

The Possibility of Contralateral Non-Sentinel Groin Node's Metastasis in Early Primary Vulvar Cancer Women After Unilateral Sentinel Node's Metastasis: A Single Center Evaluation in University Hospital of Düsseldorf

Andreas Suhartoyo Winarno (✉ dr.andreas.winarno@gmail.com)

Universitätsklinikum Dusseldorf <https://orcid.org/0000-0002-4104-4427>

Anne Mondal

Universitätsklinikum Dusseldorf

Franca Christina Martignoni

Universitätsklinikum Dusseldorf

Tanja Natascha Fehm

Universitätsklinikum Dusseldorf

Monika Hampf

Universitätsklinikum Dusseldorf

Research article

Keywords: Vulvar cancer, sentinel lymph node biopsy, non-sentinel lymph node, inguinofemoral lymphadenectomy, ipsilateral / contralateral lymph node metastasis

Posted Date: September 10th, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-50733/v1>

License:   This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Version of Record: A version of this preprint was published on January 12th, 2021. See the published version at <https://doi.org/10.1186/s12905-020-01165-5>.

Abstract

Background: Sentinel node biopsy (SLNB) technique in unifocal vulvar cancer (diameter of < 4cm) and unsuspected groin lymph nodes, the morbidity rate of patients has significantly decreased all over the world. In contrast to SLNB, bilateral inguinofemoral lymphadenectomy (IFL) has been associated with increased risk of common morbidities. Current guidelines (NCCN, ESGO, RCOG, and German) suggest that in cases of metastasis of unilateral SLNB, groin node dissection with IFL, should be performed bilaterally. However, a publication by Woelber et al. 0% (p=0/28) and Nica et al. 5.3% (p=1/19) contradicted the current guideline.

Methods: A single-center analysis conducted in the University Hospital of Dusseldorf, evaluating vulvar cancer patients treated with SLNB retrospectively from 2002 to 2018.

Result, discussion and conclusion: Current guideline for bilateral IFL should remain as the standard management because 22.2% women (n=4/18) had contralateral IFL groin metastasis after unilateral SLNB metastasis initially. The depth of tumor infiltrating cells was correlated significantly and positively with the incidence rate of groin metastasis (p=0.0038). Therefore, it is an indication for bilateral IFL.

Synopsis

Current guideline for bilateral inguinofemoral lymphadenectomy (IFL) should remain as the standard management of primary early vulvar cancer because 22.2% women in this study had contralateral IFL groin metastasis after unilateral sentinel lymph node biopsy (SLNB) metastasis initially. The depth of tumor infiltrating cells was correlated significantly and positively with the incidence rate of groin metastasis. Therefore, it is an indication for bilateral IFL. Moreover, any vulvar lesion in pregnancy, gynecologist should not hesitate to perform punch biopsy, along with facultative SLNB. Surgical resection in case of proven malignancy showed a comparable good outcome to non-pregnant women.

Data sharing is allowed as DOI for data.

Background

Vulvar cancer (VC) is the fourth most common form of gynecological cancers. Its incidence in Germany has increased to 4.5 in 100,000 women/year, with a 5-year survival rate of 71% and mortality rate of 0.9 in 100,000 persons in 2016, according to Robert Koch Institute's data (RKI).¹ This increase in trend is also observed in the United States of America (USA) (surveillance, epidemiology, and end results program (SEER)) with an incidence rate of 2.5 in 100,000 women/year, with a 5-year survival rate of 71% (86.3% for localized disease stages I-II; 52.6% for regional or local advanced disease III-IVA; and 22.7% with distant metastasis) and mortality rate of 0.5 in 100,000 women/year in 2016.²

The differentiation of VC can be performed histologically, with squamous cell carcinoma (SCC) (keratinized/differentiated) being the most predominant type, affecting 75–90% of all VC patients. It is

diagnosed mostly in older-aged women with a mean age of 69, due to degenerative and chronic inflammatory changes of the skin.¹⁻⁶ It is also associated with vulvar dystrophies, such as lichen sclerosis and chronic venereal granulomatous disease. Lymph node (LN) metastasis has been predicted to affect one in every five women. The second type of VC is classic, warty, non-keratinized squamous cell carcinoma. Human papillomavirus (HPV) 16, 18, 31 and 33 are responsible for this type of VC and it is mostly diagnosed in middle-aged women with a mean age of 55.¹⁻⁴ The other risk factors are smoking and immunosuppressed conditions following organ transplantation or human immunodeficiency virus (HIV) infection. Verrucous carcinoma (originating from condyloma acuminata), basal cell carcinoma (pigmented or pearly and gray), melanoma, sarcoma, Paget's disease (adenocarcinoma), Bartholin gland carcinoma are other minor types of VC.³⁻⁶ The symptoms and signs in clinical presentation are itchiness, ulcerative lesion, plaque, nodular or warty mass, pain, burning sensation, bleeding or groin enlargement. After the diagnosis has been established with biopsy (B), complete resection of tumor area 'residual zero' is the golden standard of current treatment.³⁻¹⁴ The spread of VC cells is as follows: contiguously (expansion into neighborhood organs, such as vagina, urethra and anus), into the lymphatic system (from inguinal to femoral region, followed by pelvic lymph nodes) and lastly, hematogenously (distant metastases into liver, lungs and bones).⁵ Complete (radical) dissection of inguinofemoral LN or lymphadenectomy (IFL), was formerly the standard treatment. Following the publication of Groningen International Study on Sentinel nodes in Vulvar cancer (GROINSS-V) in 2008, the treatment modality was replaced worldwide with sentinel lymph node (SLN) biopsy (B) with radioactive tracer technetium 99^m nanocolloid (Tc-99^m) or blue dye. The advantage of SLNB is the reduction in both morbidity (lymph cyst, lymphedema of leg, cellulitis or erysipelas) and mortality rates (septic shock due to wound infection and thromboembolism). Moreover, GROINSS-V also showed that recurrence rate of SLNB was low at 2.3% (95% CI, 0.6–5%) in unifocal VC, with excellent 3-year survival rate 97% (95% CI, 91–99%) and minimal morbidity SLNB vs IFL e.g. wound break down 11.7% vs 34%; cellulitis 4.5% vs 21.3%; erysipelas 0.4% vs 16.2%; and lymphedema of the legs 1.9% vs 25.2%.⁶

In the GOG-173 study, Levenback et al.¹⁵, the possibility of false negative value with SLNB was about 6.4%. Moreover, the recurrence rate of metastasis was 2.8% with SLNB and 1.4% with IFL. The survival rate, in the case of isolated groin recurrence, was reported worse in women with primary local VC > 4 cm than < 4 cm in initial free SLNB metastasis with 9% versus 5% respectively.¹⁵

In the case of SLNB with positive unilateral metastasis, current German guidelines suggest bilateral IFL as standard treatment option.⁴ European Society of Gynaecological Oncology (ESGO), Royal College of Obstetricians and Gynecologists (RCOG), and National Comprehensive Cancer Network (NCCN) suggest the same management as German guideline.¹⁶⁻¹⁸ However, a recent report from Woelber et al. and Nica et al. suggested that bilateral IFL could be omitted in primary VC with positive unilateral SLNB, in accordance to their risk-free findings of low rate of contralateral LN metastasis in IFL in 0 out of 28 cases (0%) and 1 in 19 cases (5.3%) respectively.^{7,8}

Methods

Patients

All patients were diagnosed with primary vulvar squamous cell carcinoma at the Obstetrics (O) and Gynecology (G) clinic in the University Hospital of Düsseldorf (UHD) between 2002 and 2018 (Diagram 1). Ethics committee in the medical board of Heinrich Heine UHD has approved the retrospective investigation of patients' medical records (reference number 2019-491). Out of 420 women who were evaluated, 369 women with negative metastasis of SLNB were ruled out. Of the remaining 51 women, we divided them into women with unilateral SLNB metastasis (n=30) and women with bilateral SLNB metastasis (n=21).

Removal of primary tumor and identification of sentinel node

Vulvar tumor was resected locally with \geq 3mm tumor free margin or partial/total vulvectomy. Regional flaps for wound closure were used when indicated.⁴ In pregnancy, primary tumor was resected immediately in any gestational age after punch biopsy confirmed malignancy.

A day before surgery, all patients underwent peritumoral intradermal injection of Tc-99^m at three, six, nine and twelve o'clock using a 27-gauge needle. An hour following the injection, a planar lymphoscintigraphy was performed with anterior and lateral static view. This procedure followed GROINSS-V protocol. However, a short protocol with dose reduction was chosen for pregnant woman. SLNB procedure was performed after 14 weeks of pregnancy (WP). The administration of Tc-99m was lower than 100MBq. An abdominal shield was used to protect fetus from radiation in performing planar lymphoscintigraphy. These procedures were done two hours before the SLNB operation.

On the day of surgery, a handheld gamma probe (Neoprobe GDS, BT Devicor Mammotomo, Cincinnati, OH, USA) was used to identify marked groin nodes bilaterally. In the case of SLNB metastasis, IFL was further performed separately with patient consent. Pelvic node dissection was indicated in accordance with German guideline: more than two metastatic nodes or one metastatic node \geq 5mm or extracapsular spread.

Histopathology

Pathological examination was performed in the Department of Histopathology of UHD. A standard protocol has been established which included frozen sections of LNs, hematoxylin and eosin staining, subsequent ultra-staging and immunohistochemistry with three sections per 5mm, similar to the GROINSS-V study protocol.

Classification

VC is classified into tumor (T), nodal (N), metastasis (M), grading (G), resection status (R) histologically. The International Federation of Gynecology and Obstetrics (FIGO) system was used for clinical staging.

Statistics

All groups were analyzed using one-way ANOVA to determine their statistical significance. P-values of <0.05 is considered to be statistically significant. One-way ANOVA analysis was done with Microsoft Excel professional plus 2016 (Table 1). Graph prism 8.3 was used to analyze the overall survival (OS) using Kaplan Meier curve (Figure 1). The minimum follow-up period of the patients was 12 months after initial diagnosis. Thereafter, some patients were lost in subsequent follow-ups as they were examined by the local gynecologists or at the nearest hospitals.

Results

Our data were collected from 420 women with early primary VC and bilateral SLNB from 2002 to 2018. Fifty-one women (12.1%) had either unilateral SLNB metastasis (n=30; 58.8%) or bilateral SLNB metastasis (n=21; 41.2%). Those with unilateral SLNB metastasis (n=30) had a median age of 51.5 (SD \pm 14.4; max 82; min 27) years old and were further divided into two groups (Diagram 1):

Group 1. Twelve women (n=12/30; 40%) had **ipsilateral IFL only**, in accordance with patient desire to avoid morbidity and/or old age. Only one woman was diagnosed having an additional positive metastatic LN in IFL (group 1B) and 11 women (11/12 = 91.7%) (Group 1A) had no further metastatic LNs in IFL.

- One woman (n=1/11; 9.1%) in group 1A suffered from local recurrence 6 months after initial diagnosis and she survived at 60 months' follow-up.
- One woman (n=1/11; 9.1%) in group 1A experienced VC recurrence in the fat tissue of the groin 18 months after initial diagnosis of ipsilateral IFL without further metastatic LNs. She received re-surgery and radiotherapy and still survived at 60 months' follow-up examination.
- One woman (n=1/11; 9.1%) in group 1A had a 5mm left-sided SLN metastasis and due to their own decision only IFL on the ipsilateral side including left sided pelvic LN dissection, which the result was free from further metastatic LNs. Therefore, radiotherapy was suggested for vulvar region (R1 resection, G3 tumor) and bilateral groin. Unfortunately, she was diagnosed with metastases in both lungs, liver and bone 15 months later. Her bronchial biopsy result was negative p16 expression in tumor cells, whereas her vulvar biopsy result was positive p16. Histologically, both tumors were squamous cancer cells. Hence, she was suspected to have a primary lung cancer in addition to her vulvar cancer. She received palliative radio-chemotherapy.
- There was only one woman (n=1/12; 3.3%) with subsequent metastatic LN in ipsi-unilateral IFL. She had received radiotherapy to her right groin. She survived 24 months after initial diagnosis and then was lost in subsequent follow-up.

Group 2. Eighteen women (n=18/30; 60%) who received complete bilateral IFL were further divided into three subgroups:

A: Thirteen women (n=13/18; 72.2%) had negative IFL results in both groins.

- Interestingly, a 30-year old woman from Subgroup 2A was diagnosed with VC in her second pregnancy. Her clinical complaints were persistent itchiness, pain and ulceration of vulva. A punch biopsy showed keratinized squamous cell cancer. Therefore, removal of the vulvar ulcerative lesion was done at 7th weeks of pregnancy (WP) and SLNB and IFL were performed at 19th and 20th WP, respectively. She had subsequently an uneventful pregnancy and delivered her baby via caesarean section at term. Her most recent examination, 60 months after initial diagnosis, at our clinic showed no sign of recurrence.
- Another 36-year old woman had similar complaints at 23rd WP and her punch biopsy results showed low-grade chronic inflammation, reactive squamous cell hyperplasia and hyperkeratosis. Fourteen months later, within breastfeeding period, vulvar cancer was diagnosed with non-keratinized squamous cells located at right labia minora with extension close to the clitoris. Left-sided SLNB metastasis of 3mm was diagnosed with extra-capsular tumor cells and negative IFL lymph node. As a result, she received radiotherapy on her left groin and follow-up examination at 60 months after initial diagnosis showed no sign of recurrence.

B: One woman (n=1/18; 5.8%) had further metastatic lymph nodes in the ipsilateral IFL.

C: Four women (n=4/18; 22.2%) had contralateral groin metastatic lymph nodes in IFL after unilateral SLNB metastasis initially (Table 2).

- One woman (n=1/4; 25%) from Group 2C developed mons pubis malignant squamous cell tumor 18 months later and received radio-chemotherapy after surgery.

All of the 30 women (n=30/51; 58.8%) with positive unilateral SLNB had pT1b VC, except for one with pT2. Most of the women with positive unilateral SLNB (n=24/30; 80%) suffered from anterior midline lesion in between clitoris and urethra. The median size of tumors is 1.9 cm (SD ± 1.4 cm) and the median depth of tumor cell infiltration is 5 mm (SD ± 4.4mm). Only one woman (n=1/30; 3.3%) had posterior midline vulvar lesion. Five women (n=5/30; 16.7%) had lateralized lesions. In contrast, all women with contralateral groin metastatic lymph nodes in IFL (Subgroup 2C) had anterior midline lesions.

In this study, we would like to emphasize on the side effects and complications post-surgery from Groups 1 and 2. Thirteen women (n=13/30; 43.3%) suffered edema of the foot and required lymphatic drainage therapy. Nine women (n=9/30; 30%) developed lymph cysts and five women (n=5/30; 16.7%) had erysipelas and required antibiotic therapy. Three women (n=3/30; 10%), one woman from each Group 1, 2A and 2C, developed local recurrence of VC.

OS analysis was performed for all 30 women with unilateral SLNB metastasis. The five years' survival rates were 90.9% in Group 1, 80% in Group 2A/B and 75% for the four women in Group 2C.

Discussion

Since the introduction of GROINSS-V study in 2008, SLNB of the groin has played a central role in the management of VC. Firstly, SLNB has reduced morbidity and mortality rates, whereas radical IFL has high side effects.⁶ Secondly, the necessity for IFL remains controversial in the case of positive unilateral SLNB, as to whether it should be done ipsilaterally or bilaterally.^{1–8} This must be considered due to the fact that when recurrent groin metastasis occurs, the survival rates of these patients decrease significantly. The long-term follow-up of GROINSS-V showed that the 10-year disease-specific survival rates in the cases of local recurrence was reduced from 93.5–68.7% and in patients with positive SLNB from 77.7–44.6%.^{9–22}

A German study, on this issue of Woelber et al.⁷, showed in none of the cases of primary VC with positive unilateral SLN contralateral positive lymph nodes in consecutive bilateral IFL (0/28 cases, 0%). A Canadian study (Nica et al.)⁸ showed that only 1 of 19 patients (5.3%) had contralateral IFL metastasis after unilateral SLNB metastasis. But, two of their patients with positive unilateral SLNB had groin recurrence metastasis (one located unilaterally and the other contralaterally) several months following negative IFL.⁸ Therefore, they suggest for the omission of contralateral IFL in positive metastasis of unilateral SLNB. Both studies are in contrast to our findings with 4/18 (22.2%) women with unilateral positive SLN diagnosed with contralateral positive nodes in IFL. In our study, the tumors of these four women were located in the midline. Unfortunately, Woelber et al. and Nica et al. studies had not specified the location of the tumors, if they were midline or lateral.^{7,8,12}

Over the past decade, there is an increasing trend for midline vulvar cancer^{23–26}. This was confirmed with the majority cases in our recent study located at anterior fourchette. Four cases with contralateral IFL metastasis in our study had originated from midline lesions. Therefore, our data suggests if the patient has unilateral SLN metastasis, clinicians should offer radical bilateral IFL in case of midline tumors. This is the current recommendation in German guideline.⁴ Our retrospective single-center study suggests that current guidelines should not be amended or changed. According to our results, the depth of tumor cells infiltration is a significant factor in the prediction of contralateral metastasis ($p = 0.0038$). The median depth of tumor infiltration was 3 mm in group 1, 6 mm in group 2AB and 8.5 mm group 2C. Nonetheless, the diameter of the tumor is statistical insignificant ($p = 0.764$). This finding related to depth of tumor infiltration is also parallel to current suggestion in German guideline as follows: ≤ 1 mm; 1.1–2 mm; 2.1–3 mm; 3.1–5 mm and ≥ 5 mm with the possibility of overall groin metastasis of 0%; 7.6%; 8.3%; 26.7%; and 34.2%, respectively.⁴ The depth of tumor has also been proposed in consideration for extensive management of VC.^{17,27} Future research should aim for bigger sample size and evaluate the correlation between the depth measurement of tumor cells infiltration and risk of contralateral metastasis.

In the case of lateralized lesion, the removal of contralateral LNs in case of unilateral positive SLNB should be discussed with the patients in regards to its benefits, risks and possible side effects. According to our results, it may perhaps be omitted but due to the low number of lateralized lesions in our study, future prospective evaluation of lateralized lesions in VC is warranted. The few sample data with lateralized lesions in our study is the limiting factor to draw clear conclusions regarding the impact of contralateral IFL. In comparison, Woelber et al. and Nica et al. did not specify the location of the tumors in

their study, as to whether they were midline or lateralized.^{7,8,12} We suspect that it might be possible that the majority of their study subjects had lateralized tumors. This might explain why their radical bilateral IFL results had not shown any contralateral non-sentinel metastasis in the contrary to our findings.

Perhaps there will be an alternative treatment option to avoid morbidity of IFL: According to a recently published study GROINSS V-II, radiotherapy could replace IFL if the tumor diameter is < 4 cm and sentinel node metastasis is < 2 mm. However, in the case of sentinel node metastasis of > 2 mm, radiotherapy is not a safe alternative of IFL.²¹

Young women at premenopausal age may also suffer from VC. If the patient complained of persistent itchiness, burning sensation, pain and/or ulcer, gynecologists should not hesitate to perform a tissue biopsy in case of suspicious lesion. VC may also be diagnosed in pregnancy and if the decision to perform SLNB, this procedure should be done after the end of 14th weeks of pregnancy (first trimester) to be safe for the fetus. In pregnancy, lower dose of radioactive Tc-99^m should be injected using short-treatment protocol (SLNB can be done two hours following injection with lowest possible dose). The half-life of technetium 99 m is six hours. The threshold for fetal damage in imaging procedure regarding lymphoscintigraphy is 100 mGy. The fetal radiation exposure (X-rays) is significantly reduced to < 0.1 mGy with the use of an abdominal shield. Prompt nodal removal can reduce the chance of systemic exposure, even though fetal exposure is considered low when technetium is injected locally in the peritumoral region.²⁸ Likewise, delivery mode should then be evaluated on a case-by-case basis; dependent on the probability of vulvar wound dehiscence and/or degree of scar tissue stenosis.²⁸⁻³⁰ In our study, the pregnant woman with VC delivered her baby via caesarean section.

Moreover, diagnosis of VC in pregnancy is often delayed. A systematic review showed that the time interval from the first medical visit until first diagnosis of VC was more than eight weeks (62.5%). The first reason is low suspicion due to the rare occurrence of vulvar cancer in younger-aged women (70%), second is noncompliance of patients (30%), and third is potential risk of vulvar biopsy resulting in fetomaternal complications during pregnancy. In comparison to all gynecological cancers in pregnancy, VC is in fact considered to have the least possible complications in patients who undergo biopsy and/or operation.²⁸⁻³⁰

No groin recurrence was reported in Group 2 (bilateral IFL after unilateral SLN metastasis detected) of our study after initial follow-up at 12 months. One woman with positive contralateral LN in IFL in subgroup 2C passed away due to lung metastasis, with history of being immunosuppressed following kidney transplantation. Two patients from Subgroup 2A passed away; the first with lung cancer (adenosquamous cell) diagnosed 12 months following initial diagnosis of vulvar cancer with metastasis to bone and liver, and the second from relapsed epiglottis cancer (positive p16) at about 12 months following vulvar cancer diagnosis (initial diagnosis of epiglottis cancer was about 12 months before vulvar cancer diagnosis). In addition, one of the women with positive unilateral SLN metastasis with free ipsilateral LNs in subsequent IFL and free pelvic LNs (Group 1A) was diagnosed with lung cancer

approximately 15 months later (non-keratinized SCC with negative p16, whereas p16 was positively expressed in her vulvar cancer). She was the only patient with R1 resection histopathologically.

Our data showed comparable morbidity with the reported data in the literature in respect of infection, lymph cysts, and lymphedema of the legs being 21.3–35.4%, 11–40% and 14-48.8% after IFL respectively.³¹

Although the OS of the patients in Group 1, Group 2 A/B and Group 2C with contralateral positive LNs in IFL after negative SLNB is statistically not significant ($p = 0.623$, log rank test with Mantel Cox) ($p = 0.517$, Gehan-Breslow-Wilcoxon test, Fig. 1), there is a visible trend towards decreased survival in the women of Group 2C (Fig. 1). Interestingly and also unsuspectedly, none of the women of Group 1 who received only unilateral IFL due to unilateral positive sentinel lymph nodes developed groin recurrence in the observation time of 60 months. Neither in the contralateral groin nor unilaterally. No comparable survival rates exist in the literature since in the study of Woelber et al.⁷ and Nica et al.⁸ patients with negative SLNB were compared to women with metastatic groin LNs.

The limitations of this study were retrospective nature of data analysis, loss of some patients in follow-up examinations beyond 12 months following initial VC diagnosis in our clinic, some patients were initially diagnosed in 2018 resulting in short follow up time and small sample size of patients with lateralized tumor location.

Conclusion

According to our study results, radical bilateral IFL should be offered in treatment management of primary VC with anterior midline lesion and unilateral SLN metastasis. Our findings with 4/18 (22.2%) women with unilateral positive SLN diagnosed with contralateral positive nodes in IFL. In our study, the tumors of these four women were located in the midline. However, the need for radical bilateral IFL in cases of lateralized tumor with positive ipsilateral SLNB should be further evaluated. Furthermore, the depth of tumor infiltrating cells was correlated significantly and positively with the incidence rate of groin metastasis ($p = 0.0038$). According to our experience, in case of pregnancy, a punch biopsy is necessary in the management of suspicious vulvar ulceration, along with facultative sentinel lymph node biopsy and surgical resection methods in case of proven malignancy with comparable good outcome to non-pregnant women.

Abbreviations

B Biopsy

ESGO European Society of Gynecological Oncology

FIGO International Federation of Gynecology and Obstetrics

GOG 173 Gynecologic Oncology Group 173

GROINSS-V GRONingen INternational Study on Sentinel nodes in Vulvar cancer

HIV Human Immunodeficiency Virus

HPV Human Papilloma Virus

IFL Inguino-Femorale Lymphadenectomy / complete radical groin dissection

G Gynecology

LN Lymph Node

NCCN National Comprehensive Cancer Network

O Obstetrics

OS Overall Survival

RCOG Royal College of Obstetricians and Gynecologists

RKI Robert Koch Institute

SEER Surveillance, Epidemiology, and End Results program

SCC Squamous Cell Cancer

SLN Sentinel Lymph Node

T, N, M, G, R Tumor, Node, Metastasis, Grading, Resection status

UHD University Hospital of Düsseldorf

USA United States of America

VC Vulvar Cancer

WP Weeks of pregnancy

Declarations

Ethics approval and consent to participate

Ethics committee in the medical board of Heinrich Heine UHD has approved the retrospective investigation of patients' medical records (reference number 2019-491). All of patients had approved their clinical history for the purpose of research and publication.

Consent for publication

This publication follows the ethical guideline in the declaration of Helsinki.

Availability of data and material

All patients were diagnosed with primary vulvar squamous cell carcinoma at the Obstetrics (O) and Gynecology (G) clinic in the University Hospital of Düsseldorf (UHD) between 2002 and 2018.

Competing interest

The authors declare that there is no conflict of interest regarding the publication of this article.

Funding

None of the authors received any funding for this study. This study is purely for scientific use and aimed to provide suggestions for current clinical guidelines and future research.

Authors' contributions

ASW: validation, formal analysis, investigation, conceptualization, writing – original draft preparation, writing and editing

AM: co-investigator

FCM: review

TNF: review

MH: review, resources and supervision

All authors have read and approved the manuscript

Acknowledgements

Thanks to Rosemary Gunawan in correcting the manuscript

References

1. Christ M, Folkerts J, Hansmann J, et al. Krebs in Deutschland fuer 2015/2016 (Cancer in Germany for 2015/2016). Robert Koch-Institut (Zentrum fuer Krebsregisterdaten), Kaptitel 3, 2019 Berlin, Germany
2. Howlader N, Noone AM, Krapcho M, et al. SEER Cancer Statistics Review, 1975-2016, National Cancer Institute 2019.
3. British gynecological cancer society. Guidelines for the diagnosis and management of vulvar carcinoma. Royal College of Obstetricians and Gynecologists (RCOG) 2014: 1-35.

4. Hampl M, Schnürch HG, Ackermann S, et al. Diagnosis, Therapy and Follow-up of Vaginal Cancer and Its Precursors. Guideline of the DGGG and the DKG (S2k-Level, AWMF Registry No. 032/042, October 2018). *Geburtshilfe und Frauenheilkunde* 2019; 79 (10): 1060-1078.
5. Alkatout I, Schubert M, Garbrecht N, et al. Vulvar cancer: epidemiology, clinical presentation and management options. *International Journal of Women's Health* 2015; 7: 305-313.
6. Van der Zee AGJ, Oonk MHM, De Hullu JA, et al. Sentinel node dissection is safe in the treatment of early-stage vulvar cancer. *Journal of Clinical Oncology* 2008; 26(6): 884-889.
7. Woelber L, Eulenburg C, Grimm D, et al. The risk of contralateral non-sentinel metastasis in patients with primary vulvar cancer and unilaterally positive sentinel node (Original article). *Annals of Surgical Oncology* 2016; 23: 2508-2514.
8. Nica A, Covens A, Vicus D, et al. Sentinel lymph nodes in vulvar cancer: management dilemmas in patients with positive nodes and larger tumors. *Gynecologic Oncology* 2019; 152: 94-100.
9. Oonk MHM, Van Hemel BM, Hollema H, et al. Size of sentinel-node metastasis and chances of non-sentinel-node involvement and survival in early stage vulvar cancer: results from GROINSS-V, a multicenter observational study. *Lancet Oncology* 2010; 11: 646-652.
10. Te Grootenhuis NC, Van der Zee AGJ, Van Doorn HC, 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. *Gynecologic oncology* 2016; 140: 8-14.
11. Oonk MHM, Planchamp F, Baldwin P, et al. European Society of Gynecological Oncology Guidelines for the management of patients with vulvar cancer. *International Journal of Gynecological cancer* 2017; 27: 832-837.
12. Oonk MHM, van der Zee AGJ. The risk of contralateral non-sentinel metastasis in patients with primary vulvar cancer and unilaterally positive sentinel node (Editorial). *Annals of Surgical Oncology* 2016; 23: 2383-2384.
13. Covens A, Vella ET, Kennedy EB, et al. Sentinel lymph node biopsy in vulvar cancer: systematic review, meta-analysis and guideline recommendations. *Journal of Gynecologic Oncology* 2015; 137: 351-361.
14. Berek JS, Karam A, Goff B, et al. Vulvar cancer: epidemiology diagnosis, histopathology and treatment of rare histologies. *UpToDate* 2019; 23(3237): 1-32.
15. Levenback CF, Ali S, Coleman RL, et al. Lymphatic mapping and sentinel lymph node biopsy in women with squamous cell carcinoma of the vulva: a gynecologic oncology group study. *Journal of Clinical Oncology* 2012; 30(31): 3786-3791.
16. Van der Zee A, Oonk M, Planchamp F, et al. Vulvar cancer guidelines. European Society of Gynecological Oncology (ESGO): <https://www.esgo.org/media/2016/10/ESGO-Vulvar-cancer-Brochure.pdf>
17. Luesley DM, Tristram A, Ganesan R. Guideline for the diagnosis and management of vulval carcinoma. Royal College of Obstetricians and Gynecologists (RCOG) 2014: <https://www.rcog.org.uk/globalassets/documents/guidelines/vulvalcancerguideline.pdf>

18. Koh WJ, Greer BE, Abu-Rustum NR, et al. Vulvar cancer, version 1.2017: clinical practice guidelines in oncology. *Journal of the National Comprehensive Cancer Network* 2017; 15(1): 92-120.
19. Meads C, Sutton AJ, Rosenthal AN, et al. Sentinel lymph node biopsy in vulvar cancer: systematic review and meta-analysis. *British Journal of Cancer* 2014; 110: 2837-2846.
20. Slomovitz BM, Coleman RL, Oonk MHM, et al. Update on sentinel lymph node biopsy for early-stage vulvar cancer (Review article). *Journal of Gynecologic Oncology* 2015; 138: 472-477.
21. Sykes P, Eva L, Van der Griend R, et al. Pathological process has a crucial role in sentinel node biopsy for vulvar cancer. *Journal of Gynecologic Oncology* 2019; 153: 292-296.
22. Oonk MHM, Slomovitz B, Baldwin P, et al. Radiotherapy instead of inguinofemoral lymphadenectomy in vulvar cancer patients with a metastatic sentinel node: results of GROINSS-V II. *International Journal of Gynecological Cancer* 2019; 29(4): A14.
23. Hampl M, Deckers-Figiel S, Hampl JA, et al. New aspects of vulvar cancer: changes in localization and age of onset. *Journal of Gynecologic Oncology* 2008; 109 (3): 340-345
24. Hampl M, Hantschmann P, Michels W, German Multicenter Study Group. Validation of the accuracy of the sentinel lymph node procedure in patients with vulvar cancer: results of a multicenter study in Germany. *Journal of Gynecologic Oncology* 2008; 111(2): 282-288.
25. Hampl M, Kueppers V, Bender HG. Single large inguinal lymph node metastasis in human papillomavirus-induced early invasive vulvar cancer of the anterior fourchette in two young women. *Journal of Gynecologic and Obstetric Investigation* 2009; 67(1): 42-45.
26. Reuschenbach M, Roos J, Panayotopoulos D, et al; German Study Group for Colposcopy. Characterization of squamous cell cancer of the vulvar anterior fourchette by human papillomavirus, p16INK4a and p53. *Journal of Lower Genital Tract Disease* 2013; 17(3): 289-297.
27. Van den Einden LC, Massuger LF, Jonkman JK, et al. An alternative way to measure the depth of invasion of vulvar squamous cell carcinoma in relation to prognosis. *Mod Pathol* 2015; 28: 295-30
28. Amant F, Berveiller P, Boere IA, et al. Gynecologic cancers in pregnancy: guidelines based on a third international consensus meeting (ESMO Review). *Annals of Oncology* 2019; 0: 1-12.
29. Palmer JE, Tidy JA. Pregnancy following vulvar squamous cell carcinoma: a report of two cases. *Journal of Gynecologic Oncology* 2009; 20 (4): 254-256.
30. Matsuo K, Whitman SA, Blake EA, et al. Feto-maternal outcome of pregnancy complicated by vulvar cancer: a systematic review of literature. *Eur J Obstet Gynecol Reprod Biol.* 2014; 179: 216-223.
31. Wills A, Obermair A. A review of complications associated with the surgical treatment of vulvar cancer. *Gynecologic Oncology* 2013; 131: 467-479.

Tables

Table 1

Patient, disease and treatment characteristics. A p-value of less than 0.05 is considered to be statistically significant.

SLNB	Group 1 (n = 12)	Group 2A&B (n = 14)	Group 2C (n = 4)	p-value*
Age (years)	50	52.5	55	0.793
Median (range)	(28–79)	(27–82)	(51–67)	
Primary vulvar tumor location	9 (75%)	11 (78.6%)	4 (100%)	0.553
Midline	3 (25%)	3 (21.4%)	0	
Lateralized				
Diameter (mm)	15.5	19.5	22.5	0.7645
Median (range)	(6.0–54.0)	(9.0–60.0)	(16.0–35.0)	
Diameter categories	7 (58.3%)	7 (50%)	1 (25%)	0.246
< 20 mm	3 (25%)	5 (35.7%)	3 (75%)	
≥ 20 mm but < 40 mm	2 (16.7%)	2 (14.3%)	0	
≥ 40 mm				
Depth (mm)	3.0	6.0	8.5	0.0038
Median (range)	(1.8-6.0)	(2.0–15.0)	(5.0–23.0)	
Grade	-	-	-	0.410
1	10 (83.3%)	11 (78.6%)	2 (50%)	
2	2 (16.7%)	3 (21.4%)	2 (50%)	
3				
Radiotherapy	4 (33.3%)	6 (42.9%)	3 (75%)	
Chemotherapy	0	2 (14.3)	2 (50%)	
Local recurrence	1 (8.3%)	1 (7.1%)	1 (25%)	
Groin recurrence	1 (8.3%)	0	0	
Distant Metastases	(fat tissue) 1 (8.3%)	0	1 (25%)	

Table 2

Patient characteristics and pathological findings of four women with contralateral SLN metastasis following bilateral IFL. TZ = tumor size; TI = tumor infiltration; BMI = body mass index

	Initial diagnosis	Smoker	Pathological results and disease chronology
1	2005 54 years' old TZ = 2 cm TI = 5 mm BMI = 19.1	Yes	SLNB showed left-sided metastasis 2 mm. IFL showed right-sided metastasis 2 mm. Subsequently, she received radiotherapy bilateral inguinal region. 2011: squamous cell laryngeal cancer (negative p16) 2014: squamous cell pulmonary cancer (negative p16) 2019: still alive with no sign of recurrence
2	2015 56 years' old TZ = 3,5 cm TI = 9 mm BMI = 29.8	No	SLNB showed right-sided metastasis 9 mm with infiltration of blood vessel (V1). IFL showed left-sided metastasis 7 mm with extra capsular tumor cells. Pelvic lymphadenectomy showed no metastasis. Subsequently, she received radiotherapy bilateral of her inguinal region. 2019: still alive with no sign of recurrence.
3	6/2016 67 years' old TZ = 2,5 cm TI = 8 mm BMI = 28.8	Yes	2014: kidney transplantation (tacrolimus and mycophenolic acid) 6/2016: SLNB showed right-sided metastasis 3 mm. Complete IFL showed left-sided metastasis 3 mm. Tacrolimus was changed into Everolimus. The patient received radiotherapy bilateral of her inguinal region. 8/2017: passed away due to lung metastasis of vulvar cancer

	Initial diagnosis	Smoker	Pathological results and disease chronology
4	2018 51 years' old TZ = 1,6 cm T1 = 2,3 mm BMI = 25.6	Yes	SLNB showed right-sided metastasis 3 mm. IFL showed left-sided metastasis 8 mm. Pelvic lymphadenectomy showed no metastasis. Subsequently, she received radiotherapy bilateral of her inguinal region. 2019: recurrent vulvar cancer after eighteen months (metastasis of fat tissue at mons pubis paramedian on the left side with infiltration into venous blood vessel). After surgery followed by radio chemotherapy was performed until December 2019.

Figures

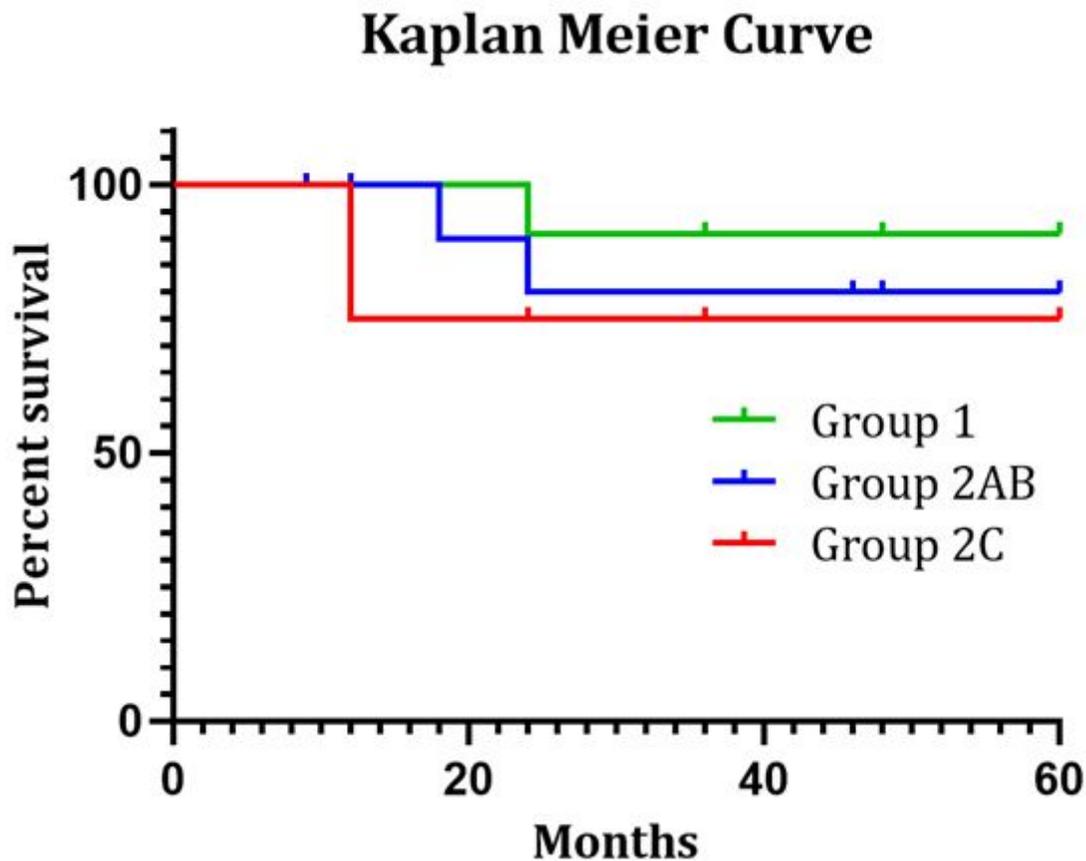


Figure 1

Kaplan Meier curve of patient's survival rates. OS analysis results show 90.9% for Group 1, 80% for Group 2AB and 75% for Group 2C. Group divisions can be seen in Diagram 1.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [Diagram1.JPG](#)