Management of patients with vulvar cancer: a perspective review according to tumour stage

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Abstract: Treatment of patients with vulvar cancer is challenging for gynaecologic oncologists. Owing to the localization in a sensitive area, surgical radicality and the indication for adjuvant treatment have to be balanced with psychosocial aspects to treat patients adequately. Clinical management is therefore highly dependent on the tumour stage. For patients with early-stage disease (FIGO I–II) therapy mainly concentrates on surgery with resection of the primary tumour and staging of the groin lymph nodes. In intermediate-stage vulvar cancer (FIGO III), advanced disease is expressed by affected inguinofemoral lymph nodes bringing radical lymphadenectomy and adjuvant therapy as well as radiation or chemoradiation into the focus of treatment. For locally advanced or metastatic vulvar cancer (FIGO IV) neoadjuvant or definitive chemoradiation has to be considered besides surgery. Owing to the low incidence of the disease, the level of evidence for different treatment modalities is poor. This review therefore puts different recommendations of clinical management in context and highlights the need for future trials.

Keywords: adjuvant therapy, chemoradiation, locally advanced tumour, radiotherapy, surgery, treatment, vulvar cancer

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Introduction

Clinical management of vulvar cancer implies several challenges for the treating gynaecologic oncologist. Although representing a rare disease of elderly women with a current incidence of 2–3 per 100,000 women and a median age of 65–70, vulvar cancer has shown an increasing incidence (20% between 1973 and 2000) with concurrently decreasing median age at onset over the past few decades [Beller *et al.* 2006; Judson *et al.* 2006]. While risk factors for the development of vulvar cancer include smoking, immunosuppressive disease and chronic skin diseases of the vulva such as lichen sclerosus [Madsen *et al.* 2008; Messing and Gallup, 1995], these trends can most likely be attributed to an increasing number of human papillomavirus (HPV) infections. Therefore, younger and sexually active women are affected and the scope of surgical treatment has been put to reduce surgical radicality and morbidity but still guarantee oncologic safety for the patients.

In contrast to preinvasive lesions (vulvar intraepithelial neoplasia [VIN]) and microinvasive carcinoma (≤2 cm size and ≤1 mm stromal invasion, International Federation of *Gynaecology and Obstetrics* [FIGO] stage IA), surgical management of vulvar cancer from FIGO stage IB includes groin surgery in addition to local tumour resection according to current treatment recommendations. Lymph-node involvement [Pecorelli, 2009] has been proven to represent the most important prognostic factor for recurrence and survival [Gadducci *et al.* 2006]. While 5-year disease-specific survival in patients with negative inguinofemoral lymph nodes is fairly good with a range from 70% to 93%, it significantly decreases to 25–41% in patients with lymph-node metastases [Gadducci *et al.* 2006; Woelber *et al.* 2009, 2012a].

In addition to surgery, treatment of vulvar cancer comprises further treatment modalities such as radiotherapy and chemotherapy, especially for

locally advanced and metastatic disease. However, due to the low incidence of the disease randomized controlled trials are lacking; indication criteria for different treatment modalities therefore remain controversial with alternating levels of evidence.

This review aims to give a perspective overview of the current literature on vulvar cancer highlighting previous changes and improvements as well as demonstrating future directions of clinical management. As therapeutic approaches differ according to tumour stage, current treatment recommendations are discussed separately for patients with early-stage (FIGO stage I–II, no lymph-node involvement), intermediate-stage (FIGO stage III, affected lymph nodes in the groins) and locally advanced or metastatic vulvar cancer (FIGO stage IV). These recommendations are put into context and the need for future trials is elaborated.

Management of early-stage vulvar cancer (FIGO I–II)

Surgical treatment of early-stage vulvar cancer

Radical surgical therapy referred to as 'butterfly resection' including radical vulvectomy *en bloc* with bilateral inguinofemoral lymphadenectomy was the standard of care up to the 1990s. The aim of this approach was to remove all tissue possibly involved including the skin bridge between vulva and groins. Given the large surgical extent in a sexually sensitive area irrespective of the stage of disease, this procedure has been experienced as mutilating by the patients with significant morbidity and consecutive psychosexual impairment. To avoid overtreatment, increasing efforts to modify surgical management were undertaken [Lin *et al.* 1992; Magrina *et al.* 1998]:

Byron and colleagues first introduced a triple incision technique consisting of radical vulvectomy with bilateral inguinofemoral lymphadenectomy from three separate incisions to overcome the extensive butterfly resection [Byron *et al.* 1962]. Concerns considering skin bridge recurrence could be refuted due to a low recurrence risk of 2.4% and significantly reduced surgical morbidity, such as wound breakdown and lymphatic drainage problems [Byron *et al.* 1962; Lin *et al.* 1992; Siller *et al.* 1995]. Several groups confirmed that vulvectomy and bilateral lymphadenectomy via three separate incisions lead to similar overall outcome [Ansink and van der Velden, 2000; Heaps *et al.* 1990; Olawaiye *et al.* 2007]. However, as this technique still requires the complete removal of the external genitalia, the overall benefit in terms of psychosocial aspects remained limited.

Overcoming the paradigm of a need for complete vulvectomy in favour of radical local excision marked another important step to further reduce surgical morbidity and especially to preserve the sexual identity of affected patients. For early-stage disease, the oncologic safety of this technique could be proven [Burke *et al.* 1995; Farias-Eisner *et al.* 1994], even though the extent of the tumour-free resection margin after wide local excision is still under debate and subject of many controversial discussions until today. Although current guidelines recommend a surgical resection margin of at least 1 cm, there are several studies indicating that the extent of resection margins seems to be of minor importance. Some studies could demonstrate a higher risk for disease recurrence when the pathological tumour-free margin was less than 8 mm, while recent analyses failed to show any impact of the margin distance for prognosis [Burke *et al.* 1995; DiSaia *et al.* 1979; Hampl *et al.* 2009; Kunos *et al.* 2009; Wittekind and Meyer, 2002; Woelber *et al.* 2011]. As it is unlikely that there will ever be randomized trials addressing this problem, this will remain an open point of discussion.

Recommendations for groin surgery in early-stage vulvar cancer

It has been shown that for microinvasive FIGO stage IA carcinomas (≤2 cm size and ≤1 mm stromal invasion) local recurrence after primary complete tumour excision is rare and lymph-node metastases were observed only in isolated cases [Hampl *et al.* 2009; Kelley *et al.* 1992; Magrina *et al.* 1979; Sidor *et al.* 2006]. Therefore, groin surgery is currently not recommended in these cases. As the risk of lymph-node metastasis considerably rises beyond 1 mm invasion depth (7–8% for 1.1–3.0 mm invasion, 26–34% for >3 mm invasion), staging of the groins is always indicated from FIGO stage ≥IB [Homesley *et al.* 1993].

However, differentiation between the need for therapeutic radical inguinofemoral lymphadenectomy in contrast to surgical staging of the groins has been progressively investigated over recent years.

Considering the substantial morbidity of radical lymphadenectomy and the fact that only 25–30% of the patients present with lymph-node metastases at first diagnosis [Bell *et al.* 2000; Gaarenstroom *et al.* 2003; Rouzier *et al.* 2002; Woelber *et al.* 2009], sentinel node dissection is considered a favourable alternative for patients with clinically node negative groins.

As this technique has become a standard procedure for surgery of breast cancer and malignant melanoma, Levenback and colleagues were the first to perform sentinel node biopsy in vulvar cancer [Levenback *et al.* 1994]. Since then, technetium-99m-labelled colloid (Tc99m) with or without blue dye is applied with very high detection rates of the sentinel lymph node ranging up to 100% [De Cicco *et al.* 2000; Sliutz *et al.* 2002]. Nevertheless, due to poor prognosis after groin recurrence, false-negative results during initial surgery have to be strictly avoided.

Conflicting results in smaller and retrospective reports have been most likely related to indistinct inclusion and exclusion criteria, while the first large prospective multicenter study (GROINSS-V) by van der Zee and colleagues revealed good evidence for the application of the sentinel technique with Tc99m [van der Zee *et al.* 2008].

In this study, 403 patients with unifocal vulvar cancer, tumour size <4 cm, stromal invasion >1 mm and clinically negative lymph nodes were included [van der Zee *et al.* 2008]. In sentinel-negative patients lymphadenectomy was omitted leading to groin recurrences in only 2.3% within a median follow up of 35 months. This rate is comparable with groin recurrence rates (0.0–2.4%) previously described in early-stage vulvar cancer patients receiving full inguinofemoral lymphadenectomy [Bell *et al.* 2000; Hacker *et al.* 1983; Rodolakis *et al.* 2000]. As morbidity was significantly reduced with similar overall disease-specific survival of 97% after 3 years [van der Zee *et al.* 2008], this approach needs to be considered in current treatment recommendations and patients with unifocal vulvar cancer, a tumour size <4 cm and clinically negative groins should be offered sentinel node dissection. An important requirement for this recommendation is that negative sentinel lymph nodes are thoroughly examined by so-called 'ultrastaging' (three sections per millimetre and immunostaining with cytokeratine AE1/AE3) according to the study protocol of the GROINSS-V trial. In this study 41.7% of all lymph-node metastases were detected solely by ultrastaging and would have been missed by the common staging procedures [Han *et al.* 2000]. As the significance of micrometastases and isolated tumour cells was not investigated in this trial, inguinofemoral lymphadenectomy should be conducted in any stage of detected nodal disease. Most centres perform this procedure as a bilateral groin dissection even in patients with only unilateral sentinel lymph-node metastasis. This approach is performed on the basis of a contralateral groin recurrence rate of 2.6% in cases of a unilateral tumour with positive ipsilateral nodes and only unilateral radical groin dissection as opposed to a rate of only 0.4% in cases with negative ipsilateral nodes [Andrews *et al.* 1994; Farias-Eisner *et al.* 1994; Stehman *et al.* 1992].

However, whether a complete bilateral groin dissection is really necessary in the case of a positive sentinel node in the ipsilateral groin of a unilateral vulvar cancer has not been assessed systematically. Based on the assumption that the negative sentinel of the contralateral groin is representative for the other lymph nodes of this side, a subsequent complete groin dissection of the respective side might be avoidable.

As preoperative differentiation between FIGO stage IA and IB vulvar cancer can sometimes be difficult even after punch biopsy, some patients will undergo vulvar surgery for diagnosis or suspected microinvasive carcinoma without nodal staging. If definitive histology then shows a tumour with invasion depth of greater than 1 mm, secondary lymph-node staging becomes mandatory. Recently, there is emerging evidence that sentinel node biopsy can be performed secondary to previous vulvar surgery in those patients, also accurately reflecting the groin status of the patients in these cases [Woelber *et al.* 2012b].

With the favourable prognosis of patients suffering from early-stage vulvar cancer with negative groin status, usually no adjuvant treatment is indicated.

Management of intermediate-stage vulvar cancer (FIGO III)

Recommendations for groin surgery in intermediate-stage vulvar cancer

As recent analyses have shown that already one intracapsular lymph-node metastasis leads to a

significantly impaired prognosis compared with node-negative disease, it is agreed that these patients require systematic groin surgery [Gadducci *et al.* 2006; Woelber *et al.* 2009]. For this procedure, it is not sufficient to concentrate on superficial inguinal lymphadenectomy as recurrences in deep femoral lymph nodes have been observed [DiSaia *et al.* 1979; Levenback *et al.* 1996; Micheletti *et al.* 1990]. Therefore, groin surgery has to comprise inguinofemoral lymphadenectomy. According to current guidelines the resection of at least six nodes per groin is recommended to ensure complete dissection [Wittekind and Meyer, 2002], although the prognostic impact of the number of removed lymph nodes is not yet clearly determined. However, for FIGO stage III disease it could be demonstrated that a high number of removed nodes seems to be associated with better survival, highlighting the importance of a radical lymphadenectomy in intermediate-stage vulvar cancer [Courtney-Brooks *et al.* 2010]. In contrast, high complication rates have to be considered. Systematic inguinofemoral lymphadenectomy is associated with leg oedema in 47.0%, lymphocysts in 40.0%, wound breakdown in 38.3% and erysipelas in 29.1% of cases as reported previously [Gaarenstroom *et al.* 2003; Rouzier *et al.* 2002].

Recommendations for radiotherapy in intermediate-stage vulvar cancer

As patients with lymph-node metastases have a significantly impaired prognosis, adjuvant radiotherapy is an established tool to improve their outcome [DiSaia *et al.* 1979].

In this context, the evidence for indication of adjuvant radiotherapy to the vulva itself is extremely poor. Apart from the indication when complete resection of the primary tumour could not be achieved [de Hullu and van der Zee, 2006], further recommendations are not clearly defined. Although lymph-node metastases, lymphangioinvasion and large primary tumours (≥4 cm) have been described to be correlated with increased risk for local recurrence, there are no clear treatment recommendations for radiotherapy to the vulva itself based on these findings [Burger *et al.* 1995; Woelber *et al.* 2009].

While some studies did not observe any association between the number of metastatic lymph nodes and the risk of recurrence, other analyses identified two or more nodes, extracapsular spread and large size of the metastases as predictors for poor prognosis [Lataifeh *et al.* 2004; Origoni *et al.* 1992; Paladini *et al.* 1994; van der Velden *et al.* 1995]. Recent analyses show that already one intracapsular lymph-node metastasis leads to a significantly impaired prognosis compared with node-negative patients [Oonk *et al.* 2010] and in a further analysis from our group, the number of affected nodes was highly relevant for prognosis in the group of patients without adjuvant treatment, diminishing in patients with adjuvant radiotherapy [Woelber *et al.* 2012a].

A substantial clinical benefit of adjuvant radiotherapy has been clearly demonstrated for patients with two or more lymph-node metastases, whereas the role of radiation in patients with a single intracapsular metastasis remains controversial [Homesley *et al.* 1986; Oonk *et al.* 2010]. Fons and colleagues could not demonstrate a benefit of adjuvant radiotherapy in patients with only one affected lymph node regarding overall or disease-free survival [Fons *et al.* 2009]. Conflicting results exhibited a Surveillance Epidemiology and End Result program (SEER) analysis, demonstrating a favourable prognosis in patients with a single positive lymph node receiving radiotherapy although information about the spread and size of metastases were not given in this study [Parthasarathy *et al.* 2006]. However, these results are supported by recently presented data from the largest retrospective multicenter study on vulvar cancer (AGO CaRE-1) with more than 1600 patients revealing an improvement of prognosis by adjuvant radiotherapy irrespective of the number of affected nodes [Mahner *et al.* 2012].

Notably, pelvic lymph nodes are also affected in 20–30% of the patients with inguinofemoral lymph-node metastases, with increasing risk according to the number of affected groin lymph nodes [Curry *et al.* 1980; Hacker *et al.* 1983]. To the best of the authors' knowledge, there are no reports of patients with negative inguinofemoral but positive pelvic lymph nodes. Therefore, adjuvant treatment of pelvic lymph nodes is solely recommended in patients with metastatic inguinofemoral lymph nodes.

The role of surgery with pelvic lymphadenectomy in the case of inguinofemoral metastasis is of minor importance for vulvar cancer as the only available randomized trial revealed that pelvic radiotherapy is superior to surgery regarding

overall survival [Homesley *et al.* 1986]. Owing to the persistent benefit for patients treated with pelvic irradiation in long-term follow up of the 114 patients, the study of Homesley and colleagues determines the current standard of care despite some methodical difficulties (e.g. patients with positive groin nodes in the surgery group did not receive adjuvant radiotherapy to the groins) [Kunos *et al.* 2009].

In conclusion, adjuvant radiotherapy of the groins and pelvis should currently be recommended after radical groin dissection in the case of two or more affected lymph nodes or in the case of one metastasis with extracapsular spread or large size. In the case of only one intracapsular metastasis, the role of radiotherapy is currently of unclear significance and needs to be further investigated.

Adjuvant chemotherapy or chemoradiation

The value of adjuvant chemotherapy or chemoradiation in vulvar cancer patients with lymph-node metastases has not been systematically addressed so far.

The first trial looking at chemotherapy as a sole adjuvant strategy was conducted by Bellati and colleagues who treated 14 patients with single-agent cisplatin after radical surgery for advanced vulvar cancer in an adjuvant setting [Bellati *et al.* 2005]. None of these patients received radiotherapy and only patients with two or more affected inguinofemoral lymph nodes were included. This treatment led to promising results with 3-year progression-free survival of 71% and overall survival of 86% [Bellati *et al.* 2005]. However, considering the small number of patients and first report of this therapeutic strategy for vulvar cancer, this approach cannot be recommended yet outside of clinical trials.

Han and colleagues compared survival rates in a group of 54 patients who received chemoradiation or radiation alone as primary treatment or in an adjuvant setting [Han *et al.* 2000]. Survival rates were generally higher in patients receiving chemoradiation but the difference was not statistically significant. There have been efforts to conduct clinical trials investigating the potential benefit of adjuvant chemoradiation, but studies were closed due to poor patient recruitment [Moore *et al.* 2005]. However, as adjuvant chemoradiation was shown to be superior to radiotherapy alone in many other squamous cell carcinomas (e.g. cervical and anal cancer), prospective phase III trials for node-positive vulvar cancer are urgently needed to address this question.

Management of locally advanced or metastatic vulvar cancer

Recommendations for surgery and radiotherapy in locally advanced vulvar cancer

In case of locally advanced vulvar cancer with affected neighbouring structures, usually radical vulvectomy with bilateral inguinofemoral lymphadenectomy and partial or complete resection of the urethra, vagina or anus is performed if the aim of clear resection margins appears feasible.

In some cases pelvic exenteration and/or (partial) resection of affected bones or muscles is indicated to completely remove all affected tissue. This surgical treatment option had been introduced and adopted for vulvar cancer in the 1970s [Thornton and Flanagan, 1973].

Plastic reconstructive surgery is usually necessary and requires experienced surgeons for adequate results. Local fasciocutaneous skin flaps can be applied for minor defects, while regional myocutaneous skin-flaps are frequently needed to cover large defects [Hockel and Dornhofer, 2008; Weikel *et al.* 2005]. Owing to high rates of post-surgical complications, long periods of hospitalization are frequently needed, limiting the quality of life of the patients.

As defined as exclusion criterion in the GROINSS-V trial [van der Zee *et al.* 2008], patients with primary tumours ≥4 cm and locally advanced vulvar cancer should not be considered for sentinel technique to stage the lymph-nodes of the groins. These patients still require systematic inguinofemoral lymphadenectomy irrespective of clinically negative groin status. In the case of bulky lymph nodes the benefit of a full groin dissection remains unclear. Although similar outcomes could be shown in patients only undergoing lymph-node debulking in contrast to systematic lymphadenectomy prior to planned radiation therapy in a retrospective analysis by Hyde and colleagues, no significant effect on surgical morbidity, especially lymph oedema, could be demonstrated [Hyde *et al.* 2007].

In the case of positive inguinofemoral lymph nodes with more than two lymph nodes affected, lymph-node metastases with extracapsular spread or great size, radiotherapy of the groins and pelvis should be performed as indicated in intermediate-stage vulvar cancer. In addition, irradiation of the vulva might be considered for these patients in cases of large, locally advanced tumours although the level of evidence for this recommendation is low (see above). Wound healing after extensive surgery, postsurgical clinical condition and size of tumour-free resection margin always have to be taken account when considering adjuvant radiotherapy of the vulva.

Radiotherapy or chemoradiation in advanced vulvar cancer

Definitive radiotherapy as primary treatment for advanced vulvar cancer is an option to treat patients not suitable for a surgical approach for different reasons (e.g. localization of the tumour, comorbidities). It can be applied by external beam radiation therapy (EBRT) or by brachytherapy. Based on a first report of 58 patients receiving primary radiotherapy in 1989 [Slevin and Pointon, 1989], further small studies have been published revealing good clinical response of the tumour [Pohar *et al.* 1995; Sharma *et al.* 2010].

In contrast to that, the concept of primary chemoradiation as a neoadjuvant therapy represents a promising option to reduce tumour volume, achieve resectability of the tumour and reduce the extent of surgery for patients with advanced vulvar cancer [Hoffman, 2003]. It might be of distinct significance in vulvar cancer to prevent radical and mutilating surgeries such as anterior or posterior exenteration. In several trials either neoadjuvant radiotherapy or combined chemoradiation have been evaluated. However, no randomized trials have been published so far.

Therefore, the clinical experiences from other squamous cell carcinoma as cervical or anal cancer serve as examples to adopt therapeutic regimens. In a first GOG phase II study chemoradiation with cisplatin and 5-fluorouracil was investigated for patients with advanced vulvar cancer [Moore *et al.* 1998]. In 24 of 71 enrolled patients (33.8%) complete pathologic remission could be achieved and in 34 patients (47.9%) all visible tumour diminished after neoadjuvant treatment. In a subsequent GOG phase II study chemoradiation with weekly single agent cisplatin was investigated. A total of 37 of the included 58 patients (63.8%) showed complete clinical response and in 29 patients (50%) complete pathologic remission could be achieved with acceptable toxicity [Moore *et al.* 2012]. Following these encouraging results, weekly cisplatin should be applied for chemoradiation although mitomycin C and 5-flurouracil might be serve as alternative regimens (complete response rates of 30–70%) in the case of contraindications for cisplatin [Tans *et al.* 2010].

However, increased morbidity of the patients and significantly higher complication rates for surgical interventions following combined neoadjuvant chemoradiation have to be considered. Furthermore, the impact of tumour bed resection in cases of pathological complete remission has not been determined so far. Therefore, a Cochrane review of five studies on neoadjuvant chemoradiation recommends this treatment modality only very cautiously although achievement of operability was reported in 63–92% of cases [van Doorn *et al.* 2006]. A further more recent Cochrane review compared neoadjuvant chemoradiation with primary surgery in three published studies. In this report no statistical significant effects on prognosis or toxicity could be shown although several bias were noted (e.g. not standardised definition for 'operable and inoperable vulvar cancer') obviously limiting the conclusions of the review [Shylasree *et al.* 2011]. Further investigations on this treatment modality are therefore required.

Systemic treatment for advanced or metastatic vulvar cancer

When surgery or radiotherapy is not an option, systemic treatment has to be considered for recurrent or metastatic disease. Combination therapy with cisplatin and vinorelbine lead to a progression-free survival of 10 months and overall survival of 19 months in a group of patients with recurrent disease after radiotherapy [Cormio *et al.* 2009]. In a further study enrolling patients with locally advanced vulvar cancer the efficacy of a combination therapy with bleomycin, methotrexate and lomustine was analyzed (median overall survival 7.8 months) although significant side effects were noted [Wagenaar *et al.* 2001]. Single-agent therapy with weekly paclitaxel appears to be less effective, with a mean progression-free survival of only 2.6 months [Witteveen *et al.* 2009]. Efficacy analysis across these trials is difficult due to heterogeneous in- and exclusion criteria, so that to date none of the regimens can be generally recommended for routine application. According to clinical

experience with other squamous cell carcinomas, it is suggestive that a platinum-based chemotherapy might be effective in vulvar cancer as well. Therefore, platinum-based regimens as recommended for advanced cervical cancer (e.g. cisplatin/paclitaxel) might be considered for vulvar cancer if palliative chemotherapy is indicated [Monk *et al.* 2009].

In addition to chemotherapy, targeted therapies might serve as an alternative therapeutic approach for metastatic and inoperable vulvar cancer. In this context, the use of the anti-EGFR tyrosine kinase inhibitor erlotinib showed promising results in selected cases [Olawaiye *et al.* 2007]. More recently, the first phase II trial evaluating erlotinib for the management of vulvar cancer has been published by Horowitz and colleagues observing an overall clinical benefit rate of 67.5% with moderate but acceptable toxicity [Horowitz *et al.* 2012]. However, this benefit was of only short duration so that the application of erlotinib in clinical routine should currently be reserved for special clinical indications.

Summary

Prognosis of vulvar cancer patients is mainly determined by the tumour stage at initial diagnosis. Patients with early-stage disease have a fairly good prognosis with the need for an individualized treatment plan and a less radical surgical approach. Local tumour resection instead of radical vulvectomy and the implementation of the sentinel technique have decreased therapy-associated morbidity and psychosocial impairment in these patients while oncologic safety could be maintained.

In contrast, management of intermediate-stage or advanced disease represents a clinical challenge requiring different treatment modalities. In addition to primary radical surgery with systematic inguinofemoral lymphadenectomy and adjuvant radiation of the vulva, groins and pelvis, neoadjuvant approaches with chemoradiation might be considered analogous to experience in other squamous cell carcinomas. For recurrent or metastatic disease, promising first efficacy results of targeted therapeutics such as anti-EGFR tyrosine kinase inhibitors need to be further investigated as the current chemotherapeutic strategies show very limited clinical benefit.

Owing to the challenging requirements for adequate oncologic treatment of vulvar cancer patients, centralization of clinical resources is important to achieve an optimal management. Furthermore, it will also be necessary for design and recruitment of the urgently needed prospective controlled trials in this still relatively rare disease.

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