Small Cell Carcinoma of Vulva

Curative Multimodal Treatment in Face of Resistance to Initial Standard Chemotherapy

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Background and Purpose: Extrapulmonary small cell carcinoma (EPSCC) is a rare disease, which has a slightly better prognosis than small cell lung cancer, but still dismal. Gynecologic small cell malignancies tend to show a better survival than similar histologies of other regions. However, of five reported cases of vulvar manifestation only one patient was disease-free at the time of publication with limited follow-up.
Case Report: The authors describe a case of locally advanced small cell vulva carcinoma infiltrating the anal sphincter and urethra with spread to inguinal lymph nodes treated by radiochemotherapy and regional hyperthermia. After three cycles of carboplatin/etoposide, computed tomography and magnetic resonance imaging indicated only little regressive transformations but overall stable disease. Surgical options were excluded. Therefore, curative radiotherapy to a total dose of > 65 Gy to macroscopic tumor, chemotherapy with cisplatin weekly, and regional hyperthermia were performed. Acute severe toxicity was limited to skin reactions. Despite the disadvantageous situation with inguinal lymph node metastases and chemoresistance, the multimodal therapy yielded a 5-year disease-free survival.
Conclusion: Thus, the trimodal regimen of radiochemotherapy plus regional hyperthermia offered a curative chance in spite of resistance to the standard chemotherapy for irresectable, locally advanced small cell carcinoma of the vulva. Therefore, this approach merits further evaluation for limited disease of EPSCC.

Key Words: Extrapulmonary small cell carcinoma · Vulva · Radiochemotherapy · Hyperthermia

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Kleinzelliges Vulvakarzinom. Kuration durch multimodale Therapie bei initialer Chemotherapieresistenz

Hintergrund und Ziel: Extrapulmonale kleinzellige Karzinome (EPSCC) sind eine seltene Tumorentität, die eine etwas bessere Prognose als kleinzellige Bronchialkarzinome besitzt. Innerhalb dieser Entität zeigen gynäkologische Tumoren ein etwas besseres Überleben. Allerdings war von den fünf beschriebenen Fällen kleinzelliger Vulvakarzinome zum Zeitpunkt der Auswertung nur eine Patientin mit kurzer Nachsorge tumorfrei.
Fallbericht: Die Autoren beschreiben den Fall einer Patientin mit lokal fortgeschrittenem kleinzelligen Vulvakarzinom, welches den Sphincter ani, die Urethra und die inguinalen Lymphknoten involvierte. Nach der initialen Chemotherapie mit Carboplatin/Etoposid zeigten sich leichte regressive Veränderungen, aber messtechnisch keine relevante Größenabnahme im Sinne einer „stabilen Erkrankung". Operative Behandlungsmöglichkeiten bestanden nicht. Daher wurde als kurative Modalität eine definitive Radiochemotherapie mit > 65 Gy auf den makroskopischen Tumor mit simultaner wöchentlicher Cisplatingabe plus lokoregionaler Tiefenhyperthermie durchgeführt (Abbildung 1). Höhergradige Akuttoxizitäten beschränkten sich auf die Haut. Trotz der ungünstigen Ausgangssituation mit lymphogener Metastasierung und fehlendem Ansprechen auf die initiale Chemotherapie konnte mit der multimodalen Therapie ein krankheitsfreies Überleben von 5 Jahren erreicht werden (Abbildung 2).
Schlussfolgerung: Die trimodale Therapie mit Radiotherapie, Chemotherapie und Hyperthermie eröffnete trotz der initialen Resistenz gegenüber der Standardchemotherapie einen kurativen Ansatz bei einem inoperablen, lokal fortgeschrittenen kleinzelligen Vulvakarzinom. Dieses Ergebnis kann einen Ausgangspunkt für die Diskussion der Therapieoptionen von lokal begrenzten EPSCC bilden.

Schlüsselwörter: Extrapulmonales kleinzelliges Karzinom · Vulva · Radiochemotherapie · Hyperthermie

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Introduction

Extrapulmonary small cell carcinoma (EPSCC) is a rare disease with a slightly better prognosis than small cell lung cancer (SCLC), yet still dismal [2, 20]. Regarding small cell carcinomas of the female genitourinary tract, in particular cervical cancer, the published results veer toward a better prognosis [9, 11]. This favorable outcome is mostly explained by lower stage at diagnosis compared to EPSCC of other sites [12]. Since squamous cell vulvar and vaginal neoplasms also represent an infrequent disease [7], the much lesser experience with small cell carcinomas of that region is evident.

In general, the treatment strategy in EPSCC tends more and more to be adjusted to the standard therapy in SCLC [19]. Most patients are treated with a multimodal approach consisting of platinum-based chemotherapy and local treatment, i.e., surgery or radiotherapy [10, 12, 19] due to the high frequency of metastases in patients with local treatment only. Efficacy of radio- or chemotherapy or both can be enhanced by hyperthermia. A sensitization was substantiated for hyperthermia in terms of bi- and trimodal therapies in various cancers [8]. We report the case of a patient presenting with initially chemoresistant, locally advanced small cell carcinoma of the vulva completely responding (CR) to radiochemotherapy plus hyperthermia for > 5 years.

Case Report

A 49-year-old female patient presented with assumed bartholinitis. The abscess was treated with surgery, but wound healing was delayed. Arterial wound bleeding and urinary retention led to resurgery including cystoscopic and rectoscopic exploration. A diffuse tumorous infiltration of the whole wound extending to the middle vagina was detected, while bladder and rectal mucosa were not involved.

Histological Finding

The biopsy specimen yielded a hyperplasia of squamous cell tissue and an infiltrating, malignant, small cell tumor. Histogenesis was evaluated immunohistochemically. Expression of chromogranin A and synaptophysin characterized the mass as neuroendocrine small cell carcinoma. Proliferation index (MIB-1 staining) was about 70%, thus the tumor was classified as poorly differentiated.

Staging

The initial staging comprised of whole-body computed tomography (CT) and magnetic resonance imaging (MRI) of the pelvis. The bulk invaded the urethra, pelvic muscles, vagina and the sphincter ani externus muscle, reaching 52 × 48 × 40 mm. Furthermore, the inguinal lymph nodes were suspicious due to increased number and uptake of contrast agent. In analogy to squamous cell carcinoma of the vulva the tumor would have been staged as T4 N1 M0.

Treatment

Surgery was interdisciplinarily excluded as treatment option because of the infiltration of surrounding anatomic structures. Therefore, systemic therapy consisting of three cycles carboplatin AUC4 (area under the curve) d1 plus etoposide 160 mg/m^2 d1–3 was initiated to achieve a downstaging. Thereafter, however, CT and MRI indicated only little regressive transformations but overall stable disease with a tumor size of 53 × 43 × 36 mm. In this "no change" situation, we decided to perform an aggressive radiooncologic treatment consisting of radiotherapy to a total dose of > 65 Gy plus simultaneous chemotherapy with cisplatin 40 mg/m^2 weekly (six cycles) in analogy to the treatment of squamous cell carcinomas of the cervix [15] and vulva [6] and due to the high significance of platinum in the therapy of small cell histologies. To further augment the radiation treatment, additional regional hyperthermia was performed as also described for cervical cancer [5] (Figure 1).

Radiotherapy was planned as box technique including the complete vulva to a total dose of 50.4 Gy (1.8-Gy single fraction dose), the primary tumor region was boosted in shrinking-field technique to 65.4 Gy with photons and the inguinal lymph nodes to 66.4 Gy with electrons. Three complete and two circulation-related shortened applications of additional regional radiofrequency hyperthermia were performed with a Sigma 60 applicator starting at 500 W with temperature probes (bladder, vagina, rectum).

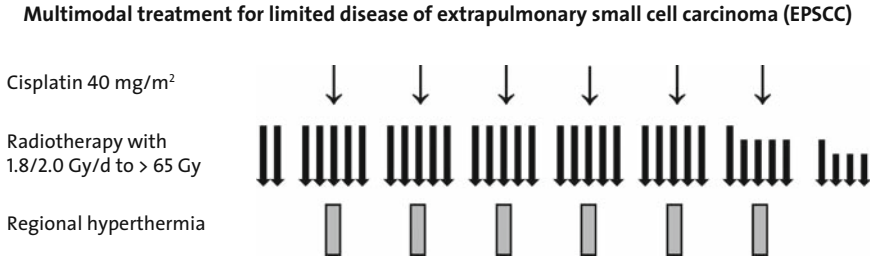
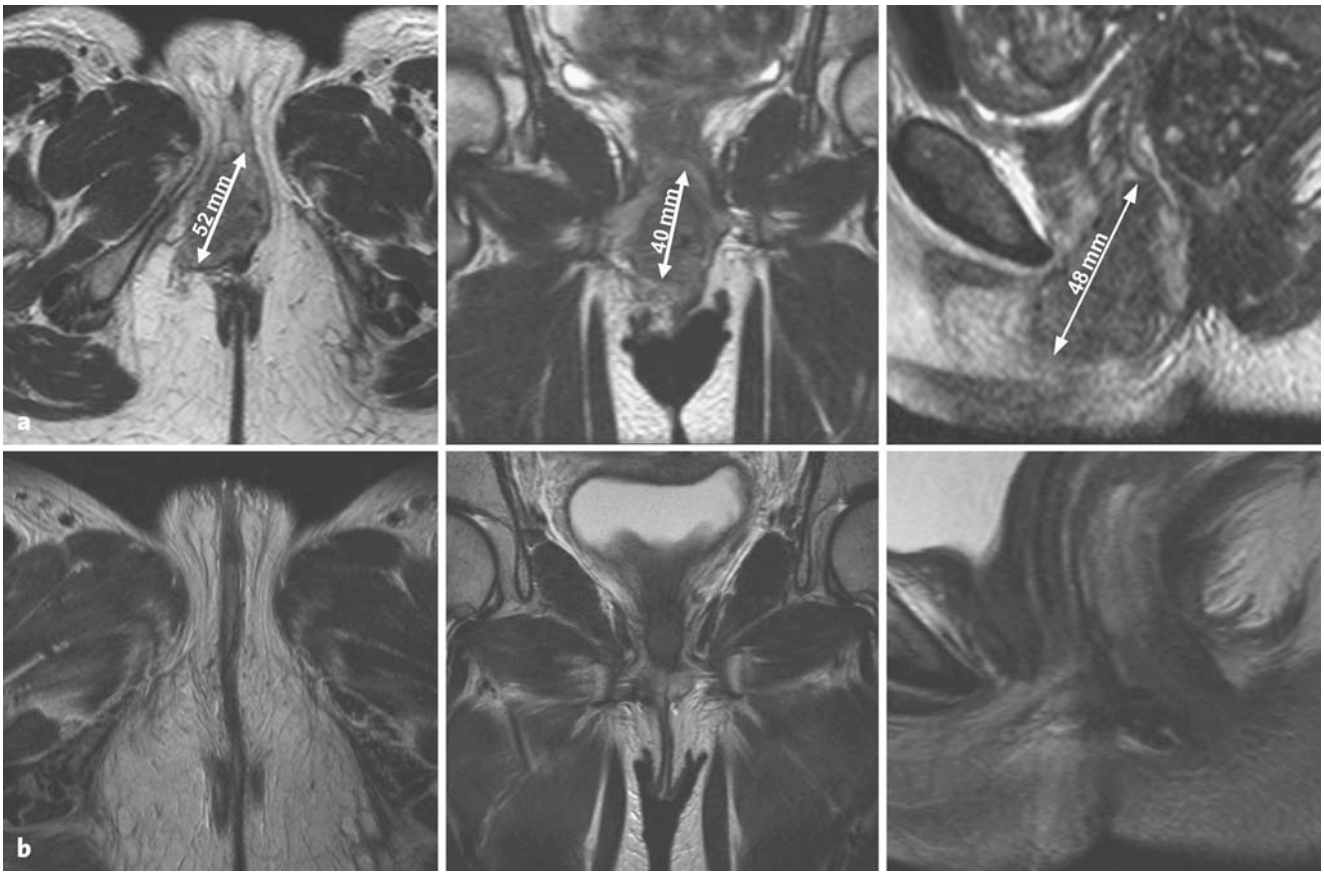


Figure 1. Radiotherapy was given in a box technique to the pelvis including the complete vulva to a radiation dose of 50.4 Gy (1.8-Gy single fraction dose). The primary tumor region (PTV) was boosted in shrinking-field technique to a total dose of 65.4 Gy with photons and the inguinal lymph nodes to a total dose of 66.4 Gy with electrons. Simultaneously, weekly 40 mg/m² cisplatin and regional hyperthermia were applied. Three complete and two circulation-related shortened applications of additional regional radiofrequency hyperthermia were administered.

Abbildung 1. Die Strahlentherapie wurde in einer Boxtechnik zunächst unter Einschluss des gesamten Beckens und der Vulva bis 50,4 Gy durchgeführt. Der Primärtumor (PTV) wurde in „shrinking-field"-Technik bis zu einer Gesamtdosis von 65,4 Gy mit Photonen und die Leistenlymphknotenmetastasen bis zu einer Gesamtdosis von 66,4 Gy mit Elektronen aufgesättigt. Parallel dazu wurden wöchentlich eine Chemotherapie mit 40 mg/m² Cisplatin und eine regionale Tiefenhyperthermie appliziert. Insgesamt konnten drei regionale Tiefenhyperthermien komplett und zwei kreislaufbedingt verkürzt gegeben werden.



Figures 2a and 2b. MRI before the start of chemotherapy showed a tumor mass of > 5 cm in diameter (a). 3 months after trimodal therapy, a complete response was achieved (b).

Abbildungen 2a und 2b. Das MRT vor Beginn der Chemotherapie zeigte eine > 5 cm große Raumforderung (a), die 3 Monate nach Abschluss der multimodalen Therapie nicht mehr nachweisbar war (komplette Remission) (b).

Acute Toxicity

The patient experienced severe skin toxicity CTC grade 3 (Common Toxicity Criteria version 2.0) requiring analgesics, which completely receded until the first follow-up examination. Rectal and urinary toxicities did not exceed CTC grade 2. Relevant hematologic toxicities did not occur.

Follow-Up and Late Toxicity

The follow-up consisted of initially 3-monthly and, after 2 years, of semi- to at least annual gynecologic examinations. 3 months after treatment, the tumor had disappeared according to the MRI except for a suspicious intravaginal lesion which was clinically related to an infection (Figure 2). 5 years after trimodal therapy, the patient reported of no problems especially concerning defecation and urination. Gynecologic examination including transvaginal ultrasound detected no abnormalities.

Discussion

Despite the disadvantageous situation with inguinal lymph node metastases and chemoresistance, the multimodal therapy yielded a 5-year disease-free survival. This is the longest reported period for small cell carcinoma of the vulva. There is only one report of a disease-free survival of < 2 years after treatment with surgery and chemotherapy [3]. All other described patients died postoperatively or within 2.5 years [1, 4, 13, 18].

The successful treatment combined systemic therapy analogous to SCLC with local therapy used in cervical cancer. Inoperable carcinomas of the vulva are treated with radiochemotherapy in analogy to cervix cancer due to histological similarities [15–17]. The addition of hyperthermia was also based on the analogy to cervical carcinoma [5]. A beneficial effect of additional hyperthermia in combination with radiochemotherapy on EPSCC was also substantiated for small cell esophageal cancer [14].

Conclusion

This is the first report of small cell vulva carcinoma with a long-term disease-free survival of 5 years treated by an encouraging multimodal concept. We arrive at the conclusion that aggressive local treatment should be considered even in

patients with advanced, inoperable and chemotherapy-refractory limited disease of EPSCC.

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