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Impact of re-excision of residual adjacent vulvar intraepithelial neoplasia (VIN III) and histological tumour-free margin (hTFM) on survival in primary squamous cell carcinoma of vulva

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Abstract

Background hTFM in primary vulvar cancer is an important prognostic factor. Ideally, a diameter of > 8 mm should be achieved after primary surgery. The role of VIN III persistence after primary surgery in vulvar cancer is still unclear. The main objective of the current study was to study the role of residual VIN III re-excision and compare differences in disease-free survival among patients with different hTFM and in primary vulvar cancer.

Methods Forty-two patients with residual adjacent VIN III after primary surgery for vulvar cancer which were operated between 2000 and 2016 in our clinic were enrolled in this retrospective study. Re-excision rates for residual adjacent VIN III were calculated. According to the histological margin patients were divided into three group: < 3, 3–8 and > 8 mm. Univariate and multivariate analyses were conducted using the Kaplan–Meier method and Cox proportional hazards models, respectively.

Results The vast majority of patients had pT1b stage (57.1%), grading G2 (71.4%) and lymph node-negative (45.3%) disease at first diagnosis. The re-excision rate was 57.1%. The 5-year disease-free survival (DFS) rates in patients with < 3, 3–8 and > 8 mm hTFM were 50.0, 50.0 and 81.0%, respectively ($p = 0.032$). The 5-year DFS rates in patients with re-excision and without re-excision for VIN III were 77.3 and 52.9%, respectively ($p = 0.060$). In univariate analysis was solely hTFM > 8 mm a prognostic factor for DFS ($p = 0.017$).

Conclusions hTFM may be a potential prognostic indicator for DFS in vulvar cancer patients. Re-excision for residual adjacent VIN III could not be established as a prognostic factor for DFS after primary surgery in squamous cell cancer of vulva.

Keywords Squamous cell carcinoma of vulva · Re-excision of adjacent VIN III · Histological tumour-free margin · Vulvar intraepithelial neoplasia (VIN III) · Disease-free survival

Introduction

Vulvar cancer is a rare condition accounting for 5% of all gynecological malignancies, but its incidence has been doubled in the last decade [1]. Because of its association with human papillomavirus (HPV) the incidence increases approximately four times in young women resulting in a lower peak age of disease [1, 2]. Vulvar intraepithelial neoplasia (VIN) is one of the numerous risk factors of vulvar cancer and even after treatment of a VIN III lesion approximately 6% of patients develop invasive vulvar carcinoma [3, 4]. Approximately 40% of vulvar cancers and 85% of high-grade VIN lesions (HSIL) are associated with HPV infection, particularly with the high-risk types 16, 18 and 33 [5, 6]. Perioperative complications decreased during the evolution of surgical techniques moving from single incision with radical vulvectomy and bilateral inguino-femoral lymphadenectomy to triple incision as radical local excision with bilateral sentinel lymph node biopsy (SLNB) [7]. Nevertheless, wound breakdown and sexual dysfunction are still considered the most common postoperative complications after vulvectomy [8, 9]. Sexual quality of life after

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vulvectomy should be considered perspectively in vulvar cancer patients, particularly in the subset of young females, as studies have shown that the extent of removed vulvar tissue of a VIN or vulvar cancer correlated with persistent sexual dysfunction [9, 10].

To assure high surgical outcome in primary early-stage vulvar cancer patients after vulvectomy, a surgical tumour-free margin of > 10 mm and a histological tumour-free margin of > 8 mm are targeted [11, 12]. However, the prognostic relevance of a histological tumour-free margin of at least 8 mm could not have been verified in recently published studies [13, 14]. In addition, there are only limited and controverse data that exist about the role of residual adjacent VIN III histological margin on local recurrence [15, 16].

The aim of our study was to clarify the relevance of re-excision of residual adjacent VIN III on disease free survival (DFS) after complete tumour resection which might result in unnecessary re-admission for re-operations and a decrease of related complications.

Materials and methods

Data collection of each patient regarding the preoperative diagnostic management, operative procedures, histological results, postoperative complications, adjuvant chemo- or radiotherapy and follow-up were performed precisely to avoid bias. The study was approved by the local ethics committee (No. 193-17) and written informed consent of all participating patients was obtained prior to the onset this study.

Regarding their histological tumour-free margin distance patients were divided into three groups (patients with < 3 mm or 3–8 mm or > 8 mm histological tumour-free margin), and regarding the re-excision of residual adjacent VIN III lesions patients were divided into two groups (patients with and without re-excision). All surgeries were performed by one of the senior-surgeons of our department and R0-resection was defined as optimal surgery. The histological tumour-free margin distance after primary and re-excision surgery was determined for each patient by a senior gyneco-pathologist of the Institute of Pathology of the University Hospital Frankfurt. Staging was defined according to the UICC-TNM-classification [17]. All patients were presented at our multidisciplinary cancer board after surgical treatment for further adjuvant procedures. If indicated, adjuvant radiotherapy was implemented for each study participant according to European guidelines [18] in the Department of Radiation Therapy and Oncology of the University Hospital Frankfurt. After completed primary therapy, patients were examined every 3 months either in our specialized dysplasia consultation hours or at their referred experienced gynecologist office. Gynecological examinations with vulvoscopy were performed at each consultation. In addition, biopsies were taken after identification of borders with areas with dilute solution of acetic acid (like vinegar) from all newly developed abnormal areas of vulvar skin. Other diagnostic tools such as ultrasound examination, computed tomography (CT) or positron emission tomography–computed tomography (PET-CT) were indicated when patients complained about symptoms or in case of suspicion of metastatic disease. The last follow-up data for each patient included in our analysis were obtained either via direct contact with patients or with their treating gynecologist or with their insurance.

Statistical analysis

All statistical analyses were performed using SPSS Statistics (Version 22; IBM, NY, USA).

For all tests, a probability value of $p < 0.05$ was considered statistically significant. Comparisons of categorical and continuous variables were performed subsequently using the Chi-square test and Kruskal–Wallis test between groups. Adjusted hazard ratios were estimated using the Cox proportional hazards model. Univariate and multivariate survival analyses were performed using the Kaplan–Meier method and Cox regression models, respectively.

Results

In this retrospective analysis, forty-two patients diagnosed with squamous cell vulvar cancer ≥ pT1a and specifically with adjacent VIN III lesion were consecutive enrolled after histological complete reductive surgery from 2000 to 2016. During this interval, a total of 64 patients with primary squamous cell carcinoma of vulva with adjacent VIN III underwent surgical treatment in our department. Twenty-two patients in whom medical reports were insufficiently documented as well as cases with doubtful data regarding histological margin distance and other relevant clinicopathological factors were excluded from this analysis. The majority of patients had tumour stage pT1b (57.1%) and tumour grading G2 (71.4%). Almost half of the patients had a negative lymph nodal status (45.3%) and only one-fifth of the patients (21.4%) had a positive lymph nodal status. In 14 cases groin staging was not indicated as for tumour stage pT1a. Only one patient showed metastases in a pelvic lymph node in terms of distant metastases. No distant metastases were observed in parenchymatous organs. Lichen sclerosis was detected in 6 patients (14.3%). In most cases (64.3%) the tumour size was < 2 cm, and solely one (2.4%) patient had wide tumour manifestation over 4 cm with bladder infiltration. Regarding surgical procedures, in 37 (88.1%) patients required solely either local wide excision or a hemivulvectomy. Only one patient received an anterior exenteration as surgical procedure due to extensive local tumour infiltration. In 17 (40.5%)

patients groin SLNB, and in 28 (66.7%) patients primary or secondary inguinal-femoral lymphadenectomy were performed. The re-excision rate of residual adjacent VIN III was 57.1%. Wound healing disturbance had occurred in six cases; three cases in re-excised and three cases in non re-excised patient groups ($p=0.68$). The most common localisation of first recurrence was local on vulvar skin (84.6%). Using the comparison analysis of groups concerning tumour-free margin, patients with histological margin < 3 mm (50%) had significantly more lymph node involvement ($p=0.020$). No significant differences were observed in all investigated groups regarding other clinicopathological factors as illustrated in Table 1.

In the univariate analysis, solely histological tumour-free margin was a prognostic factor for DFS (HR 0.22, 95% CI 0.06–0.76, $p=0.017$). However, after adjusting for other clinicopathological factors such as a re-excision rate of residual adjacent VIN III, age, tumour stage, lymph nodal status, distant metastases and grading, histological tumour-free margin did not remain statistically significant in the multivariate analysis (HR 1.32, 95% CI 0.16–10.8, $p=0.800$).

The re-excision of residual adjacent VINIII could not be established as a prognostic factor for DFS either in the univariate (HR 2.81, 95% CI 0.91–8.68, $p=0.070$) nor the multivariate (HR 2.43, 95% CI 0.79–7.49, $p=0.120$) analysis. Details of the Cox regression analysis are presented in Table 2.

The median follow-up time for DFS was 33 months (range 5–59 months). Thirteen (30.9%) patients experienced a recurrence after primary therapy. The estimated 5-year DFS rates were 77.3% in patients with re-excision of adjacent VIN III and 52.9% in patients without re-excision, respectively ($p=0.060$). The estimated 5-year DFS rates in patients with histological margin distant < 3, 3–8 und > 8 mm were 50, 50 and 81%, respectively ($p=0.032$) (Fig. 1).

Discussion

The current standard surgical treatment of an early-stage vulvar cancer consists of triple excision as a partial vulvectomy, and bilateral groin staging either via SLNB and/or inguino-femoral lymphadenectomy [19]. The objective of surgical treatment of primary vulvar cancer is to achieve of at least 8 mm histological tumour-free margin distance [11]. However, its relevance is still a matter of debate [12–14].

The results of our current study could not definitely confirm the prognostic relevance of histological margin distance in patients with squamous cell carcinoma of vulva. However, patients with histological margin distance > 8 mm showed a significant better estimated 5-year DFS rate of over 80% ($p=0.032$) in univariate analysis.

Similar results were detected in 90 patients with primary vulvar cancer after median follow-up of 58 months in the study of Chan et al. [12]. In their study, 30 patients with a histological tumour-free margin > 8 mm obtained no local recurrence during this period, whereas 23% of patients with histological tumour-free margin of < 8 mm evolved local recurrence. Positive groin nodes and margin distance were important prognostic factors for recurrence in their multivariate analysis. Furthermore, in a recently performed meta-analysis based on 10 studies the authors found out a twofold increased recurrence risk for tumour-free margins < 8 mm (pooled risk ratio 1.99; 95% CI 1.13–3.51) [20].

In the framework of the large multicenter retrospective AGO-CaRE 1, Woelber et al. [13] studied 289 lymph node negative patients with primary squamous cell carcinoma of the vulva. No significant association between margin distance based on 8 mm cut-off and local recurrence could have been revealed neither in the univariate ($p=0.125$) nor in the multivariate ($p=0.267$) setting.

Because of the delayed diagnosis of vulvar cancer several biopsies should be taken carefully and in particular from broad and multifocal lesions thereby to capture all histological transformations [21]. Two distinct pathways for the development of vulvar squamous cell carcinoma and VIN lesions have been put forth. The first pathway, the so called''HPV-dependent" or "usual type VIN", is triggered by infection with HPV and subsequently forms a warty- or basaloid-type vulvar cancer. The second pathway is the so called''HPV-independent or differentiated VIN'' and leads to developed keratinizing vulvar cancer within a background of lichen sclerosus [22, 23]. Some of the risk factors for VIN and vulvar cancer are vulvar dystrophies, other genital neoplasia, nicotine abuse, genital infections, chronic inflammation and socioeconomic status [24].

Another main finding of this study is that we did not find any significant difference in estimated 5 years DFS after re-excision of residual adjacent VIN III in primary setting of vulvar cancer (77.3% vs. 52.9%, $p=0.060$). Groenen et al. [25] revealed similar results by analysing 93 patients with squamous cell carcinoma of vulva. Lichen sclerosis or VIN lesions in 37% of cases could not be established as a risk factor for local recurrence. After long-term follow-up, local recurrence of vulvar cancer presents itself as a second primary tumour [15]. Modesitt et al. [26] analysed the relevance of margin status on disease recurrence of 73 patients with VIN III lesion. After initial treatment, less than half of the cases with positive margin status developed recurrence throughout the course of the disease. Post-surgery, one-fifth of the patients showed invasive carcinoma on a base of VIN III. In their study, multifocality of disease and history of genital warts were observed to be independent factors for recurrence ($p=0.03$). However, it was uncertain whether the recurrence was developed from the residual VIN III after

Table 1 Patients' characteristics

Parameter	All patients ($n=42$)	Histological tumour-free margin			
		<3 mm ($n=8$)	<8 mm ($n=11$)	>8 mm ($n=23$)	p value
Age (years)					
<70	25 (59.5%)	3 (37.5%)	8 (72.7%)	14 (60.9%)	0.297
≥ 70	17 (40.5%)	5 (62.5%)	3 (27.3%)	9 (39.1%)	
Tumour stage (pT)					
T1a	14 (33.4%)	2 (25.0%)	2 (18.2%)	10 (43.4%)	0.206
T1b	24 (57.1%)	4 (50.0%)	9 (81.8%)	11 (47.8%)	
T2	3 (7.1%)	1 (12.5%)	0 (0.0%)	2 (8.6%)	
T3	1 (2.4%)	1 (12.5%)	0 (0.0%)	0 (0.0%)	
Node status (pN)					
Negative	19 (45.3%)	1 (12.5%)	5 (45.5%)	13 (56.5%)	**0.020**
Positive	9 (21.4%)	4 (50.0%)	3 (27.3%)	2 (8.7%)	
Unknown (pNx)	14 (33.3%)	3 (37.5%)	3 (27.3%)	8 (34.8%)	
Distant metastasis					
No	41 (97.6%)	8 (100%)	10 (90.9%)	23 (100%)	0.253
Yes	1 (2.4%)	0 (0.0%)	1 (9.1%)	0 (0.0%)	
Grading					
G1	7 (16.7%)	1 (12.5%)	1 (9.1%)	5 (21.7%)	0.203
G2	30 (71.4%)	4 (50.0%)	9 (81.8%)	17 (73.9%)	
G3	5 (11.9%)	3 (37.5%)	1 (9.1%)	1 (4.4%)	
Lymphovascular space invasion					
Negative	38 (90.5%)	5 (62.5%)	11 (100%)	22 (95.6%)	0.022
Positive	4 (9.5%)	3 (37.5%)	0 (0.0%)	1 (4.4%)	
Lichen sclerosis					
No	36 (85.7%)	8 (100%)	10 (90.9%)	18 (78.3%)	0.160
Yes	6 (14.3%)	0 (0.0%)	1 (9.1%)	5 (21.7%)	
Tumour diameter					
<2 cm	27 (64.3%)	4 (50.0%)	7 (63.6%)	16 (69.6%)	0.431
2–4 cm	14 (33.3%)	3 (37.5%)	4 (36.4%)	7 (30.4%)	
>4 cm	1 (2.4%)	1 (12.5%)	0 (0.0%)	0 (0.0%)	
Surgical procedures vulva surgery					
Local wide excision	20 (47.7%)	2 (25.0%)	5 (45.5%)	13 (56.5%)	0.166
Hemivulvectomy	17 (40.4%)	4 (50.0%)	6 (54.5%)	7 (30.4%)	
Total vulvectomy	4 (9.5%)	1 (12.5%)	0 (0.0%)	3 (13.1%)	
Others	1 (2.4%)	1 (12.5%)	0 (0.0%)	0 (0.0%)	
Groin surgery					
Sentinel node biopsy	17 (40.5%)	3 (37.5%)	6 (54.6%)	8 (34.8%)	0.541
Lymph node dissection	28 (66.7%)	5 (62.5%)	8 (72.7%)	15 (65.2%)	0.985
Unilateral	7 (25.0%)	1 (20.0%)	2 (25.0%)	4 (26.7%)	
Bilateral	21 (75.0%)	4 (80.0%)	6 (75.0%)	11 (73.3%)	
No lymph node dissection	14 (33.3%)	3 (37.5%)	3 (27.3%)	8 (34.8%)	
Number of metastasized groin LN					
0 or unknown	32 (76.2%)	4 (50.0%)	8 (72.7%)	20 (86.9%)	0.187
1	8 (19.0%)	3 (37.5%)	2 (18.2%)	3 (13.1%)	
2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
3	1 (2.4%)	0 (0.0%)	1 (9.1%)	0 (0.0%)	
4	1 (2.4%)	1 (12.5%)	0 (0.0%)	0 (0.0%)	
Re-excision of residual adjacent VIN III					
Yes	24 (57.1%)	3 (37.5%)	3 (27.3%)	18 (78.3%)	**0.009**
No	18 (42.9%)	5 (62.5%)	8 (72.7%)	5 (21.7%)	

Bold values indicate statistical significance ($p < 0.05$)

Staging according to the UICC-TNM-classification

LN lymph node, *VIN III* vulvar intraepithelial neoplasia III

Table 2 Cox regression analysis after optimal surgery of primary vulvar cancer

Parameter	Univariate HR	95% CI	*p* value	Multivariate HR	95% CI	*p* value
hTFM > 8 vs. ≤ 8 mm	0.22	0.06–0.76	**0.017**	1.32	0.16–10.8	0.800
Re-excision of residual adjacent VIN III no vs. yes	2.81	0.91–8.68	0.070	2.43	0.79–7.49	0.120
Age per year	1.02	0.98–1.06	0.310	0.98	0.93–1.04	0.520
Tumour stage (pT) per stage	1.29	0.54–3.06	0.560	2.00	0.47–8.62	0.350
Node status (pN) pos. vs. neg.	0.75	0.15–3.69	0.720	0.15	0.02–1.31	0.087
Distant metastasis (pM) M1 vs. M0	0.05	0–10e6	0.730	N/A	N/A	0.990
Grading per grade	1.61	0.57–4.54	0.370	3.32	0.52–21.4	0.206

Bold values indicate statistical significance ($p < 0.05$)

HR hazard ratio, *CI* confidence interval, *hTFM* histological tumour-free margin, *VIN III* vulvar intraepithelial neoplasia III

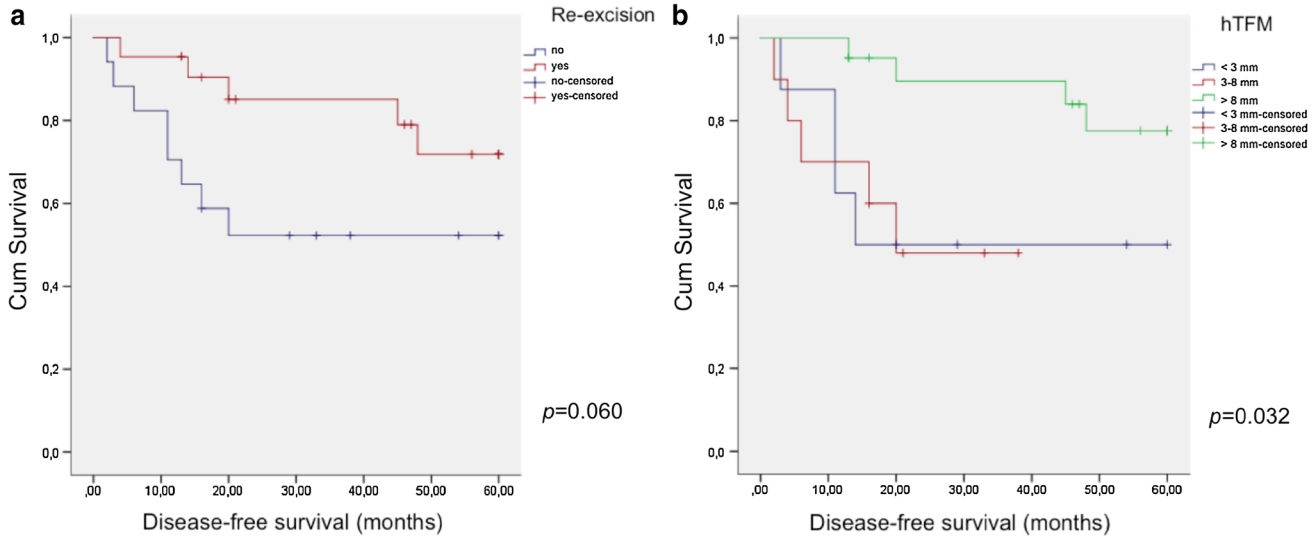

Fig. 1 Survival analysis according re-excision of adjacent VIN III (**a**) and different hTFM (**b**) in primary vulvar cancer. *Cum* cumulative

the initial surgery, or it was developed as a new lesion by multifocality of disease and genital warts.

The recurrence of vulvar cancer often occurs after more than 2 years [15]. Usually the recurrence takes place distant from the primary tumour location. Due to this fact, it seems to be developing as a secondary primary tumour rather than recurrence from residual disease [13, 16, 27, 28]. In the study of identifying the prognostic factors for recurrence, Preti and colleagues [16] detected the adjacent VIN II and III as a significant independent predictor for DFS in multivariate analysis (Risk radio 3.34, $p = 0.001$). Fourteen of 27 patients experienced recurrence of vulvar squamous cell carcinoma after primary therapy. However, only 50% of recurrence in this report was located on vulvar skin which etiolated the probability of residual VIN III as independent factor for recurrence.

The results of our current study remain limited due to its retrospective nature and lymph node-positive patients in the cohort, despite the inclusion of solely well-documented cases as well as a sufficient number of vulvar cancers with residual adjacent VIN III as a rare disease combination. The strength of this analysis was its' homogeneity in performance of standardized surgical procedures and adjuvant therapy in compliance with European guidelines in our hospital.

Our results confirmed that the histological tumour-free margin distance was not an independent prognostic factor for recurrence. In addition, the re-excision of residual adjacent VIN III after complete tumour resection could not be established as a prognostic factor for DFS in patients with primary squamous cell carcinoma of vulva. Up until today, there has been no clear recommendation in the literature in this regard. Therefore, we recommend deciding individually, for each patient for whom risks and benefits are weighed, regarding the comorbidities and age of patients for re-excision surgery. For this purpose, indication for adjuvant

radiotherapy and re-hospitalization also play a decisive role. To validate these results and further understand the role of adjacent VIN III in recurrence of vulvar cancer, multicenter and prospective studies using a standardized pathological examination are urgently required.

Author contributions KG: data collection and management, data analysis, statistical analysis (descriptive), manuscript writing and editing; MS: data collection and management, data analysis; IS: data collection; RW: histological examination; TK: data analysis, statistical analysis (correlation, survival); SB: project development; AE-B: protocol and project development, manuscript correction.

Compliance with ethical standards

Conflict of interest No financial or personal conflict of interest by any of the authors to declare.

References

1. Hampl M, Deckers-Figiel S, Hampl JA et al (2008) New aspects of vulvar cancer: changes in localization and age of onset. Gynecol Oncol 109(3):340–345
2. Al-Ghamdi A, Freedman D, Miller D et al (2002) Vulvar squamous cell carcinoma in young women: a clinicopathologic study of 21 cases. Gynecol Oncol 84(1):94–101
3. van Seters M, van Beurden M, de Craen AJM (2005) Is the assumed natural history of vulvar intraepithelial neoplasia III based on enough evidence? A systematic review of 3322 published patients. Gynecol Oncol 97(2):645–651
4. Reyes MC, Cooper K (2014) An update on vulvar intraepithelial neoplasia: terminology and a practical approach to diagnosis. J Clin Pathol 67(4):290–294
5. De Vuyst H, Clifford GM, Nascimento MC et al (2009) Prevalence and type distribution of human papillomavirus in carcinoma and intraepithelial neoplasia of the vulva, vagina and anus: a meta-analysis. Int J Cancer 124(7):1626–1636
6. Insinga RP, Liaw K-L, Johnson LG et al (2008) A systematic review of the prevalence and attribution of human papillomavirus types among cervical, vaginal, and vulvar precancers and cancers in the United States. Cancer Epidemiol Biomark Prev Publ Am Assoc Cancer Res Cosponsored Am Soc Prev Oncol 17(7):1611–1622
7. Helm CW, Hatch K, Austin JM et al (1992) A matched comparison of single and triple incision techniques for the surgical treatment of carcinoma of the vulva. Gynecol Oncol 46(2):150–156
8. Raimond E, Pelissier A, Etienette Emeriau M et al (2017) Use of negative pressure wound therapy after vulvar carcinoma: case studies. J Wound Care 26(2):72–74
9. Likes WM, Stegbauer C, Tillmanns T et al (2007) Correlates of sexual function following vulvar excision. Gynecol Oncol 105(3):600–603
10. Grimm D, Eulenburg C, Brummer O et al (2016) Sexual activity and function after surgical treatment in patients with (pre)invasive vulvar lesions. Support Care Cancer 24(1):419–428
11. Heaps JM, Fu YS, Montz FJ et al (1990) Surgical-pathologic variables predictive of local recurrence in squamous cell carcinoma of the vulva. Gynecol Oncol 38(3):309–314
12. Chan JK, Sugiyama V, Pham H et al (2007) Margin distance and other clinico-pathologic prognostic factors in vulvar carcinoma: a multivariate analysis. Gynecol Oncol 104(3):636–641
13. Woelber L, Griebel L-F, Eulenburg C et al (1990) Role of tumour-free margin distance for loco-regional control in vulvar cancer—a subset analysis of the Arbeitsgemeinschaft Gynäkologische Onkologie CaRE-1 multicenter study. Eur J Cancer Oxf Engl 2016(69):180–188
14. Baiocchi G, Mantoan H, de Brot L et al (2015) How important is the pathological margin distance in vulvar cancer? Eur J Surg Oncol 41(12):1653–1658
15. Woolderink JM, de Bock GH, de Hullu JA et al (2006) Patterns and frequency of recurrences of squamous cell carcinoma of the vulva. Gynecol Oncol 103(1):293–299
16. Preti M, Ronco G, Ghiringhello B et al (2000) Recurrent squamous cell carcinoma of the vulva: clinicopathologic determinants identifying low risk patients. Cancer 88(8):1869–1876
17. Sobin L, Gospodarowicz M, Wittekind C (2011) TNM classification of malignant tumours, 7th edn. Wiley-Blackwell, PA
18. Oonk MHM, Planchamp F, Baldwin P et al (2017) European society of gynaecological oncology guidelines for the management of patients with vulvar cancer. Int J Gynecol Cancer 27(4):832–837
19. Woelber L, Kock L, Gieseking F et al (2011) Clinical management of primary vulvar cancer. Eur J Cancer 47(15):2315–2321
20. Nooij LS, van der Slot MA, Dekkers OM et al (1990) Tumour-free margins in vulvar squamous cell carcinoma: does distance really matter? Eur J Cancer Oxf Engl 2016(65):139–149
21. Dittmer C, Fischer D, Diedrich K et al (2012) Diagnosis and treatment options of vulvar cancer: a review. Arch Gynecol Obstet 285(1):183–193
22. Del Pino M, Rodriguez-Carunchio L, Ordi J (2013) Pathways of vulvar intraepithelial neoplasia and squamous cell carcinoma. Histopathology 62(1):161–175
23. Sideri M, Jones RW, Wilkinson EJ et al (2005) Squamous vulvar intraepithelial neoplasia: 2004 modified terminology, ISSVD vulvar oncology subcommittee. J Reprod Med 50(11):807–810
24. Edwards CL, Tortolero-Luna G, Linares AC et al (1996) Vulvar intraepithelial neoplasia and vulvar cancer. Obstet Gynecol Clin North Am 23(2):295–324
25. Groenen SMA, Timmers PJ, Burger CW (2010) Recurrence rate in vulvar carcinoma in relation to pathological margin distance. Int J Gynecol Cancer 20(5):869–873
26. Modesitt SC, Waters AB, Walton L et al (1998) Vulvar intraepithelial neoplasia III: occult cancer and the impact of margin status on recurrence. Obstet Gynecol 92(6):962–966
27. Stehman FB, Bundy BN, Ball H et al (1996) Sites of failure and times to failure in carcinoma of the vulva treated conservatively: a gynecologic oncology group study. Am J Obstet Gynecol 174(4):1128–1132 **(discussion 1132–1133)**
28. Te Grootenhuis NC, van der Zee AGJ, van Doorn HC et al (2016) Sentinel nodes in vulvar cancer: long-term follow-up of the GROningen INternational Study on Sentinel nodes in Vulvar cancer (GROINSS-V) I. Gynecol Oncol 140(1):8–14