Primary Melanoma of the Female Genital System: 
A Report of 10 Cases and Review of the Literature

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Abstract. Background: Primary melanoma of the female genital system are extremely rare (2-3%). Patients and Methods: A retrospective review was undertaken of patients with primary melanoma of the female genital system treated from 1990-2003 at Rostock University Hospital, Germany. Different treatments (sentinel node biopsy, inguinofemoral lymphadenectomy, en bloc resection, adjuvant Interferon-alpha-therapy, adjuvant chemotherapy) are discussed. The complicated classification is reduced to a clinical path for daily use (UICC stage and invasion depth of Breslow, Clark’s level and Chung’s level). Results: We report on 10 patients, aged 26 to 76 years, with primary melanoma of the female genital tract. Seven women developed a vulvar melanoma and one woman a malignant melanoma of the cutaneous inguinal region, while another 2 women had an unusual primary location of the malignant melanoma, the cervico-vaginal region (n=1) and the left ovary (n=1). Conclusion: Initial surgical modality did not influence long-term survival, but affected disease-free survival significantly.

Primary melanomas of the female genital system are extremely rare (2-3%). They have been reported to occur in the vulva, vagina, uterus, cervix and ovaries, but the latter are not common and rarely curable (1). Despite its rarity, vulvar melanoma is the second most common vulvar malignancy after squamous cell carcinoma and represents between 3-4% (2, 3) and 8-10% (4) of all vulvar malignancies. Although the biological behavior of vulvar and vaginal melanoma is similar to cutaneous melanoma (5), the prognosis is very poor, as there is a high risk of local progression as well as distant metastases. Malignant melanoma can form metastases primarily in the skin, tissue, the lymph nodes and the lung ("limited disease") as well as in other organ systems (visceral, ossary and cerebral system: "extensive disease") (6). If there is a minimal suspicion of melanotic change, the affected area has to be removed completely and to be examined (immuno-) histopathologically (Vimentin, S-100-Protein, HMB45). Different types of melanoma can be categorized according to clinical and histological parameters: superficially spreading melanoma (SSM), nodular melanoma (NM), acral lentiginous melanoma (ALM) and lentigo-maligna-melanoma (LMM).

A retrospective review was undertaken of patients with primary melanoma of the female genital system, treated from 1990-2003 at Rostock University Hospital, Germany. The purpose of this analysis was to determine whether less radical surgery, such as that performed for cutaneous nonvulvar melanoma, makes a difference for the outcome of the patients. Different treatments (sentinel lymphadenectomy, inguinofemoral lymphadenectomy, en bloc resection, adjuvant Interferon-alpha-therapy, adjuvant chemotherapy) are discussed.

Patients and Methods

From January 1990 to December 2003, ten patients were diagnosed with primary malignant melanoma of the female genital system at the University Hospital Rostock, Department of Obstetrics and Gynecology, Rostock, Germany. A retrospective review of clinical, pathological and surgical data was done to identify the outcome of patients at different stages of disease following different surgical procedures. Clinical features, type of surgery, adjuvant therapy, recurrences and distant metastases were recorded. Using the data of the pathological review, all patients were staged using the 2002 AJCC and UICC histological classification for malignant melanoma (Table I) (7). The complicated classification was reduced to a clinical path for daily use (UICC stage and invasion depth of Breslow, Clark’s level and Chung’s level, Tables I and II).
Results

Between January 1990 and December 2003, 10 patients with primary melanoma of the female genital system were diagnosed in our hospital. The clinical features, pathological characteristics, stages, type of surgery, adjuvant therapy, recurrences and distant metastases are given in Table III.

Seven women developed a vulvar melanoma (Figures 1 and 2) and one woman a malignant melanoma of the cutaneous inguinal region, while another two women had an unusual primary location of the malignant melanoma: the cervico-vaginal region (n=1, Figure 3) and the left ovary (n=1, Figures 4 and 5).

The median age was 53.3 years (range 26-76) for patients suffering malignant melanoma of the female genital tract. The median age of patients with vulvar melanoma was 48.4 years (range 26-67), the woman with malignant melanoma of the cervico-vaginal region was 67 years old, of the cutaneous inguinal region 56 years and with ovary melanoma 76 years old at the time of diagnosis.

After a long symptom-free time, the first clinical symptoms were mostly unspecific. A dark-pigmented lesion in the external genitalia was the most common sign present (6 out of 10: 60%), followed by pruritus (40%) and increasing fluor vaginalis, vaginal bleeding (20%) or pain. The patient with the melanoma of the ovary complained...
Table III. Patients’ data.

<table>
<thead>
<tr>
<th>Patients</th>
<th>Age</th>
<th>Central location (Histology)</th>
<th>Exulceration</th>
<th>TNM-classif. (DDG-Stage)</th>
<th>Infiltration depth</th>
<th>Primary treatment</th>
<th>Follow-up</th>
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<tbody>
<tr>
<td>1. FI</td>
<td>63</td>
<td>Labium minus dextrum near clitoris: SSM formed in NZN</td>
<td>-</td>
<td>pT1a cN0 cM0 R0 Stage I</td>
<td>Breslow 0.85mm</td>
<td>WLE SD 1-2cm</td>
<td>→5a+11m pd: CR</td>
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<td>2. WM</td>
<td>50</td>
<td>Labium majus dextrum: MM Labium maj sin: Lentigo maligna</td>
<td>+</td>
<td>pT3b pN0 (0/25) M0 L0 R0 Stage IIB</td>
<td>Breslow 2-4mm</td>
<td>HVLNE r SD 2cm</td>
<td>→10m pd: CR</td>
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<td>3. GA</td>
<td>67</td>
<td>Clitoris: LMM</td>
<td>+</td>
<td>pT3b cN0 cM0 Stage IIB</td>
<td>Breslow 3mm</td>
<td>WLE SD 2cm →Radiation inguinal region (GHD 54 Gy)</td>
<td>→5a+6m pd:</td>
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<td>Exitus letalis</td>
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<td>4. AE</td>
<td>36</td>
<td>Suburethral: Multiform MM</td>
<td>-</td>
<td>pT4a pN0 (0/7) cM0 Stage IIB</td>
<td>Breslow 18+2mm</td>
<td>WLE + ing LNE SD 0.7cm →Immuno-CHT: Dacarbacin (6aDTIC)+ IFN-alpha (4-8/1991)</td>
<td>→7m pd (10/91):</td>
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<td>(left parietal vaginal wall)</td>
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<td>5. BM</td>
<td>48</td>
<td>Labium majus sinistrum: spino us cells MM Labium majus dextrum: Melanoma in situ developed of junctional nevus</td>
<td>+</td>
<td>pT4b pN0(0/18) cM0 R0 Stage IIC</td>
<td>Breslow 12mm (8mm invasion of subcutis) Clark’s V; Chung’s IV</td>
<td>RVLNE SD 3-5cm ing-fcm LNE li+ ing LNE re) →IFN-alpha</td>
<td>*13m pd (4/99):</td>
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<td>Progression</td>
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<td>*1a+4m pd (07/99):1:</td>
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<td>LR (r vaginal wall) = &gt;DE + @(GD:51Gy)</td>
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<td>*2a+9m pd (12/00):2:</td>
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<td>LR(r post commissur) = &gt;DE + @(GD 36 Gy)</td>
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<td>*3a+8m pd (11/01):</td>
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<td>3. LR = &gt;PE+ @ (GD 40Gy)</td>
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<td>*4a+1m pd (4/02):</td>
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<td>4. LR = &gt;PE+ @ (GD 40Gy)</td>
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<td>→5a+9m pd: CR</td>
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<td>6. BU</td>
<td>49</td>
<td>Labium minus sinistrum: Malignant nodular Melanoblastoma- LMM</td>
<td>+</td>
<td>pT4b N1a (1/25): Inguinal (1/12) = &gt;N1 ing. re. Pelvin (0/13)</td>
<td>Breslow 4+2mm, (10x10mm); Clark’s IV Chung’s III</td>
<td>RVLNE SD 3-4cm Ing. LNE bil: r N1 →pelv LNE bds +BSO</td>
<td>* 8a pd (07/00):</td>
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<td>Breast cancer right</td>
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<td>(invasive ductal,pT1c (1.3cm) LCIS pN0 (0/12) cM0 L0 R0 G2:</td>
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<td>Operation, Radiation,</td>
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*continued*
abdominal pain and ascites (patient 10). The time between the first symptom and diagnosis ranged from less than one month in four patients, less than four months in five patients and one year in one patient (patient 9). The primary therapeutic approach was surgery in all patients. There were different surgical treatments depending on the location and surgical characteristics of the primary lesion. More than half of the patients (n=6) had to undergo radical surgery. Surgical treatments ranged from wide local excision, hemivulvectomy or radical vulvectomy with bilateral inguinal lymphadenectomy, or more radical surgery (30%). Five out of seven patients with vulvar melanoma had to undergo bilateral inguinal lymphadenectomy (71.4%). In histopathological examinations, two of these patients with vulvar melanoma (28.6%) presented tumor in the groin lymph nodes. The reason for not performing inguinal lymphadenectomy in one of the two patients was multimorbidity and the high risk of extended surgery. This woman received adjuvant radiation of the groin region (patient 3). The reason that the second woman with

Table III (continued)

<table>
<thead>
<tr>
<th>Patients</th>
<th>Age (a)</th>
<th>Central location (Histology)</th>
<th>Exulceration</th>
<th>TNM-classif. (DDG-Stage)</th>
<th>Infiltration depth</th>
<th>Primary treatment</th>
<th>Follow-up</th>
</tr>
</thead>
</table>
| 7. BP    | 26     | Labium minus sinistrum near clitoris: uniform, round and spinal cells MM | + | pT4b  
N1b (1/32)  
N1 ing. re cM0  
Stage IIIC | Breslow  
12mm  
Clark's V  
Chung's V | RVLNE (+clitoridecctomy  
SD 3-4cm  
ing LNE bds: r N1)  
+pelv LNE bds  
+Immu-no-CHT:  
Dacarbizin (6xDTC)  
+ IFN-alpha (06-10/1991) | *8m pd (12/91): hepatogen mets  
*11m pd (3/92): pulmonal mets  
*1a+4m pd (8/92): Progression of pulmonal mets  
*1a+6m pd (10/92): breast mets  
*1a+7m pd (11/92):cerebral mets  
->1a+8m pd (12/92): Exitus letalis |
| 8. PS    | 51     | Cutaneous left inguinal region near vulva: | + | pT3b  
P0 (0/2)  
cM0  
Stage IIb | Breslow  
2.5mm  
(10x10x2.5 mm)  
Clark's IV  
Chung's IV | WLE + ing LNE l  
SD 3-4cm  
+CHT | *4a+9m later (05/95): last contact: CR |
| 9. ME    | 67     | Cervico-vaginal region Suburethral: spinal, pleomorphic and clear cell MM | + | pT2b  
P0(0/37)  
cM0 R0  
Stage IIA | Breslow  
1.9-2mm  
(1.3cm)  
Clark's IV  
Chung's IV | Radical WLE + ing+pelv LNE bil (Colphysterecctomy, BSÖ)  
SD 3-4cm  
+IFN-alpha | *2m later CCT (07/99):cerebral metastases  
+10m later (03/03): Exitus letalis |
| 10. PA   | 76     | Left ovary: epithelioid cell MM + benign | + | pT1c  
CN0  
Stage IV | 40x0x10 mm  
abdominal HE + BSO,AE, omentectomy partial  
-> CHT refuged | At FD: pulmonal and peritoneal metastases  
->7m pd (6/96): LC |

a...years, AE...appendectomy; BSO...bilateral salpingo-oophorectomy; CHT...chemotherapy; FD...first diagnosis; HE...hysterecctomy; HV...hemivulvectomy; IFN...Interferon, ing...inguinal, L...left, LC...last contact with the doctors, LNE...lymphadenectomy, LR...local recurrence, m...month, ®...radiation, r...right; RV...radical vulvectomy; RVLNE...radical vulvectomy with lymphadenectomy; SD...safety distance.; WLE...wide local excision.
malignant melanoma of the vulva did not receive lymphadenectomy was the early diagnosis in DDG Stage Ia, at which stage radical surgery is not required (patient 1).

Patients with primary locations close to the introitus, suburethral or cervico-vaginal regions had to undergo radical vulvectomy for security distance (patients 5-7), occasionally with resection of the urethra (patient 4) or with colpohysterectomy (patient 9).

Different histological types are reported (SSM, NM, ALM, LMM and pleomorphic melanoma). On microstaging, the Breslow depth was between 0.85 to 18 mm, Clark’s level II to V and Chung’s level II to V. In six patients immunohistological investigations were done. The melanoma cells were positive for S-100 protein, HMB-45 and Vimentin (Figures 6 and 7). Three patients had postoperative complications (secondary healing in three cases, inguinal lymphocyst in one case).

Six out of ten women had adjuvant immunotherapy with IFN-alpha, since the invasion depth was more than 1.5 mm or lymph node metastases had already occurred. Three patients had a combined immunochemotherapy with Dacarbacin (6 cycles DTIC + IFN-α) owing to the tumor thickness (18 mm; patient 4) or contralateral lymph node metastases (patients 6 and 7).

The average follow-up was 48.4 months (range, 10-138 months), but one of the patients was diagnosed in 2003 with
a very early stage of melanoma and has been followed for 10 months (patient 2). Three out of ten patients (30%), with follow-up longer than five years, were still alive and disease-free at the last visit. One woman with follow-up of four years and nine months was still alive and the malignant melanoma in complete remission. Four patients (40%) died at 10 to 66 months after the initial diagnosis. One of these four patients died five years and six months after the first diagnosis because of a sudden heart incident, but the malignant melanoma was still in complete remission (patient 3). The other three patients died of widespread malignant melanoma and had either an unusual primary location of the malignant melanoma [suburethral (patient 4; died 36 months after first diagnosis) and cervico-vaginal region (patient 9; died 10 months after first diagnosis] or a wide-spread malignant melanoma at time of first diagnosis (minor labia, stage IIIC; patient 7; died 20 months after first diagnosis). The outcome of the patient with malignant melanoma of the left ovary (patient 10) is not reported, her last contact with the doctors being 7 months after initial diagnosis.

Two of the seven women with vulvar melanoma developed local recurrences (28%, patients 4 and 5) and the patients with malignant melanoma, melanoma of the cervico-vaginal region and the wide-spread melanoma (patient 7) developed distant metastases (three in ten: 30%).

**Discussion**

The patients’ median age was 53.3 years when the melanoma was first diagnosed (Table II), which confirms that vulvar melanoma occurs especially in postmenopausal women. For precise assessment of the prognosis of patients with cutaneous melanoma, the Clark’s tumor invasion level (8) and Breslow’s tumor thickness (9) classification were used (Table I). The prognosis of malignant melanoma is not only determined by...
tumor size, but by tumor invasion. This is the reason for using the 2002 AJCC- or UICC-classification of malignant melanoma of the skin, which reveals tumor thickness and tumor invasion, and not the FIGO-classification of gynecological tumors. The correlation between progression-free survival and AJCC- or UICC-classification is higher than with FIGO-classification (5). The worse prognosis of vulvar melanomas (5-YSR 8-55, mean 36%) (10, 11) in comparison to malignant melanomas of the skin (10-YSR 75-80%) (12) is probably due to the morphological peculiarity of vulvar skin. The subepithelial tissues of the clitoris and labia (the lack of a defined papillar dermis) differ in morphology from the rest of the skin of the body (13). This is considered in the classification with a modified Clark system, the Chung’s level (13, 14) (see Table II). The 5-YSR of primary malignant melanoma of the cervix uteri is only 14% (15) despite radical tumor surgery. The vaginal melanoma was the vaginal localization (16, 17) with a poor prognosis (patient 9, Figure 3). The worst prognosis belongs to malignant melanoma with primary localisation of the ovaries. These survival rates correlate with the outcome of our patients.

The recommended treatment for vulvar melanoma has been radical vulvectomy with bilateral inguino-femoral lymphadenectomy, regardless of lesion size, thickness, or depth of invasion (13, 18). However, most authors conclude that radical surgery does not improve the survival of patients with early disease when compared to local excision (19). However, such radical surgery, which is disfiguring and associated with severe morbidity (lymphedema, secondary disabilities), has not been shown to improve the survival of patients with vulvar malignant melanoma and, thus, has been questioned (3, 20, 21). But a small safety distance could be accompanied with a high risk of local progression. With regard to malignant cutaneous melanoma, the recommendations for treatment of vulvar melanomas with thin lesions (<1 mm) are wide local excision with a safety distance of 1 cm and, with deeper lesions, an en bloc resection with safety distance of 2-3 cm with regional (inguino-femoral) lymphadenectomy (22). In intraoperative examinations the pathologist cannot safely distinguish invasive melanoma from melanoma in situ. Thus, it is advisable that maculouss-lentiginous hyperpigmented areas should be excised.

Although the duration of follow-up was shorter in those patients who underwent less radical surgery, the absence of recurrence in patients with lesions of a depth of 2 mm or less suggest that patients with superficial lesions may be spared the morbidity of radical resection. Patients with vulvar melanoma lesions deeper than 4 mm have a high risk of distant metastases that is unlikely to be significantly decreased, even with the use of radical vulvectomy and bilateral inguino-femoral lymphadenectomy.

Cases with primary melanomas close to the introitus, urethra or cervico-vaginal regions may require a radical vulvectomy (patients 5-7), a resection of the urethra (patient 7) or colpohysterectomy (patient 4) to have a safety distance. We could confirm that, despite radical surgery in cases of progressive tumor (patients 4, 5, 7 and 9), no difference in recurrence-free survival time and no decrease of metastatic risk was reached (Table II).

The diagnostic and therapeutic meaning of elective groin lymph node dissection (“sentinel node biopsy”) is being evaluated in various studies. In view of the relative ease and minimal trauma, sentinel node biopsy could be a routine procedure in malignant melanoma of the vulva and vagina (23) as it is already established in surgical treatments of breast cancer and cutaneous malignant melanoma.

Patients with local recurrence of vulvar melanoma should undergo local excision and, in addition or alternatively, local radiation. At clinical stage IV (distant metastases), single or small numbers of metastases should be removed completely if possible, but no general recommendation for palliative mono-chemotherapy (DTIC) or for combined immunochemotherapy (no study) exists. The follow-up evaluation should be intensive in the first five years, as this is the time period when 90% of the metastases appear. The German Dermatological Society has recommended a gynecological examination every 3 months for up to 3 to 5 years, including inspection of the skin and mucous, palpation and lymph node sonography (24). In cases of locoregional metastases, chest X-ray and abdominal sonography biannually is recommended. Patients with distant metastases should undergo CT scan (abdomen, chest) and cerebral MRI.

**Conclusion**

Vulvar melanoma is an aggressive neoplasm, with a poorer prognosis than cutaneous melanoma. An extremely bad prognosis independent of primary treatment is shown by malignant melanoma of the vagina, uterine cervix and ovary.

Melanoma of the vulva has traditionally been treated with radical vulvectomy and bilateral inguino-femoral lymphadenectomy, regardless of lesion size, thickness, or depth of invasion (18). The initial surgical modality did not influence long-term survival, but affected disease-free survival significantly. The increased local recurrence rate is not attributed to surgical failure, but to the inherent abnormality of melanocytes (25). That is why the treatment of invasive vulvar melanoma has become more individualized during the past decade. Superficial lesions may need only wide local excision, thus avoiding the morbidity associated with more radical operation (26).

**References**
