly noteworthy was that both in the CaRE-1 cohort and in the UKE cohort, a not insignificant number of inguinal node-negative patients underwent pelvic LAE (CaRE: inguinal pN0: 22.8%, 16/70; UKE: inguinal pN0 19%, 4/21). In the UKE cohort, 6/17 patients who were inguinal node-positive (35.3%) were also pelvic node-positive, with a median of 2.5 affected pelvic lymph nodes (range: 1.0–8.0) and a median of 4.5 affected inguinal lymph nodes (range: 2.0–9.0). Correspondingly, 5/6 pelvic node-positive patients (83.4%) underwent adjuvant therapy (▶ **Table 1**). In accordance with the results of earlier studies, no patients with pelvic lymph node metastasis who did not also have inguinal lymph node involvement were found in either the CaRE-1 subgroup or the UKE cohort.

In contrast to the CaRE-1 study, the UKE analysis also recorded the side on which metastasis occurred; analysis showed that the side on which inguinal and pelvic metastasis occurred was consistent, i.e., no contralateral pelvic metastasis was observed in cases with unilateral inguinal metastasis. Bilateral pelvic LAE was performed in 15/21 patients (71.4%), 2/15 of whom (13.3%) were found to have ipsilateral pelvic involvement together with unilateral inguinal LN metastasis, while a further 2/15 patients (13.3%) had bilateral inguinal and pelvic metastasis. ▶ **Table 2** shows the correlation between inguinal and pelvic metastasis for both cohorts.

In the CaRE-1 subgroup analysis, 42.9% (30/70 patients) developed recurrence after a median of 9.2 months (range: 1.5–73.1 months) (▶ **Table 3**). Notably, no cases with additional pelvic recurrences occurred in the pelvic node-positive group during progression of disease; instead, distant (28.6%, 4/14 patients) and vulvar recurrence (21.4%, 3/14 patients) were most common sites of recurrence in this cohort. In the pelvic node-negative group, vulvar recurrence was most common (10/43 patients; 23.3%), followed by pelvic and distant locations (3/43 patients, respectively, in each group; 7%). 8/70 patients (11.4%) died before recurrence occurred (median follow-up: 21.13 months). As expected, the risk of recurrence in patients with pelvic lymph node involvement was higher compared to patients without pelvic lymph node involvement (8/14 patients, 57.1% vs. 17/43 patients, 39.5%) [15]. The single-center evaluation at the UKE found that 23.8% of patients (5/21) developed recurrence: 3/6 of pelvic node-positive patients (50%) and 2/15 of pelvic node-negative patients (13.3%) developed recurrence. In accordance with the data from the CaRE study, the pelvic node-positive UKE cohort also did not develop pelvic recurrence; instead, distant locations (33.3% 2/6 patients) were the most common site of recurrent metastasis, followed by inguinal locations (16.6%, 1/6 patient).

▶ **Table 2** Correlation between inguinal and pelvic LN status in patients with verified pelvic LN metastasis.

| Number of inguinal LN+ | Number of patients who were pelvic LN+ UKE | Number of patients who were pelvic LN+ CaRE-1 |
|---|---|---|
| 1 | 0 | 1 |
| 2 | 1 | 0 |
| 3 | 1 | 1 |
| 4 | 1 | 0 |
| 5 | 1 | 0 |
| 6 | 1 | 4 |
| 8 | 0 | 2 |
| 9 | 1 | 1 |
| 10 | 0 | 0 |
| 11 | 0 | 1 |
| 12 | 0 | 1 |
| 30 | 0 | 1 |

LN = lymph node

The median PFS in the CaRE-1 subgroup analysis for all patients, irrespective of their pelvic lymph node status, was 35.2 months while the median OS has not (yet) been reached. The median PFS for patients with no pelvic lymph node involvement was 41.3 months. However, the prognosis for cases with pelvic lymph node metastasis was significantly poorer, with a median PFS of just 12.5 months and a median OS of 30.8 months. In the UKE cohort, pelvic lymph node metastasis was also associated with an unfavorable prognosis (median PFS: 9.9 months; median OS: 31.1 months).

Since the publication of the above mentioned GOG study [4], performing pelvic LAE in patients with vulvar cancer and the question of who exactly benefits from pelvic LAE has been a topic of ongoing controversial discussion in Germany. The low incidence of pelvic metastasis in patients with fewer than 3 inguinal lymph node metastases, the potentially higher surgical morbidity, and

▶ **Table 3** Incidence and location of recurrence.

| | UKE | | | CaRE-1 | | | |
|---|---|---|---|---|---|---|---|
| **Location** | **Total (n = 21 pts.)** | **Pelvic N− (n = 15 pts.)** | **Pelvic N+ (n = 6 pts.)** | **Total (n = 70 pts.)** | **Pelvic N− (n = 43 pts.)** | **Pelvic N+ (n = 14 pts.)** | **Status unknown (n = 13 pts.)** |
| **Number of recurrences** | **5 (23.8%)** | **2 (13.3%)** | **3 (50%)** | **30 (42.9%)** | **17 (39.5%)** | **8 (57.1%)** | **5 (38.5%)** |
| **No recurrence** | 16 (76.2%) | 13 (86.6%) | 3 (50%) | 32 (45.7%) | 22 (51.2%) | 4 (28.6%) | 6 (46.2%) |
| **Vulva** | 2 (9.5%) | 2 (13.3%) | 0 | 15 (21.4%) | 10 (23.3%) | 3 (21.4%) | 2 (15.4%) |
| **Groin** | 1 (4.8%) | 0 | 1 (16.6%) | 1 (1.4%) | 1 (2.3%) | 0 | 0 |
| **Vulva + groin** | 0 | 0 | 0 | 3 (4.3%) | 0 | 1 (7.1%) | 2 (15.4%) |
| **Pelvis (± other)** | 0 | 0 | 0 | 4 (5.7%) | 3 (7%) | 0 | 1 (7.7%) |
| **Distant metastasis (± other)** | 2 (9.4%) | 0 | 2 (33.3%) | 7 (10%) | 3 (7%) | 4 (28.6%) | 0 |

pts. = patients

the fact that the prognosis is unfavorable if pelvic LN metastasis is detected make it more difficult to decide on a useful indication for carrying out the procedure. Nevertheless, a precisely defined patient population with a high risk of pelvic involvement could benefit from pelvic LAE, particularly if LAE would make it possible to avoid adjuvant pelvic irradiation if the pelvic lymph nodes are found to be negative. This could be important for younger patients who have not yet completed their family planning.

Even though the evidence for a correlation between inguinal and pelvic lymph node metastasis in patients with VSCC is limited and largely based on older data from the 1970/80s, no cases of pelvic lymph node metastasis have been reported to date without simultaneous inguinal metastasis. This was once again confirmed by the recent data. Moreover, the UKE analysis was also able to show that inguinal and pelvic metastasis followed an ipsilateral pathway, i.e. no contralateral pelvic lymph node metastasis was observed in cases with unilateral inguinal lymph node involvement.

The results of the CaRE-1 subgroup analysis and the UKE evaluation which are compared here show that pelvic lymph node metastasis occurs in around 30% of inguinal node-positive patients; this was found repeatedly in both cohorts. These figures are in line with the prevalence of pelvic metastasis of 28.3% (15/53 patients) previously reported by Homesley et al. [4]. However, it is important to be aware of the impact of the negative selection created by the retrospective collection of data. In both cohorts described here, the respective decision to perform pelvic LAE was made on an individual basis and before the updated guideline was published. A relative overestimation of the extent of pelvic involvement with regard to all node-positive patients is therefore quite probable for both cohorts. This means that the impact of a negative selection and thus a possible relative overestimation of the extent of pelvic involvement in all node-positive patients in both cohorts must be considered. It should additionally be noted that the data of both cohorts were collected or generated at a time when preoperative imaging (e.g. ultrasound/CT) in patients with VSCC was not a standard part of the clinical diagnostic process. It is therefore, unfortunately, not possible to make any valid statements about whether and to what extent suspicious inguinal and pelvic LNs would have been visible on preoperative imaging. Even though this certainly is a limitation for both cohorts, nevertheless the data from the two cohorts does highlight the correlation between inguinal and pelvic LN involvement. Interestingly, around 20% of patients in both cohorts were node-negative (CaRE: inguinal pN0: 22.8%, 16/70; UKE: inguinal pN0 19%, 4/21). A second review of these patients in the UKE cohort showed that 3 of the 4 inguinal node-negative patients had an initial clinical diagnosis (on sonography and palpation) of highly suspicious lymph nodes (median diameter: 4 cm), which postoperatively turned out to be only reactively enlarged. It should be noted in this context that the reliability of palpation is limited with regard to detecting metastases: in around one third of cases, the findings on palpation did not correspond with the subsequently histologically verified lymph node findings [16]. Similarly, Gonzalez Bosquet et al., reported that 16–24% of inguinal lymph nodes considered to be unremarkable on palpation turned out to be metastatic and that 24–41% of lymph nodes which were suspicious on palpation turned out to be tumor-free on histological examination [17]. This again raises the question regarding the best preoperative diagnostic procedure and challenges the approach of simultaneously performing LAE in both lymphatic drainage areas without previously verifying the extent of inguinal metastasis. The question in this context is whether preoperative punch biopsy should be carried out to investigate suspicious lymph nodes in the same way as it is carried out in patients with breast cancer. Irrespective of this, the preoperative examination of inguinal lymph nodes by inspection, palpation and sonography is very important in terms of predicting lymph node involvement. But while preoperative imaging has become the established approach when planning systematic (and non-surgical) treatment of advanced-stage disease, the role of imaging in the early stages of disease is still disputed. The diagnostic accuracy of sonography for the detection of lymph node involvement is reported to be 67–89% [18, 19], the sensitivity of MRI is 89% [20] and the sensitivity of PET is around 80% [21]. Of

all of the available imaging methods, CT has the lowest predictive accuracy, with a sensitivity of 58 % and a specificity of 75 % for metastatic LNs with a minimum diameter of 1 cm [22]. The current data on preoperative imaging indicates that for metastatic LNs with a diameter of 5 mm, the sensitivity of MRI was higher (87 %) than that of sonography (76 %), However this was accompanied by a relatively low specificity (MRI 81 % vs. sonography 91 %) [19, 23]. In cases with larger affected lymph nodes (i.e., metastatic LNs with diameters of at least 1 cm), the sensitivity and specificity of MRI and sonography are roughly comparable (MRI: sensitivity 89 %, specificity 91 % [20] vs. sonography: sensitivity 83 %, specificity 90 %) [18]. It is important to be aware that although using imaging to obtain a valid prediction of inguinal and pelvic lymph node involvement would be very desirable as this might mean it would be possible to avoid unnecessary surgery when treating (pelvic) node-negative patients, imaging can currently neither replace surgical staging nor (in most cases) reliably predict pelvic lymph node involvement [19].

In 1993, Hacker et al. proposed that pelvic LAE should only be carried out in patients with ≥ 3 positive inguinal lymph nodes [9]. In their study, neither initial pelvic involvement nor the development of pelvic recurrence was observed in patients with ≤ 2 positive inguinal lymph nodes, whereas pelvic metastasis was detected in 2/3 patients (66.6 %) with 3 positive inguinal lymph nodes and in 5/6 patients (83.3 %) with ≥ 4 positive inguinal lymph nodes. Although there are reports that in some patient populations the risk of pelvic involvement already begins to increase when patients have ≥ 3 positive inguinal LNs [12, 24], the CaRE-1 subgroup analysis was only able to make a valid prognosis about pelvic involvement for patients with ≥ 6 positive inguinal LNs [15]. In the UKE cohort, the positive predictive value for pelvic involvement in patients with ≥ 3 ipsilateral inguinal lymph nodes was 62.5 % and the negative predictive value was 88.5 %.

As regards the location of recurrence, recurrences in the pelvic node-positive groups in both cohorts tended to be distant (28.6 %); there were no cases of pelvic recurrence. In the pelvic node-negative subgroup, the most common site of recurrence was the vulva (23.2 %) but 7 % of recurrences were also found in the pelvic area. One might therefore speculate that not carrying out pelvic radiotherapy because pelvic staging was negative could increase the risk of pelvic recurrence in this group. Interestingly, Curry et al. also reported a pelvic rate of recurrence of at least 8 % in patients who had fewer than 4 positive inguinal LNs and whose pelvic LNs were initially node-negative [13]. However, Homesley et al. reported a somewhat lower rate of pelvic recurrence of 4.4 % (5/114 patients) in their total patient population and 1.8 % (1/55 patients) in the cohort which had been treated with pelvic LAE [16]. It should be noted that the number of detected cases with recurrence depends on the respective follow-up period and can therefore not necessarily be compared between different studies.

In summary, it can be stated that only a small number of patients in Germany underwent pelvic LAE even before the changes to the guideline (CaRE: 70/1618, 4.3 %; UKE: 21/514, 4.0 %). Detection of pelvic metastasis was associated with a poor prognosis, with a PFS von 12.5 months (CaRE) and 9.9 months (UKE), respectively.

Ultimately, the decisive and clinically relevant questions about which patient cohorts benefit from LAE and about the number and size of inguinal metastases above which patients have a significantly higher risk of pelvic metastasis cannot be conclusively answered based on the current data which was exclusively collected retrospectively. Because the existing data is only retrospective, systematic data collection is required and has already been initiated by the AGO working group, the AGO Vulva Vagina Commission and the NOGGO. The aim is to review the implementation of guideline recommendations on pelvic LAE and pelvic treatment in general in clinical practice and investigate the potential reasons which prevent their implementation as well as recording the correlation between inguinal and pelvic LN involvement.

## Conclusion

Given the unfavorable prognosis, the low incidence of pelvic lymph node metastasis, and the higher surgical morbidity, pelvic lymph node staging is not useful for the majority of patients with node-positive VSCC. Nevertheless, a well-defined cohort with an increased risk of pelvic metastasis could benefit from pelvic LAE. Studies such as those planned by the AGO working group, the AGO Vulva Vagina Commission and the NOGGO are urgently needed to investigate both the indication criteria for pelvic LAE and the impact of pelvic LAE on the clinical course and prognosis of affected patients.

### Conflict of Interest

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