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Vulvar malignancies: an interdisciplinary perspective

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Summary

Vulvar cancer represents the fourth most common gynecologic malignancy and is often encountered by the general Dermatologist or Gynecologist. Dermatooncologists and Gynecologic Oncologists share expertise in this field and the diagnosis and treatment should ideally be interdisciplinary. All subtypes are typically seen in the later decades of life, although all histologic subtypes have been described in women younger than 30 years. The diagnosis is often delayed. Exact mapping of biopsies is of high importance, as the location and distance from the midline guides the surgical approach depending on the underlying histology. Squamous cell carcinoma accounts for more than 76 % of vulvar cancer with vulvar intraepithelial neoplasia being an important precursor. Basal cell carcinoma is the second most common vulvar malignancy. Melanoma accounts for 5.7 % of vulvar cancer and has a worse prognosis compared to cutaneous melanoma. Most of the trials on checkpoint inhibitors and targeted therapy have not excluded patients with vulvar melanoma and the preliminary evidence is reviewed in the manuscript.

Surgery remains the primary treatment modality of locally resectable vulvar cancer. In view of the rarity, the procedure should be performed in dedicated cancer centers to achieve optimal disease control and maintain continence and sexual function whenever possible.

Overview

With an incidence of 2.5–4.4 per 100,000 persons per year, vulvar cancer is the fourth most common gynecologic malignancy.

Anatomically, the vulva includes the mons pubis, labia majora, labia minora, clitoris, vestibule, vestibular bulb and the greater vestibular glands [1]. With an annual incidence of 2.5–4.4 per 100,000 persons per year, vulvar cancer is the fourth most common gynecologic malignancy after uterine, ovarian and cervical cancer in Europe and the US [2, 3]. Squamous cell carcinoma (SCC) represents the most common histologic subtype, followed by basal cell carcinoma (BCC), extramammary Paget's disease (EMPD) and vulvar melanoma (Figure 1) [4]. Initially, the disease entities are usually encountered by general Dermatologists and Gynecologists, but in view of the rarity, these should be referred to dedicated cancer centers and the diagnosis and treatment should be interdisciplinary involving Dermatooncologists and Gynecologic Oncologists. Although morphology and clinical examination form critical aspects of the diagnostic work up, histologic confirmation is the gold-standard for the diagnosis of any suspicious lesion. Meticulous mapping of all biopsy sites is vital and the report should include the precise anatomic location as well as the location on a clock-face with distance from the midline and vaginal introitus (Figure 2a, b), as the location and distance from the midline guides the surgical approach depending on the underlying histology [5]. Surgical, medical and adjuvant treatment vary depending on the histopathology and are reviewed in the subsections below.

Histologic confirmation is the gold-standard for the diagnosis of any suspicious lesion.

Surgical, medical and adjuvant treatment vary depending on the histopathology.

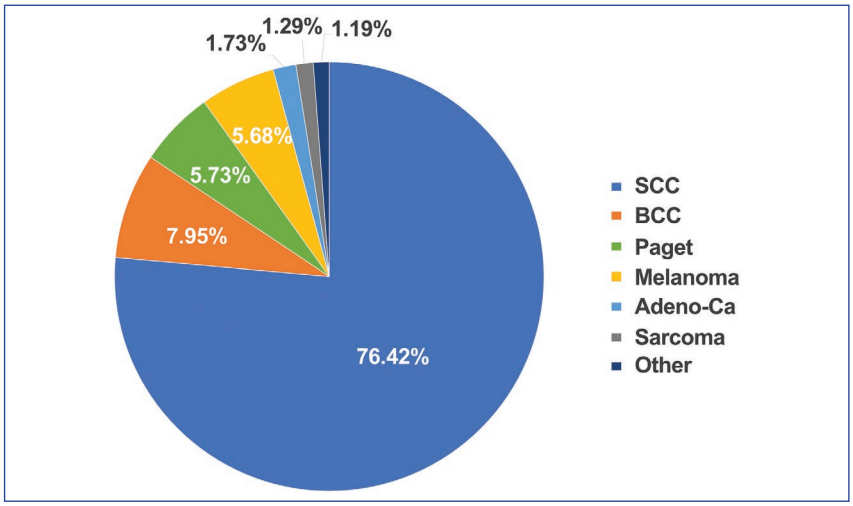

Figure 1 Relative frequency of histologic subtypes of vulvar malignancies. Percentage of histologic subtypes of vulvar malignancies from the National Cancer Institute, Surveillance, Epidemiology and End Results, SEER-18 population, Nov 2018 submission [4].
Abbr.: Adeno-Ca, Adenocarcinoma; BCC, basal cell carcinoma; SCC, squamous cell carcinoma.

Squamous cell carcinoma

Squamous cell carcinoma accounts for the majority of vulvar cancers and its incidence is increasing.

Its precursor lesion, vulvar intraepithelial neoplasia (VIN), can be subdivided into two broad categories: HPV-dependent usual type VIN (uVIN) and HPV-independent differentiated VIN (dVIN).

Due to its association with HPV infection, a pelvic examination with inspection of the vagina, cervical cytology and colposcopy of the vulva, vagina and cervix is recommended.

Vulvar SCC is staged according to the International Federation of Gynecology and Obstetrics (FIGO) staging system.

Squamous cell carcinoma accounts for the majority of vulvar cancers and its incidence is increasing [4, 6]. The risk factors for the development of vulvar SCC include increasing age, infection with human papillomavirus (HPV), smoking, inflammatory conditions of the vulva and immunodeficiency [7]. Its precursor lesion, vulvar intraepithelial neoplasia (VIN), can be subdivided into two broad categories: HPV-dependent usual type VIN (uVIN) and HPV-independent differentiated VIN (dVIN), where uVIN typically affects younger women, is less likely to progress to SCC and has a strong association with smoking [8–10]. Histologically, uVIN typically progresses to basaloid/warty SCC, while dVIN typically progresses to keratinizing SCC [11] (Figure 3). On immunohistochemistry, uVIN is typically positive for p16 and negative for p53 [8]. On the other hand, dVIN is associated with chronic dermatoses, with lichen sclerosus et atrophicans and lichen planus being the most important [12]. A Finnish study of 7,616 women with lichen sclerosus showed a 33.6 fold increased standardized incidence ratio for vulvar cancer [13]. It typically affects women in the sixth to eighth decade; p16 is typically negative and p53 positive [11, 14] (Figure 3). SCC can be asymptomatic or present with pruritus, irritation or irritation or pain. The majority of cases is diagnosed in early stages of the disease [15]. Clinically SCC can present as erythematous scaly patch, plaque, ulcer or ill-defined mass (Figure 4a, b). Any suspicious lesion warrants histologic workup and with larger lesions vulvar mapping may be necessary (Figures 2, 4c). Imaging by CT or PET-CT and MRI may be useful adjuncts for delineating the extent of the disease. In cases with suspected invasion into the bladder or rectum, cystoscopy and/or proctoscopy should be performed. Due to its association with HPV infection, a pelvic examination with inspection of the vagina, cervical cytology and colposcopy of the vulva, vagina and cervix is recommended; HPV testing can be considered [5]. Vulvar SCC is staged according to the International Federation of Gynecology and Obstetrics (FIGO) staging system [16]. Surgery is the primary treatment for

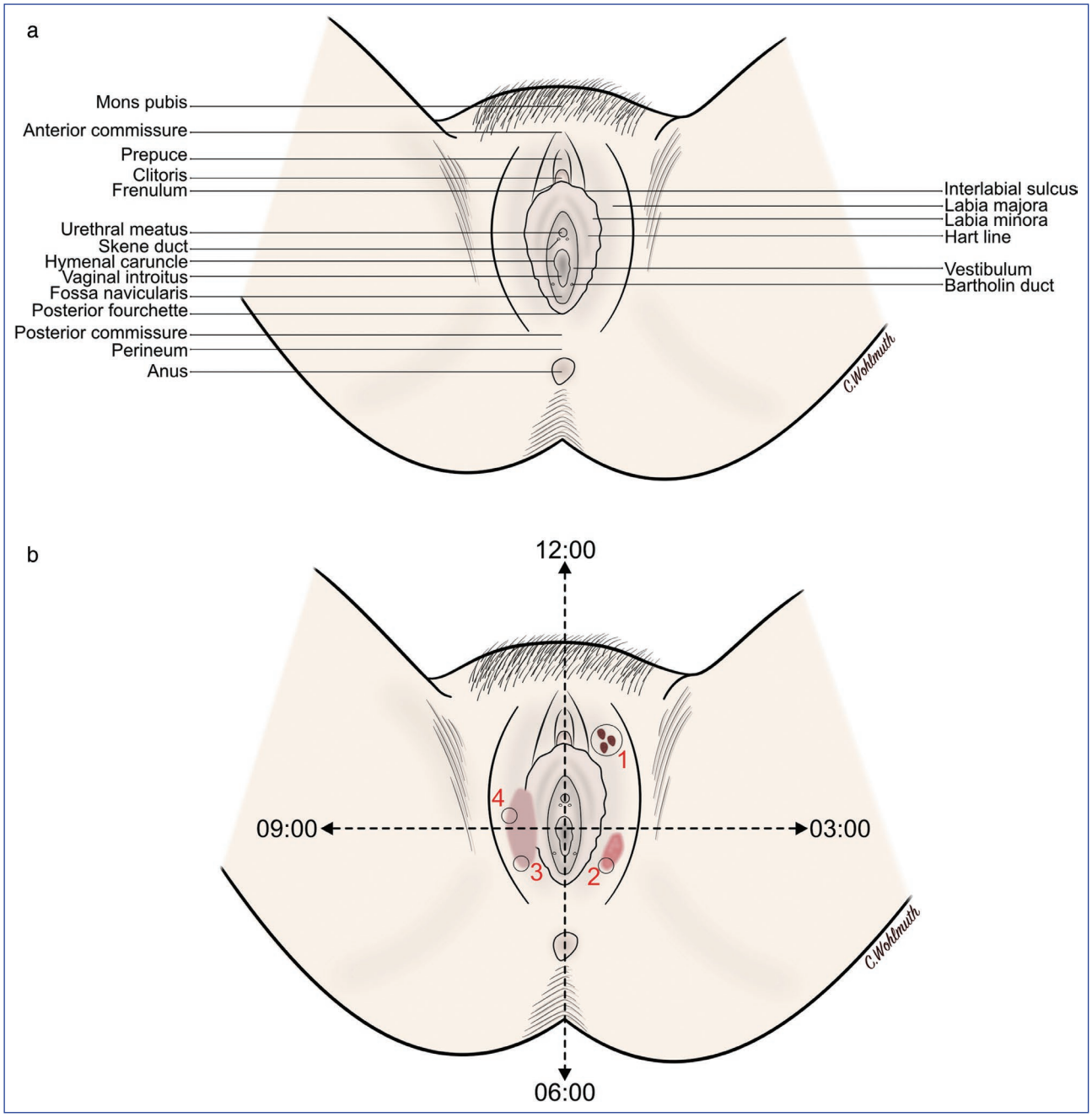

Figure 2 Vulvar anatomy and mapping of lesions. Vulvar anatomy (a). Vulva-mapping, biopsy sites should be reported using the exact position on the clock-face with distance from midline and vaginal introitus as well as describing the anatomic location (b).

Surgical lymph node evaluation should be performed for lesions with a depth of invasion > 1 mm.

early stage and resectable stage II disease. Although prospective data are lacking, a meta-analysis of retrospective data suggests no difference in survival with local excision compared to radical vulvectomy [17]. For SCC with a depth of invasion ≤ 1mm (stage Ia), a wide-local excision of the tumor without lymphonodectomy is sufficient [5]. A surgical margin of 1–2 cm is recommended [18], although this has recently been questioned by a retrospective study of 29 German gynecologic-cancer-centers [19]. Surgical lymph node evaluation should be performed for lesions

with a depth of invasion > 1 mm. If the primary SCC lesion is ≥ 2 cm from vulvar midline, a unilateral lymph node assessment can be performed as the risk for contralateral lymph node involvement is less than 1 % [20]; if it is within 2 cm from the vulvar midline a bilateral lymph node assessment is warranted. The GOG-173 study prospectively assessed the reliability of sentinel-node biopsy in vulvar cancer and reported a false-negative predictive value of 2.0 % if the primary tumor diameter was smaller than 4 cm (vs. 7.4 % > 4 cm) [21] and if technetium-99 is combined with intraoperative blue dye the detection rate for the sentinel node is close to 100 % [22]. More recently, indocyanine green has been successfully tested in vulvar cancer [23]. Sentinel node biopsy is now generally recommended if generally recommended if the tumor is unifocal, has a diameter of less than 4 cm, and the lymph nodes are clinically negative [5, 24].

If the sentinel-node is positive, external beam radiation therapy (EBRT) with or without concurrent chemotherapy or completion of inguinofemoral node dissection followed by EBRT with or without concurrent chemotherapy (especially if ≥ 2 positive nodes or 1 positive node with > 2 mm metastasis) is recommended [5]. For locally advanced disease, primary radio-chemotherapy is generally recommended and any residual disease (clinically or histologically) after treatment should be resected if possible [5]. The retrospective AGO-CaRE-1 multi-center study has underlined the importance of lymph node involvement as a prognostic factor for outcome: women with one or more positive lymph nodes had a 3-year overall survival rate of 56.2 % compared with 90.2 % if the lymph nodes were negative; the progression-free survival was better in those node-positive patients who received adjuvant radiotherapy

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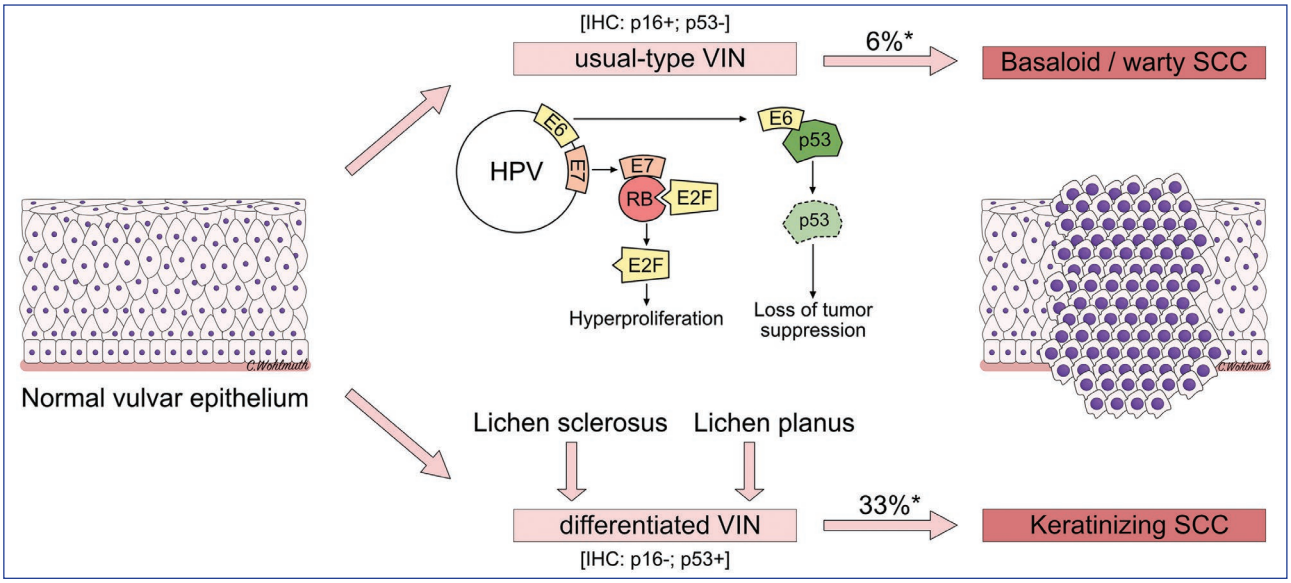

Figure 3 Pathophysiology of usual-type and differentiated VIN and its progression to SCC. Suggested progression of usual-type (uVIN) and differentiated vulvar intraepithelial neoplasia (dVIN) to squamous cell carcinoma (SCC).
uVIN: HPV-protein E6 degrades the tumor suppressor p53; HPV-protein E7 inactivates the tumor suppressor RB and releases E2F resulting in hyperproliferation. On IHC p16 is typically positive and p53 negative.
dVIN: chronic dermatoses, especially Lichen sclerosus and Lichen planus, can progress to dVIN and SCC. On IHC p16 is typically negative and p53 positive.
Abbr.: HPV, human papilloma virus; IHC, immunohistochemistry; SCC, squamous cell carcinoma; VIN, vulvar intraepithelial neoplasia.
*Rate of progression according to van de Nieuwenhof et al. [11].

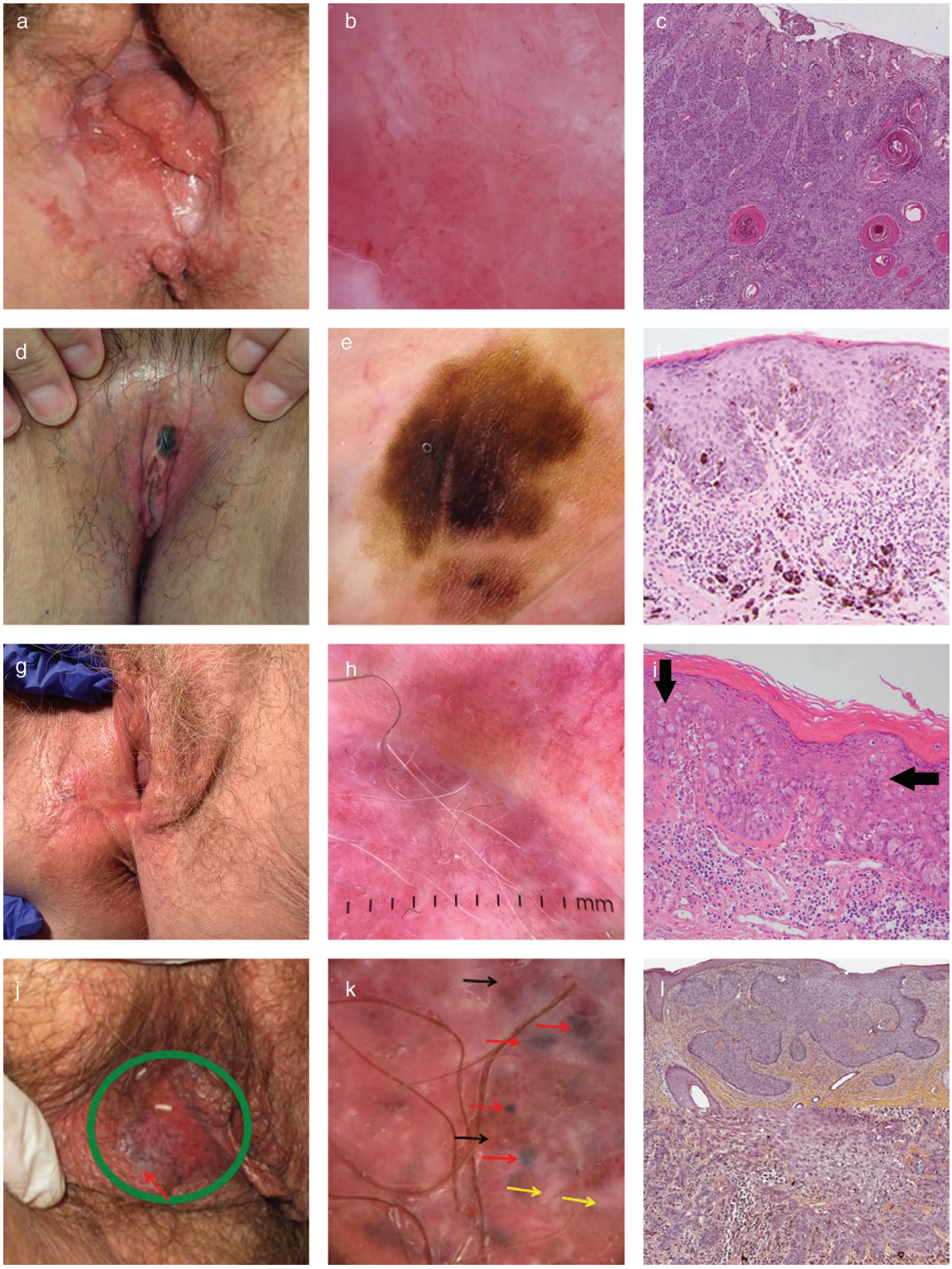

Figure 4 Macroscopic, dermoscopic and histopathologic features of vulvar malignancies. Vulvar squamous cell carcinoma (reproduced with permission of John Wiley & Sons from Vaccari et al. [113] and under the CC license from Alkatout et al. [114]) (a–c). Vulvar melanoma (reproduced under the CC license from Rogers et al. [115]) (d–f). Extramammary Paget's disease (i reproduced under the CC license from van der Linden et al. [116]) (g–i). Basal cell carcinoma (reproduced under the CC license from Cinotti et al. [97]) (j–l).

Patients presenting with distant metastases generally have a poor prognosis.

[25]. The overall recurrence rate is 37 % at five years and therefore patients should be closely monitored after completion of treatment [26]. Patients presenting with distant metastases generally have a poor prognosis. There are no prospective trials regarding first-line chemotherapy and treatment is extrapolated from metastatic cervical cancer and usually comprises of platinum-based chemotherapy, e.g. carboplatin/paclitaxel [5]. Erlotinib, an anti-epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor, has been tested in vulvar SCC. While a partial response was observed in 27 %, the progression-free survival was poor [27]. Recently, cemiplimab, a PD-1 blocker, has been tested in a Phase-II trial in patients with locally advanced or metastatic cutaneous squamous-cell carcinoma and has shown a response rate of 47 %, with 57 % showing a sustained response exceeding six months. Cemiplimab has been FDA and EMA approved for metastatic cutaneous SCC [28], data on vulvar SCC are, however, lacking and only one case report on pembrolizumab has been published [29]. Future studies are warranted to assess the role PD-1/PD-L1 inhibitors in vulvar SCC.

Verrucous carcinoma

Verrucous carcinoma (VC) is now considered as a separate disease entity.

Verrucous carcinoma (VC) was first described as a subtype of SCC by Ackerman in 1948 [30]. Based on its histopathologic and clinical features it is now considered as a separate disease entity [31]. Vulvar VC typically occurs in postmenopausal women; the median age at diagnosis is 66 years [32], but several cases in women < 40 years have been reported [32–35]. The etiology of vulvar VC remains unknown and no precursor lesion has been described, although an association with lichen simplex chronicus and lichen sclerosus has been reported in seven cases [36]. The association with HPV remains controversial – several articles report an association with HPV 6/11 [37, 38], others have found no association with HPV [36, 39].

Histologically, VC is a well-differentiated tumor with marked acanthotic epithelial proliferation and minimal nuclear atypia.

Histologically, VC is a well-differentiated tumor with marked acanthotic epithelial proliferation and minimal nuclear atypia. The tumor expands and is characterized by the elongating rete ridges that advance into the dermis causing a pushing rather than infiltrating pattern [40]. Proliferation mainly occurs at the basal and parabasal layers as shown by increased Ki67, MCM2 and TOP2A expression [39, 41]. As opposed to SCC, p53 is not overexpressed in VC [39].

Clinically, VC of the vulva has a cauliflower-like appearance and is characterized by locally invasive growth; tumors of up to 15 cm in size have been reported [32, 42] with little to no risk of lymph node metastasis, although one case with lung metastasis has been reported in an 88-year-old patient [43]. But this must be interpreted in the context of the fact that coexistence of VC and SCC has been reported in up to 35 % in a series of 17 patients [31]. Coexistence should be ruled out by obtaining adequately large and deep punch biopsies including the base of the lesion since the management between SCC and VC differs considerably.

Little to no risk of lymph node metastasis.

Standard treatment for VC is local excision, where care must be taken to achieve adequate margins with maximal effort to preserve sexual, bladder and bowel function.

Standard treatment for VC is local excision, where care must be taken to achieve adequate margins with maximal effort to preserve sexual, bladder and bowel function [18]. Mohs micrographic surgery has been reported in two VC cases with no recurrence after twleve and 27 months and may be considered in selected cases [44]. Advanced disease stages may require pelvic exenterative surgery to obtain clear margins.

Japaze et al. reported 27 cases (17 own patients and ten previously published cases), where groin node dissection was performed, and all women had negative inguinal nodes [45]. This is in agreement with smaller cases series and several case reports covering lymph node status from sentinel lymph node biopsy or groin node dissection [31, 39, 46]. Therefore, routine lymph node dissection should be omitted

in proven VC where coexistent SCC has been excluded. Clinically or radiographically enlarged lymph nodes have been observed, but mainly reflect reactive changes and treatment decision needs to be individualized in these cases [31, 33, 47]. Traditionally, radiotherapy was contraindicated in VC because of reports of anaplastic transformation, but the evidence is scarce and generally no adjuvant treatment is given following complete surgical excision [48]. With a recurrence rate of around 20 %, regular follow up is recommended; most of the cases have been managed by repeat-excision [31, 32, 39].

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Melanoma

Data on mucosal and specifically vulvovaginal melanoma are scarce. To date only one prospective study was completed on vulvar melanoma. Over a period of seven years, the Gynecologic Oncology Group (GOG-)73 protocol followed 81 women with vulvar melanoma; 71 patients with histology-proven melanoma were included in the final analysis: American Joint Committee on Cancer (AJCC) staging was the best predictor for survival; Breslow's depth of invasion and lympho-vascular space invasion were predictive of lymph node metastases [49].

Vulvar melanoma is typically encountered in the later decades of life, the median age at diagnosis is 68 years with a range from 10–107 years and approximately 32% present with regional and/or distant metastases at diagnosis [50, 51]. With a median overall survival of 53 months and median disease specific survival of 99 months, the prognosis remains poor [50].

The biology of vulvar melanoma differs significantly from cutaneous melanoma.

The biology of vulvar melanoma differs significantly from cutaneous melanoma and mutational analyses have shown that only 7–26 % harbor a BRAF mutation [52–54], while c-KIT is significantly more common in vulvar melanoma and PD-L1 is frequently expressed [52, 54]. On immunohistochemistry, mucosal and cutaneous melanomas share the same markers: S100B, HMB45 and Melan-A [55].

The AJCC staging system should be used for vulvar melanoma instead of the FIGO system used in SCC.

In retrospective series, only 16–25 % of patients presented because of a melanocytic lesion or vulvar mass (Figure 4d–f), the remaining patients already had symptoms from melanoma including bleeding, pain and pruritus [56, 57]. Once diagnosed, the AJCC staging system should be used for vulvar melanoma instead of the FIGO system used in SCC [50, 55]. Imaging is recommended in the evaluation due to the high rate of locally advanced disease and regional/distant metastases [58]. Magnetic resonance imaging may help to delineate the local extension and aid in surgical planning and CT or PET-CT can be used for the evaluation of distant metastases [58].

Surgery remains the mainstay of treatment for melanoma without evidence of metastases.

Surgery remains the mainstay of treatment for melanoma without evidence of metastases and the same surgical margins apply as in cutaneous melanoma: 0.5–1 cm for melanoma in situ, 1 cm for invasive melanoma with a Breslow's thickness ≤ 1 mm, 1–2 cm for Breslow 1.01–2 mm and 2 cm for Breslow > 2 mm is generally recommended [55, 59, 60]. While this may be feasible without major functional impairment in most parts of the body, it can be challenging for vulvar melanoma in terms of preservation of continence and sexual function. More radical procedures have been attempted in the past [49] in view of the poor prognosis of genital melanoma, but retrospective data indicate that there is no benefit compared with local excision using the margins above [56, 57, 61]. Sentinel lymph node biopsy is recommended in all melanomas with a depth of invasion greater than 1 mm without evidence of regional or distant metastases; in those less than 1 mm it should be considered if additional risk factors are present (i.e. high mitotic rate, ulceration or age less than 40 years) [55, 62]. Data regarding recommendation for unilateral or bilateral nodal assessment are lacking for melanoma and usually

Data regarding recommendation for unilateral or bilateral nodal assessment are lacking for melanoma and usually follow the same criteria as in SCC.

follow the same criteria as in SCC [5]. The MSLT-II trial showed that immediate completion lymph node dissection increased the rate of regional disease control and provided prognostic information but did not increase melanoma-specific survival among patients with melanoma and sentinel-node metastases and therefore full inguinofemoral lymph-node dissection may be omitted, although again vulvar melanoma specific data are lacking [63].

A pooled analysis of six clinical trials reported the results for 121 patients with advanced/metastatic mucosal melanoma: 86 patients received nivolumab monotherapy and 35 patients combined nivolumab and ipilimumab. The study has shown improved progression-free survival and similar safety profiles for mucosal melanoma, but the objective response rate is lower compared to cutaneous melanoma (37.1 % vs. 60.4 %).

The medical treatment of melanoma has drastically changed with the ground-breaking survival improvements and the subsequent FDA- and EMA-approval of CTLA-4-, PD-1-, BRAF- and MEK-Inhibitors [64–67]. Many of the trial protocols allowed inclusion of mucosal and vulvovaginal melanomas, however, the results have not been reported separately. Recently, a pooled analysis of six clinical trials reported the results for 121 patients with advanced/metastatic mucosal melanoma: 86 patients received nivolumab monotherapy and 35 patients combined nivolumab and ipilimumab. The study has shown improved progression-free survival and similar safety profiles for mucosal melanoma, but the objective response rate is lower compared to cutaneous melanoma (37.1 % vs. 60.4 %) [68]. Similar results were reported for pembrolizumab in a post-hoc analysis of the Keynote-001, 002 and 006 trials, where the objective response rate was only 19 % for mucosal melanoma [69]. Data on BRAF/MEK inhibitors are limited by the fact that fewer vulvar melanomas carry a BRAF mutation, but in those with a BRAF V600 mutation this provides a good option [52, 67]. Due to the relatively high number of KIT mutations in vulvovaginal melanoma, tyrosine kinase inhibitors may be a treatment option in the future. In two phase II trials, imatinib had a combined response rate of 10/24 (42 %) in patients with mucosal melanoma harboring a KIT mutation [70, 71]. The results for dasatinib, a tyrosine kinase inhibitor targeting mutations in exon 11, were disappointing and imatinib should remain the first choice [72]. Data on mucosal melanoma from studies on adjuvant treatment are scarce. While the EORTC-18071 and Keynote-054 protocol excluded mucosal melanoma, the Checkmate-238 trial included 29 patients, of whom 16 received nivolumab, but the study was not sufficiently powered to show differences in subgroups [73–75]. Given the beneficial results from studies on advanced or metastatic mucosal melanoma, adjuvant treatment should be offered to eligible patients with a discussion on the risks and possible benefits. Ideally, future clinical trials should collect primary disease site in addition to mucosal vs. cutaneous melanoma to facilitate subgroup analyses specifically for vulvovaginal melanoma.

Due to the relatively high number of KIT mutations in vulvovaginal melanoma, tyrosine kinase inhibitors may be a treatment option in the future.

Adjuvant treatment should be offered to eligible patients with a discussion on the risks and possible benefits.

Extramammary Paget's disease

EMPD is a skin malignancy that affects the apocrine gland-bearing skin.

Extramammary Paget's disease is a skin malignancy that affects the apocrine gland-bearing skin. With 65 % of all cases the vulva is the most commonly affected body site [76]. Extramammary Paget's disease mostly affects caucasian women in their 6th to 7th decade of life. Clinical lesions of vulvar EMPD may present as circumscribed erythematous or leukoplakic plaques, with occasional crusting, ulceration or bleeding [77] (Figure 4g–i).

Due to its nonspecific presentation, the diagnosis is often delayed by a median of two years, after topical steroids or antifungals have failed.

Due to its nonspecific presentation, the diagnosis is often delayed by a median of two years, after topical steroids or antifungals have failed. Extramammary Paget's disease can mimic several benign and malignant vulvar diseases, including atopic dermatitis, psoriasis, lichen sclerosus, contact dermatitis, candidiasis, pemphigus vegetans, mycosis fungoides and SCC [80, 81]. Pruritus has been reported to be the presenting symptom in up to 73 % of patients with vulvar EMPD [79, 82, 83].

Table 1 Classification of extramammary Paget's disease (EMPD).

Primary EMPD of the vulva	
Type I	EMPD as a primary intraepithelial neoplasm.
Type II	EMPD as an intraepithelial neoplasm with invasion.
Type III	EMPD as a manifestation of an underlying primary adenocarcinoma of a skin appendage or subcutaneous vulvar gland.
Secondary EMPD of the vulva	
Type I	Secondary to an anorectal or urothelial neoplasia
Type II	Paget disease secondary to adenocarcinomas or related tumors of other sites

Reproduced and modified with permission from Wilkinson EJ et al. [84].

Pathogenetically, EMPD can be subdivided into primary and secondary EMPD.

Pathogenetically, EMPD can be subdivided into primary and secondary EMPD (Table 1). Primary EMPD is defined as an intraepithelial adenocarcinoma with Paget cells arising within the epidermis and extending into the epithelium of adjoining skin appendages [84]. In some cases, the disease can become locally invasive, where Paget cells break through the basement membrane and infiltrate the dermis and/or subcutaneous fat. Both primary intraepithelial and invasive EMPD have to be distinguished from secondary EMPD, a variant that occurs less frequently and is associated with epidermotropic metastases or direct invasion of an underlying adenocarcinoma [84].

The prevalence of a noninvasive intraepithelial EMPD with underlying adenocarcinoma ranges from 2–17 % [79, 82, 85, 86] and the exact prevalence of invasive EMPD remains a subject of debate. A recent retrospective cohort study from the Netherlands analyzed 113 women with vulvar EMPD and found that the majority of women (77 %) had noninvasive EMPD, followed by (micro-)invasive EMPD (15.0 %) and 5.3 % with underlying adenocarcinoma. In a total of three women (2.7 %) the disease had already metastasized [87].

To diagnose EMPD at least one skin biopsy is required, however in a large Dutch cohort vulvar mapping was performed in 42.5 % of all patients.

To diagnose EMPD at least one skin biopsy is required, however in a large Dutch cohort vulvar mapping was performed in 42.5 % of all patients [87] (Figure 2). Histopathologically, EMPD presents with epithelial tumor cells with clear cytoplasm (Paget cells) that can either heterogeneously invade the epidermis or spread in a nest-like fashion. Dermatopathologists from the Duke University investigated 56 cases of vulvar EMPD and the diagnosis was made based on histology in only 14 (25 %) cases, whereas ancillary immunohistochemistry was used in the majority (75 %) of cases [83]. Immunohistochemical markers, including CK7, CEA, pan-CK and EMA are usually reactive in vulvar EMPD [83]. Further markers include mucicarmine and PAS; S100, HMB-45 and Melan-A help differentiate pagetoid melanoma from EMPD, where these markers are usually negative [83, 88]. CK20 and CDX2 are more prevalent among secondary EMPD cases and can be useful in the differentiation from primary EMPD [83, 88].

Physicians are often faced with high rates of positive margins and local recurrences.

The management of EMPD remains challenging, since physicians are often faced with high rates of positive margins and local recurrences (rates range from 15–70 %) [86, 87, 89]. Nevertheless, local excision remains standard of care for EMPD. Mohs micrographic surgery provides a different surgical option and may be associated with higher rates of negative margins and fewer recurrences compared to wide-local excision [90]. Other treatment options include topical

5 % imiquimod cream [91], photodynamic therapy (PDT) and radiotherapy [92]. To exclude underlying malignancies, all patients with EMPD should undergo a thorough work-up, including pelvic examination (including cervical cytology), transvaginal ultrasound, CT scan of the pelvis and abdomen, mammography, colonoscopy and cystoscopy.

Women with intraepithelial primary EMPD in general have a favorable prognosis, despite experiencing recurrences. The prognosis for patients with EMPD and an underlying adenocarcinoma depends on the type and management of the underlying adenocarcinoma [86, 87].

Basal cell carcinoma

Approximately 2 % of all BCC involve the vulva.

Approximately 2 % of all BCC involve the vulva [93]. The median age at diagnosis is in the 7th and 8th decade of life and the clinical presentation is heterogeneous, ranging from small, indurated plaques to shiny sharp demarcated papules with a diameter of 0.5–5 cm [93–96]. Ulceration, bleeding, pain and pruritus may be the presenting symptoms and are indicative of a delayed presentation [93, 97]. High numbers of genital BCC were found among patients with basal cell nevus syndrome, indicating that regular and thorough full body skin exams need to be performed in this patient population [95].

Dermoscopy can be diagnostic in some vulvar BCC cases and observed features include the presence of arborizing vessels, linear telangiectasia, blue ovoid nests, blue globules and white shiny structures.

Dermoscopy can be diagnostic in some vulvar BCC cases and observed features include the presence of arborizing vessels, linear telangiectasia, blue ovoid nests, blue globules and white shiny structures [97, 98] (Figure 4j–l). Most reported BCC of the vulvar have a nodular subtype, followed by superficial BCC [99, 100].

Analogue to BCC on other body sites, surgery with negative margins and preservation of function is the mainstay of treatment. Location is a well-known risk factor for BCC recurrence, independent of size. Although the genital area counts for a high-risk location, prognosis of vulvar BCC is good and does not affect overall survival [93, 101]. Mohs micrographic surgery represents a successful surgical technique and has been successfully performed in vulvar BCC in a case series of seven patients, where all women were free of recurrences at three years of follow up [100]. Alternative treatment options in cases where surgery is contraindicated, include topical 5 % imiquimod cream, topical 5-fluoruracil and photodynamic therapy. Lymph-node biopsy is generally not performed. Work-up includes a physical examination with a full skin examination, to rule out other skin cancers. Imaging studies are reserved for extensive local disease where local destructive involvement of underlying structures are suspected [101].

Sarcoma

Sarcomas are rare tumors of mesenchymal origin.

Sarcomas are rare tumors of mesenchymal origin, which can develop in soft tissue and viscera. Vulvar sarcomas represent a heterogenous group [102–104].

The most common are leiomyosarcomas (LMS), accounting for 53 %.

The most common are leiomyosarcomas (LMS), accounting for 53 % in a Dutch study reviewing 47 published patients with vulvar sarcoma [103]. Dermatofibrosarcoma protuberans (DFSP), epithelioid sarcoma and malignant fibrohistiocytomas accounted for 19 %, 17 % and 11 % respectively [103]. The median age at diagnosis for LMS was 50 years with a wide range from 15–84 years [103]. Although the evidence is limited, lymph node metastases are uncommon (18/18 cases with LMS where the lymph node status was known had negative nodes) and lymph node dissection should be reserved for clinically positive lymph nodes. Radical local excision is the usual treatment [103]. A tumor diameter greater than 5 cm, infiltrating margins, and high mitotic rate have been described as risk factors for

Radical local excision is the usual treatment.

DFSP is a low-to-intermediate grade sarcoma of the dermis and subcutis.

local recurrence [105]. In the series of Aartsen et al. inadequate margin was the most important predictor for recurrence [103].

Dermatofibrosarcoma protuberans is a low-to-intermediate grade sarcoma of the dermis and subcutis. A recent systematic review summarized the characteristics of 53 cases with vulvar DFSP [106]. The mean age at diagnosis was 45 (range 1–83) years and all patients underwent surgical excision; 26 % had a local recurrence. Metastatic disease is rare and was reported in two cases. Since DFSP often harbor a translocation t(17; 22)(q22; q13), tyrosine kinase inhibitors may be a treatment option in these rare cases [106, 107].

DFSP often harbor a translocation t(17; 22)(q22; q13).

Epithelioid sarcoma of the vulva occurs in younger women; the mean age at diagnosis is 31 (range 17–84) years and it tends to be more aggressive. In a systematic review of 31 patients, 13 women (42 %) had a recurrence and ten patients (32 %) died from the disease. Radical excision is the primary treatment modality. In view of the limited evidence, the role of lymphadenectomy, radiotherapy and chemotherapy remain unclear [108]. Other histologic subtypes have been published as case reports and small case series and treatment must be individualized. Referral to dedicated sarcoma clinics should be strongly considered.

Bartholin gland carcinomas and other adenocarcinomas

BGC is characterized by a painless visible tumor on the labia majoria and is frequently misdiagnosed as a cyst or an abscess, before histology is obtained and proper management initiated.

Staging is done according to the FIGO classifications and surgery remains the gold standard of treatment.

Due to its rarity, the management of BGC and other vulvar adenocarcinomas should be reserved for dedicated centers of expertise.

Primary carcinoma of the Bartholin gland (BGC) is a rare vulvar malignancy. It is typically diagnosed in the 5th to 6th decade [109]. BGC is characterized by a painless visible tumor on the labia majoria and is frequently misdiagnosed as a cyst or an abscess, before histology is obtained and proper management initiated [110]. Carcinomas arise either from the Bartholin gland or duct and show a broad variety of histopathologic subtypes, with SCC and adenocarcinomas being the most common [111]. All BGC patients should undergo extensive work-up to rule out distant metastases. Staging is done according to the FIGO classifications and surgery remains the gold standard of treatment. Since management guidelines are lacking, treatment recommendations are based on small cohort studies. Most cases are managed with radical local excision, with bilateral inguinofemoral lymphadenectomy or sentinel lymph node biopsy followed by adjuvant radiotherapy. Bhalwal et al. investigated all BGC cases treated at the MD Anderson Cancer Center and found positive lymph nodes in 42 % and a recurrence rate of 33 % after initial surgery [111]. Prognosis is stage dependent and does not differ from SCC when compared to disease stage [111].

In most cases, vulvar adenocarcinomas arise in the Bartholin gland or are associated with EMPD. Other less frequently observed variants include sweat gland carcinomas and apocrine adenocarcinomas [112]. Due to its rarity, the management of BGC and other vulvar adenocarcinomas should be reserved for dedicated centers of expertise [110, 111].

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Lernerfolgskontrolle

1. Which of the following represents the most common histologic subtype of vulva malignancies?

a) Melanoma
b) Squamous cell carcinoma
c) Basal cell carcinoma
d) Verrucous carcinoma
e) Extramammary Paget's disease

2. Which of the following is true regarding usual-type (uVIN) and differentiated vulvar intraepithelial neoplasia (dVIN) and progression to squamous cell carcinoma (SCC)?

a) Typically, dVIN is associated with human papillomavirus.
b) uVIN has a higher risk (33 %) for progression to SCC compared with dVIN (6 %).
c) dVIN typically affects younger women.
d) dVIN is associated with chronic dermatoses, especially Lichen sclerosus and Lichen planus.
e) dVIN typically progresses to basaloid or warty SCC.

3. A 73-year-old woman presents with a 27 mm ulcerated lesion on the left labia majora at 2 o'clock, 3.1 cm from the midline, 5.6 cm from the vaginal introitus. On clinical examination no pathologic lymph node can be palpated. A punch biopsy of the primary lesion has been obtained and shows invasive squamous cell carcinoma, depth of invasion 2.3 mm. Based on these findings, what is the recommended initial surgical approach with regards to lymph node assessment?

a) Lymph node assessment is not recommended in this patient.
b) Ipsilateral sentinel lymph node assessment followed by full inguinofemoral lymph node dissection or external beam radiation if positive.
c) Bilateral sentinel lymph node removal followed by full inguinofemoral lymph node dissection or external beam radiation if positive.
d) Bilateral full inguinofemoral lymph node dissection.

4. Which of the following statements is true for verrucous carcinoma (VC) of the vulva?

a) The classic precursor lesion is usual-type vulvar intraepithelial neoplasia (uVIN).
b) Approximately 30 % of patients presenting with VC will have lymph node involvement or distant metastases.
c) The tumor growth is characterized by the elongating rete ridges that advance into the dermis causing a pushing rather than infiltrating pattern.
d) The primary surgical approach includes wide-local excision with bilateral lymphadenectomy.
e) Adjuvant radiotherapy is recommended following surgical excision with clear margins.

5. Compared to melanoma of the skin and uvea, which of the following mutations are commonly encountered in vulvar melanoma?

a) KIT
b) BRAF
c) MEK
d) GNA11
e) BAP1

6. A 68-year-old woman presents with an 18 mm ulcerated hyperpigmented lesion on the right labia majora at 8 o'clock, 2.2 cm from the midline, 3.9 cm from the vaginal introitus. A punch biopsy has been obtained by the referring physician and shows invasive melanoma, nodular subtype, Breslow's depth of invasion 3.6 mm, 8 mitoses/mm^2. Based on these findings, what is the recommended surgical margin if a local excision was performed?

a) 0.5 cm
b) 0.5–1.0 cm
c) 1.0–2.0 cm
d) 2.0 cm
e) 4.0 cm

7. The immunohistochemical markers S100, HMB45 and Melan-A help to differentiate extramammary Paget's disease from...

a) Lichen sclerosus
b) Squamous cell carcinoma
c) Mycosis fungoides
d) Pagetoid melanoma
e) Basal cell carcinoma

8. Which of the following statements is true regarding extramammary Paget's disease of the vulva?

a) Primary extramammary Paget's disease is always associated with an underlying adenocarcinoma.
b) The most common treatment approach for primary extramammary Paget's disease is a watch and wait strategy.
c) All patients with extramammary Paget's disease of the vulva need a thorough work-up to exclude an underlying adenocarcinoma.
d) Lesions usually don't itch.
e) The diagnosis can be made on a clinical bases only and histologic confirmation is only reserved for severe cases.

9. Sarcomas represent an exceedingly rare subtype of vulvar malignancies. Which of the following types is commonly associated with a translocation t(17; 22)(q22; q13) that may be targeted by tyrosine kinase inhibitors in selected advanced-stage or metastatic diseases?

a) Leiomyosarcoma
b) Rhabdomyosarcoma
c) Dermatofibrosarcoma protuberans
d) Epithelioid sarcoma
e) Malignant fibrohistiocytomas

10. Which of the following is true regarding basal cell carcinoma (BCC)?

a) BCC is typically encountered in women < 40 years.
b) All patients with BCC must undergo extensive staging by CT and MRI regardless of the size of the lesion.
c) All patients with BCC should undergo lymphonodectomy.
d) BCC tends to metastasize early.
e) Standard treatment is wide local excision; Mohs surgery can be considered.

Liebe Leserinnen und Leser,
der Einsendeschluss an die DDA für diese Ausgabe ist der 10. Februar 2020. Die richtige Lösung zum Thema „Begutachtung in der Dermatologie“ in Heft 8 (August 2019) ist: (1e, 2d, 3d, 4a, 5d, 6d, 7b, 8a, 9d, 10e).

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