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Patterns of distant metastases in vulvar cancer

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HIGHLIGHTS

- Distant metastases is a rare event in vulvar cancer (5.1%)
- Tumor diameter, invasion depth, nodal status, number of metastatic lymph nodes were predictive for occurrence of metastases
- Median survival from first diagnosis of metastases was 5.6 months
- 2 year overall survival rate after diagnosis of distant metastases was 11.3%

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ABSTRACT

Objective. Metastatic vulvar cancer is a rare disease. Information on metastatic patterns and corresponding prognosis or therapeutic approaches is scarce. We therefore analyzed pattern and course of metastatic disease in a large single center cohort.

Methods. All patients with primary squamous-cell cancer of the vulvar [$n = 391$, median age: 60 years (range 20–94)] treated at the Gynecological Cancer Center Hamburg-Eppendorf 1996–2013 were retrospectively evaluated for occurrence of distant metastasis. Furthermore, a systematic Medline database search was performed using the terms: 'vulvar cancer' AND 'metastasis', 'chemotherapy', 'patterns of recurrence', or 'prognosis'.

Results. Out of 391 patients with primary squamous cell vulvar cancer, 20 patients (5.1%) eventually presented with distant metastases. In these 20 patients, median time to first diagnosis of metastasis after primary diagnosis was 13.4 months (range 4–104). Often patients experienced one or more local recurrences before distant spread (12/20, 60.0%). Documented metastatic sites were lung ($n = 9$), liver ($n = 7$), bone ($n = 5$), skin ($n = 4$) and lymph-nodes (axillary/thoracic/paraaortic, $n = 3$). The majority of patients presented with unilocal metastases (13/20, 65.0%). In univariate analysis tumor diameter, invasion depth, nodal status and number of metastatic lymph-nodes were identified predictive for occurrence of distant metastases. 2-year-overall-survival-rate after metastases of all metastatic patients was 11.3%; median survival from first diagnosis of metastases was 5.6 months.

Conclusion. The occurrence of distant metastasis from vulvar cancer is a rare event with very limited prognosis. Further efforts, especially translational research will be crucial to identify prognostic markers as well as therapeutic targets to improve survival in these patients.

1. Introduction

As the incidence of vulvar cancer has been rising over the past decades to now 2–5 in 100.000 women per year in Europe, increased clinical and scientific interest has emerged to improve therapeutic options [1]. The treatment of early stage vulvar carcinoma is relatively standardized with radical local excision and surgical staging of the groins [2]. Approximately 30% of patients initially present with locally advanced vulvar cancer [Fédération Internationale de Gynécologie et

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d'Obstétrique (FIGO) stage III and IVa disease]. Treatment is then considerably less standardized with a significantly higher risk of recurrence (40–50%); and 30–40% will ultimately die from their disease [3–5]. Treatment options have to be discussed individually and range from ultra-radical surgery in form of pelvic exenteration to multimodal treatment including neoadjuvant or definitive chemoradiation [6]. In not surgically resectable recurrent vulvar cancer, and in case of distant metastases, therapeutic options are extremely limited and generally experimental due to the absence of established clinical data. Furthermore, patients with recurrent and metastatic disease are often heavily pretreated. Even though neoadjuvant chemotherapy has shown promising results in primary disease, much lower activity can therefore be expected in recurrent settings [7–9]. This reflects in a 1-year survival rate of 31% in patients with recurrent or metastatic vulvar carcinoma [4]. Over the past decade a few small prospective studies for advanced or metastatic vulvar cancer have been initiated [4,10,11]. However, results are difficult to interpret as in- and exclusion criteria vary considerably among the different studies, patient numbers are small and patient cohorts range from chemo-and radiotherapy naïve to heavily pretreated patients. To improve treatment for metastatic vulvar cancer, the level of information regarding incidence and localization of metastases has to be improved. So far, very few publications included patients with metastatic vulvar cancer. Still, it is unknown if localization of metastases impacts prognosis and if treatment strategies should account for these characteristics. We therefore conducted a review of literature and an analysis of incidence and pattern of metastases as well as the treatment applied in a large clinical cohort.

2. Methods

2.1. Patients

All patients with primary squamous cell cancer of the vulva ($n = 391$) treated at our gynecological cancer center between 1996 and 2013 were retrospectively evaluated. Patients presenting with distant metastasis e.g. for second opinion were excluded to minimize selection bias. The institutional approach to the treatment of primary vulvar cancer during the investigated period consisted of resection of the primary tumor and staging of the inguino-femoral lymph-nodes via three separate incisions in case of locally restricted disease (except stage 1a disease, where lymph-node assessment is generally not recommended). Adjuvant radiotherapy of the groins and pelvis was performed in case of advanced disease (>1 metastatic lymph-node, lymph-node metastasis with extracapsular spread or a diameter >10 mm), and radiotherapy of the vulva was performed when resection was incomplete, the primary tumor was large and/or invaded the urethra/vagina/anus or in case of multiple or bilateral lymph-node metastases. Cumulative doses ranged between 50.4 and 59.4 Gy. In case of locally advanced disease, radical surgery or primary chemoradiation with cisplatin 40 mg/m^2 weekly was performed on an individual basis. Informed consent had been obtained from all included patients to access their tissue and review their medical records when they first attended the clinic according to the Investigational Review Board and Ethics Committee guidelines (Ethics Committee of the Medical Board Hamburg reference number 190504). Clinicopathological factors were evaluated by reviewing medical charts and pathological reports. For tumor staging, UICC TNM classification and stage groupings version 6 were used. During follow-up patients were only subjected to CT scan if presenting with specific clinical symptoms. Otherwise only clinical examination of the vulva including vulvoscopy, palpation and sonography of groins was performed. Patients who presented with distant metastases at some point during the course of their disease were further analyzed. Metastatic patients were divided into subgroups according to the site of metastases (pulmonary, hepatic, osseous, distant lymph node, cutaneous). In case of more than one metastatic site, patients could be distributed in more than one group. However, to improve readability of the tables, patients were listed only once. The allocation to a metastatic group was then based on the leading clinical symptom.

2.2. Review of literature

MEDLINE (Pubmed) was searched for articles and case reports on the incidence and localization as well as treatment of metastatic vulvar cancer. Search terms used were: 'vulvar cancer' AND 'metastasis', '(systemic) treatment', 'patterns of recurrence', or 'prognosis'. We selected only studies reporting on squamous cell cancer [4,12–18]. Only three prospective clinical trials systematically including patients with metastatic vulvar cancer could be identified. We reviewed the available literature on treatment of metastatic and recurrent vulvar cancer with emphasis on conservative (mainly chemotherapeutical) strategies. With regard to chemotherapeutical agents we also systematically searched for drug names ('cisplatin', 'carboplatin', 'paclitaxel', '5-fluorouracil', 'topotecan' 'bleomycin', 'mitomycin-C', or 'cyclophosphamide') AND 'vulvar cancer'.

2.3. Statistics

Data was describes as counts (percent) or median and range for event times. The primary endpoint in this analysis was the time between primary surgery and the diagnosis of metastases. Univariate Cox regression analyses were used to compare subgroups of patients. We refrained from multivariate adjustment because of the low event count and missing values in continuous variables. The level for significance was set to 5%.

3. Results

3.1. Review of literature

Only sparse information could be found on pattern and incidence of distant metastatic spread in vulvar cancer. One Italian retrospective multicenter study evaluated the patterns of recurrence in 502 cases of vulvar cancer [14]. Distant metastases were documented in 7.9% of patients. The 5-year survival rate for these patients was 15%. The presence of inguinal lymph-node metastases was identified as a risk factor for multiple and distant recurrences. In a smaller retrospective analysis of 125 patients, the rate of distant metastases reported was 3% [15].

Regarding treatment strategies, prospective studies are exceptionally rare. Those available did not only include patients with metastatic vulvar carcinoma but also locally advanced and recurrent disease: In a phase II multicenter prospective study published in 2009 by Witteveen and colleagues [4] 31 patients with locally and advanced, recurrent and/or metastatic vulvar cancer were treated with paclitaxel as a single agent, in a three weekly regimen. Eight of these patients (25.8%) presented with distant metastases. Median progression free survival (PFS) was 2.6 months (95%CI: 2–4.2 months) with an overall response rate of 13.8% (4/29). As overall response was only moderate in this study, the authors reasoned, that the addition of carboplatin or cisplatin to paclitaxel might be superior to paclitaxel monotherapy, as in advanced cervical or head and neck cancers response rates of 30–50% could be achieved with a taxane/platinum combination [19–21]. However, in a prospective pilot study of 6 patients with primary locally advanced ($n = 4$) and recurrent ($n = 2$) vulvar cancer of which only one also presented with distant metastases to the lungs, no objective response was observed with the addition of carboplatin to paclitaxel, administered in a weekly schedule [13].

Another phase II trial investigated erlotinib as a single agent in vulvar cancer [12]. Erlotinib is an epidermal growth factor receptor (EGFR) inhibitor that has shown antitumoral activity in a variety of other malignancies e.g. head and neck cancers with tolerable toxicity in phase II and III trials. In this study, patients were divided into two cohorts. Cohort one comprised patients with an assessable lesion at the