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Review

Clinical management of primary vulvar cancer

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ABSTRACT

Aims: Vulvar cancer is a rare disease with increasing incidence over the last decades. Treatment includes surgical, radio- and chemotherapeutical options; however, due to the low incidence of the disease and the lack of randomised trials many questions regarding indication of different treatment approaches remain unanswered. This article discusses the current literature to elaborate recommendations for the management of primary vulvar cancer in clinical routine.

Methods: We reviewed the available literature on treatment of invasive vulvar cancer with emphasis on therapeutic strategies such as surgery and radio/chemotherapy.

Results: Surgery of the primary tumour and the groins remain the cornerstone of treatment in vulvar cancer with a strong trend towards a less radical approach in early stage disease. Complete vulvectomy was replaced by radical local excision with plastic reconstruction and the sentinel node technique was implemented to avoid the morbidity of complete groin dissection in node negative patients. In patients with advanced primary disease, treatment decisions are still a challenge. Criteria for the indication and performance of chemo/radiotherapy of the vulva/groins/pelvis are still not fully established and vary between different countries and institutions due to the low level of evidence. Often an individualised therapeutic approach aside from guidelines is necessary to treat these patients adequately.

Conclusions: To enable reasonable treatment decisions and avoid unnecessary morbidity, treatment in specialised centres should be intended at any time. Clinical studies performed by several study groups on an international level are urgently needed to further improve therapy.

1. Introduction

Vulvar cancer is a rare disease with an incidence of 2–3 per 100,000 women. Traditionally it affects elderly women with a median age of 65–70.[1] The vast majority are squamous cell carcinomas (90%). Prognosis is strongly correlated to lymph-node involvement and therewith the stage of disease: five-year survival varies from 78.5% in FIGO stage I to 13.0% in

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FIGO IV disease.[1] Risk factors for development of vulvar cancer include smoking, human papilloma virus (HPV) infection, immunosuppressive disease, and chronic skin diseases of the vulva such as lichen sclerosus.[2] Incidence of vulvar cancer has risen during the past decades with an increase of 20% between 1973 and 2000.[3] In addition, there is a trend towards younger women being affected.[4] Both trends are likely associated with an increasing number of HPV infections. The higher number of young and sexually active women affected has caused efforts to change practice with emphasis on organ preserving interventions.

Treatment of vulvar cancer includes surgical, radio- and chemotherapeutical options; however, due to the low incidence of the disease and the lack of randomised trials many questions regarding indication of different treatment approaches remain unanswered. Most of the changes in treatment of vulvar cancer were not preceded by and grounded on large clinical trials but are based on scarce evidence.

This article discusses the current literature to elaborate recommendations for the clinical management of patients with primary vulvar cancer. Different treatment modalities and their indication are addressed under consideration of the levels of evidence (LoE) available. Figs. 1 and 2 demonstrate possible approaches with respect to different stages of disease.[5]

2. Surgical management

To date, surgery is still the therapy of first choice for locoregional vulvar cancer. Surgical procedures comprise resection of the primary tumour as well as the inguinofemoral lymph-nodes. Exceptions are so called microinvasive carcinomas ($\leqslant$2 cm size and $\leqslant$1 mm stromal invasion): Local recurrence after excision of these tumours is rare and lymph-node metastases were observed in isolated cases only.[6–9] Therefore, groin surgery is currently not recommended for microinvasive vulvar cancer (LoE 4). In tumours with an invasion depth >1 mm, surgical staging of the groins is indicated as the risk of lymph-node metastasis is considerably increasing beyond 1 mm invasion (7–8% for 1.1–3.0 mm invasion, 26–34% for >3 mm invasion).[10]

Up to the 1990's, radical vulvectomy en bloc with bilateral inguinofemoral lymphadenectomy ('butterfly resection') has been the standard therapy. The aim of radical en bloc resection was to remove all tissue possibly involved in vulvar cancer including the skin bridge between vulva and groins. However, the severe morbidity of this mutilating procedure as well as the consecutive psychosexual impairment was a very high price for the treatment. Therefore increasing efforts to modify the therapeutic strategy were undertaken.[11,12]

2.1. *Triple incision technique*

An approach to reduce morbidity while preserving adequate local control was made by Byron who first introduced the triple incision technique.[13] To date, no prospective randomised controlled trials comparing butterfly procedure and triple incision technique with regard to oncologic safety have been performed. However, several groups could retrospectively demonstrate that vulvectomy and inguinofemoral lymphadenectomy via three different incisions probably provide similar outcome compared to butterfly resection with a low risk of skin bridge recurrence (2.4%) (LoE 3b).[14–17] Compared to en bloc resection, rates of associated morbidity, such as wound breakdown and lymphatic drainage problems, were significantly lower with the triple incision technique.[12] Nevertheless, this technique still includes the complete removal of the external female genitals.

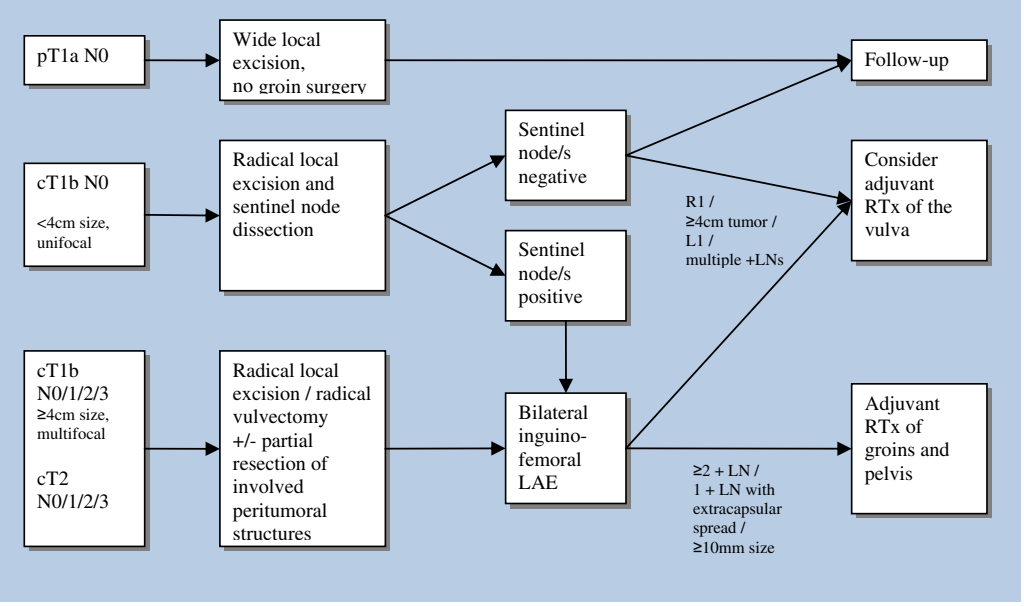

Fig. 1 – Treatment strategies in locally restricted vulvar cancer (RTx = radiotherapy, LN = lymph-node, LAE = lymphadenectomy, R1 = non in sano resection after completion of the surgical treatment).

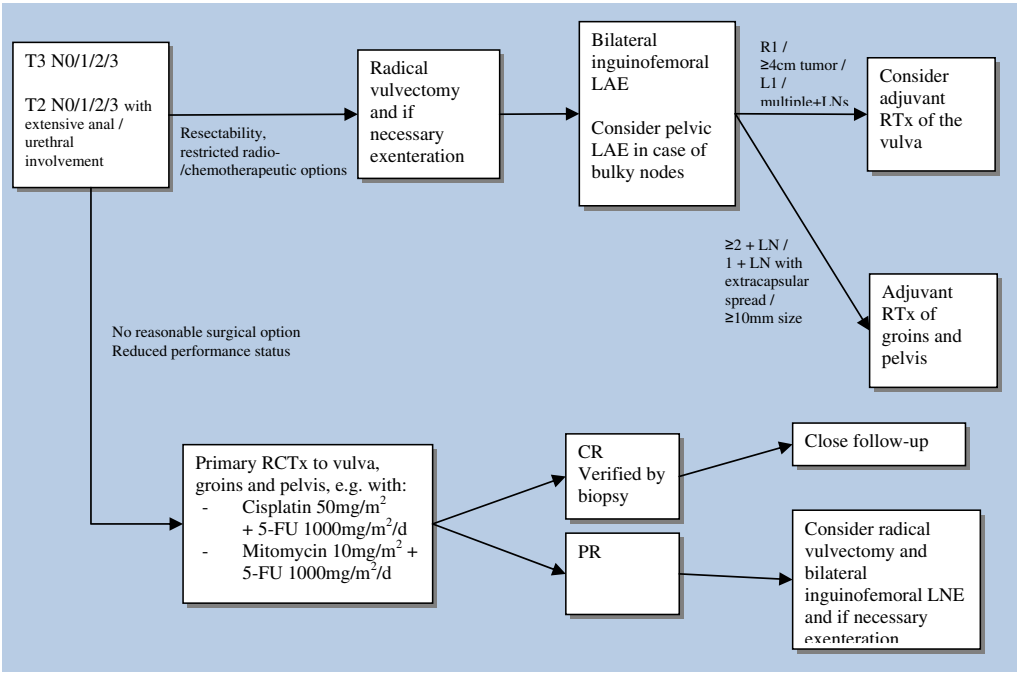

Fig. 2 – Treatment strategies in advanced vulvar cancer (RTx = radiotherapy, LN = lymph-node, LAE = lymphadenectomy, R1 = non in sano resection after completion of the surgical treatment, CR = complete remission, PR = partial remission).

2.2. *Radical local excision*

The introduction of radical local excision instead of complete vulvectomy was an important step towards further reduction of surgical morbidity. In case control studies, no confinement in oncologic safety was observed in patients with early stage disease.[18,19] As for butterfly procedure and triple incision technique, no randomised controlled trials comparing radical local excision and complete vulvectomy have been performed. A Cochrane review by Ansink and van der Velden[14] and others[18,19] considering two observational studies concluded, however, that radical local excision represents a safe alternative to radical vulvectomy (LoE 3b).

The extent of the tumour-free resection margin in radical local excision remains a matter of debate until now. Despite current guidelines recommending a surgical resection margin of at least 1 cm, available literature provides conflicting information: 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[15,20–24] (LoE 3b). These recent findings challenge current recommendations and point out that the extent of resection margins may be of minor importance when the tumour has been excised completely.

2.3. *Groin surgery*

Systematic inguinofemoral lymphadenectomy comprises resection of superficial inguinal lymph-nodes as well as deep femoral nodes; as recurrences in deep femoral lymph-nodes have been observed after superficial lymphadenectomy only (LoE 3b).[14,15,19] For the resection of inguinal lymph-nodes, the fatty tissue beneath the subcutaneous tissue down to the fascia lata is removed. Recommendations for the cranial and caudal limits of this resection vary between authors. After splitting the fascia lata, the fatty tissue medial to the femoral vessels within the opening of the fossa ovalis is resected to perform femoral lymphadenectomy. The fascia lata lateral to the femoral vessels can be preserved.[25] The prognostic impact of the number of lymph-nodes removed is unclear. In FIGO stage III patients, a high number of removed nodes might be associated with a better survival, underlining the importance of a radical lymphadenectomy.[26] Current guidelines therefore recommend a number of at least six nodes per groin to assure complete dissection (LoE 4).[27]

However, systematic inguinofemoral lymphadenectomy is associated with substantial morbidity. Leg oedema (47.0%), lymphocysts (40.0%), wound breakdown (38.3%) and erysipelas (29.1%) are the most common complications.[28,29] With inguinal lymph-node metastases present in approximately 25–30% of vulvar cancer patients, more than two thirds of patients are probably overtreated by radical groin dissection facing the high risk of morbidity.[30,31] Sentinel node dissection might therefore be a favourable approach in patients with clinically negative nodes.

Sentinel lymphadenectomy is a standard procedure in surgery of breast cancer and malignant melanoma. In vulvar cancer, Levenback et al. was the first to perform sentinel node biopsy, applying blue dye intraoperatively.[32] Consecutively, technetium-99m-labelled colloid (Tc99m) was used together with or instead of blue dye, resulting in better detection rates.[33,34] In vulvar cancer, detection rates of the sentinel lymph-node are very high ranging up to 100%, even with labelled colloid alone.[35,36] Given the poor prognosis of groin recurrence in vulvar cancer, a very low rate of false negative

sentinel nodes is mandatory. Several groups performed sentinel node biopsy followed by systematic inguinofemoral lymphadenectomy within the same operation, showing a low rate or even no false negative sentinel nodes when using nanocolloid.[35,37] Unfavourable safety results have also been published: In a German multicentre trial of 127 patients a false negative rate of 7.7% was reported.[38] However, neither multifocal disease nor large tumour size had been the exclusion criteria in this trial. Furthermore surgeons' experience with sentinel procedures was no prerequisite.

The first large prospective multicentre study (GROINSS-V) was conducted by van der Zee et al.: 403 patients with unifocal vulvar cancer stages I and II, tumour size <4 cm, stromal invasion >1 mm and clinically negative lymph-nodes were included.[39] In sentinel-negative patients, lymphadenectomy was omitted. Groin recurrences occurred in 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 systematic inguinofemoral lymphadenectomy.[40–42] Overall disease-specific survival was 97% after 3 years and morbidity was clearly reduced in patients with sentinel lymphadenectomy compared to patients with radical inguinofemoral lymphadenectomy.[39]

It is important to emphasise that all negative sentinel nodes in the GROINSS-V trial were thoroughly examined by so-called 'ultrastaging' (three sections per millimetre and immunostaining with cytokeratine AE1/AE3) and 41.7% of all lymph-node metastases were detected solely by this approach.

Based on the convincing results of the GROINSS-V trial, every patient with unifocal vulvar cancer, a tumour size <4 cm and clinically negative groins should be offered sentinel node dissection (LoE 1b). As the significance of micrometastases and isolated tumour cells is currently not clear, bilateral inguino-femoral lymphadenectomy should be performed when disease of any stage is detected in the sentinel nodes.

In case of bulky nodes the benefit of complete inguinofemoral lymphadenectomy is not clear. Hyde et al. performed a retrospective analysis showing that lymph node debulking followed by irradiation might provide equivalent outcome compared with complete lymphadenectomy prior to irradiation[43] (LoE 4). However, a significantly decreased morbidity after lymph node debulking only, especially concerning lymph oedema, could not be demonstrated by this analysis.

3. Radiotherapy

Lymph-node metastases are the most important prognostic factor in vulvar cancer. Five-year survival is 70–93% in patients with negative inguinofemoral lymph-nodes compared to 25–41% in patients with lymph-node metastases.[44] Adjuvant radiotherapy was shown to improve prognosis in patients with nodal involvement.[45] However, due to varying results regarding the prognostic impact of the number of metastatic lymph-nodes, the parameters determining adjuvant radiotherapy after groin dissection are still controversial. There are some studies not showing any association between the number of metastatic lymph-nodes and the risk of recurrence, while in other analyses involvement of two or more nodes, extracapsular spread and large size of the metastases were predictive of poor prognosis.[46–49] Recent analyses show that already one intracapsular lymph-node metastasis leads to a significantly impaired prognosis compared to node negative patients, with larger metastasis resulting in worse outcome.[50] The benefit of adjuvant radiotherapy was clearly demonstrated in patients with two and more lymph-node metastases (LoE 1b), while the role of radiation in patients with a single intracapsular lymph-node metastasis is still subject to discussion.[45,51] A recently published analysis by Fons et al. could not demonstrate a benefit of adjuvant radiotherapy in these patients regarding disease-free and disease-specific survival.[52] In contrast to that, a SEERs analysis demonstrated a favourable 5-year survival in patients with a single positive lymph-node receiving radiotherapy, however, information about the spread and size of metastases was not provided in this study.[53]

In case of positive inguinofemoral lymph-nodes, pelvic lymph-nodes are also affected in 20–30% of the patients.[54] The risk of metastases in pelvic lymph-nodes increases with the number of positive inguinofemoral nodes.[55] As there is no known case of positive pelvic and negative inguinofemoral lymph-nodes, adjuvant treatment of pelvic lymph-nodes is only recommended in patients with metastatic inguinofemoral lymph-nodes. There is one randomised trial comparing pelvic lymphadenectomy with pelvic irradiation showing that pelvic irradiation is superior to surgery with regard to overall survival.[45] This study has methodical difficulties as patients with positive groin nodes in the surgery group did not receive adjuvant radiotherapy to the groins. However, long-time results of this trial revealed a persistent benefit for patients treated with pelvic irradiation and it determined the current standard of care.[56]

In conclusion, adjuvant radiotherapy of the groins and pelvis should currently be performed after radical groin dissection in case of two or more affected lymph-nodes (LoE 1b). It should be considered in case of one metastasis with extracapsular spread and can be considered in case of large size of the metastasis (LoE 5). However, the value of adjuvant irradiation in cases with one intranodal metastasis remains unclear. The problem is further engraved by the increased detection of micrometastases in ultrastaging during sentinel procedures as we do not know the implications of $\geqslant 1$ micrometastases for adjuvant radiotherapy.

Criteria for the application of adjuvant radiotherapy to the vulva are even less clearly defined: irradiation is generally recommended when the primary tumour cannot be resected completely.[57] Few authors have described lymph-node metastases, lymphangio invasion and large primary tumours to be associated with an increased risk of local recurrence in vulvar cancer, but no clear recommendations regarding radiotherapy could be drawn from these findings so far (LoE 4).[58,59]

4. Chemoradiation

Combined chemoradiation is mainly used in advanced vulvar cancer involving neighbouring structures, where exenteration and/or (partial) resection of affected bones or muscles would be necessary to remove the cancer tissue with clear resection margins.[60]

Primary chemoradiation in a neoadjuvant setting is an option to reduce tumour volume, achieve resectability of the tumour and reduce the extent of surgery. Several trials have been conducted to evaluate neoadjuvant radiotherapy or combined chemoradiation, although no randomised trials have been published so far. Regimens are usually adopted from those used in cervical or anal cancer. A GOG phase II study examined patients with advanced vulvar cancer receiving chemoradiation with cisplatin and 5-fluorouracil.[37] Of 71 patients, 34 had no visible tumour after the treatment and 24 showed complete pathologic remission. Other authors used mitomycin C and 5-flurouracil as alternative regimen with complete response rates of 30–70%.[61]

The main disadvantage of combined chemoradiation is increased morbidity. Surgical interventions after completed chemoradiation have high complication rates and the impact of tumour bed resection in cases of complete remission is unclear. A Cochrane review of five studies on neoadjuvant chemoradiation showed considerable toxicity, therefore cautious indication of this treatment modality was recommended.[62] Nevertheless, this review also showed a high efficacy of chemoradiation as operability was achieved in 63–92% of cases. A recent second Cochrane analysis evaluated three studies regarding primary surgery versus neoadjuvant chemoradiation, including one randomised controlled trial. None of the studies showed a benefit for either treatment option and no differences in morbidity could be demonstrated. However, data are scarce with small study populations and the randomised controlled trial discussed has not been published as a full paper version but abstract only.[63]

In summary, information on neoadjuvant chemoradiation in vulvar cancer is limited; recommendations regarding the optimal drug regimen can therefore not be given. So far, platinum-based combined regimens seem to be the treatment of choice (LoE 3b).

The value of chemoradiation in an adjuvant setting in patients with lymph-node metastases has not been systematically addressed so far. Han et al. compared survival rates in a group of 54 patients who received chemoradiation or radiation alone as primary treatment or in an adjuvant setting.[64] Survival rates were generally higher in patients receiving chemoradiation but the difference was not statistically significant (LoE 3b). There have been efforts to conduct clinical trials investigating the potential benefit of adjuvant chemoradiation, but studies were closed due to poor patient recruitment.[65]

5. Chemotherapy and other agents

In primary vulvar cancer, chemotherapy as a single treatment modality is not a common approach. Adjuvant application of chemotherapy instead of radiotherapy in node positive primary disease was proposed by Bellati et al. They treated 14 patients with single agent cisplatin after radical surgery. Only patients with $\geqslant 2$ affected inguinofemoral lymph-nodes were included and radiotherapy was not performed. Three-year progression-free survival of 71% and overall survival of 86% were observed and represent promising results.[66] However, this small analysis is the only study addressing this therapeutic concept and consequently, this regimen cannot be recommended yet outside of clinical trials (LoE 4).

Chemotherapy without concomitant radiotherapy is mainly applied in primary metastatic disease when surgery or radiotherapy is not an option. Different chemotherapeutic regimens have been applied with varying benefit. Combination therapy with cisplatin and vinorelbin resulted in progression free survival of 10 months and overall survival of 19 months in a group of patients with recurrent disease after radiotherapy.[67] Another study demonstrated efficacy of the combination bleomycin, methotrexate and lomustine in patients with locally advanced vulvar cancer (median overall survival 7.8 months).[68] Probably less effective, with a mean progression-free survival of 2.6 months, was single agent therapy with paclitaxel, although comparison of efficacy across trials is difficult and patient cohorts in all these studies were very heterogeneous.[69] To date, sufficient data is not available for any of the applied regimens to generally recommend routine application (LoE 4). The use of Erlotinib, an anti-EGFR tyrosine kinase inhibitor, has raised some hope in the search for more efficient drugs beyond chemotherapy but so far, only case reports have been published (LoE 5).[70]

6. Summary

Vulvar cancer is a rare disease with good prognosis if diagnosed in early stage. Individualisation of surgery with less radical local approaches and implementation of the sentinel technique in early stages has led to decreased therapy-associated morbidity while preserving oncologic safety.

Advanced disease is a challenge for clinical management and requires an individualised approach. Combined chemoradiation achieves good response rates but can be associated with increased complication rates. Chemotherapeutic options in vulvar cancer are limited; targeted therapeutics like anti-EGFR tyrosine kinase inhibitors might be effective and potentially represent a future treatment option.

Given the low incidence of vulvar cancer and the lack of randomised multicentre studies, centralisation of care is highly desirable, not only to ensure optimal treatment but also to facilitate recruitment for upcoming trials.

Conflict of interest statement

The authors have no relevant affiliations or financial involvement with any organisation or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, Grants or patents received or pending, or royalties. No writing assistance was utilised in the production of this manuscript.

REFERENCES

1. Beller U, Quinn MA, Benedet JL, et al. Carcinoma of the vulva. *Int J Gynecol Obstet* 2006;**95**(Suppl. 1):S7–S27.

2. Madsen BS, Jensen HL, Van den Brule AJ, Wohlfahrt J, Frisch M. Risk factors for invasive squamous cell carcinoma of the vulva and vagina – population-based case–control study in Denmark. *Int J Cancer* 2008;**122**(12):2827–34.
3. Judson PL, Habermann EB, Baxter NN, Durham SB, Virnig BA. Trends in the incidence of invasive and in situ vulvar carcinoma. *Obstet Gynecol* 2006;**107**(5):1018–22.
4. Messing MJ, Gallup DG. Carcinoma of the vulva in young women. *Obstet Gynecol* 1995;**86**(1):51–4.
5. OCEBM Levels of Evidence Working Group. "The Oxford 2011 Levels of Evidence". Oxford Centre for Evidence-Based Medicine. http://www.cebm.net/index.aspx?o=5653
6. Hampl M, Kueppers V, Bender HG. Single large inguinal lymph node metastasis in human papillomavirus-induced early invasive vulvar cancer of the anterior fourchette in two young women. *Gynecol Obstet Invest* 2009;**67**(1):42–5.
7. Kelley 3rd JL, Burke TW, Tornos C, et al. Minimally invasive vulvar carcinoma: an indication for conservative surgical therapy. *Gynecol Oncol* 1992;**44**(3):240–4.
8. Magrina JF, Webb MJ, Gaffey TA, Symmonds RE. Stage I squamous cell cancer of the vulva. *Am J Obstet Gynecol* 1979;**134**(4):453–9.
9. Sidor J, Diallo-Danebrock R, Eltze E, Lelle RJ. Challenging the concept of microinvasive carcinoma of the vulva: report of a case with regional lymph node recurrence and review of the literature. *BMC Cancer* 2006;**6**:157.
10. Homesley HD, Bundy BN, Sedlis A, et al. Prognostic factors for groin node metastasis in squamous cell carcinoma of the vulva (a Gynecologic Oncology Group study). *Gynecol Oncol* 1993;**49**(3):279–83.
11. Magrina JF, Gonzalez-Bosquet J, Weaver AL, et al. Primary squamous cell cancer of the vulva: radical versus modified radical vulvar surgery. *Gynecol Oncol* 1998;**71**(1):116–21.
12. Lin JY, DuBeshter B, Angel Cynthia, Dvoretsky P. Morbidity and recurrence with modifications of radical vulvectomy and groin dissection. *Gynecol Oncol* 1992;**47**(1):80–6.
13. Byron RL, Lamb EJ, Yonemoto RH, et al. Radical inguinal node dissection in the treatment of cancer. *Surg Gynecol Obstet* 1962;**114**:401–8.
14. Ansink A, van der Velden J. Surgical interventions for early squamous cell carcinoma of the vulva. *Cochrane Database Syst Rev* 2000;(2):CD002036.
15. De Hullu JA, Hollema H, Lolkema S, et al. Vulvar carcinoma. The price of less radical surgery. *Cancer* 2002;**95**(11):2331–8.
16. Hacker NF, Leuchter RS, Berek JS, Castaldo TW, Lagasse LD. Radical vulvectomy and bilateral inguinal lymphadenectomy through separate groin incisions. *Obstet Gynecol* 1981;**58**(5):574–9.
17. Siller BS, Alvarez RD, Conner WD, et al. T2/3 vulva cancer: a case–control study of triple incision versus en bloc radical vulvectomy and inguinal lymphadenectomy. *Gynecol Oncol* 1995;**57**(3):335–9.
18. DiSaia PJ, Creasman WT, Rich WM. An alternate approach to early cancer of the vulva. *Am J Obstet Gynecol* 1979;**133**(7):825–32.
19. Burke TW, Levenback C, Coleman RL, et al. Surgical therapy of T1 and T2 vulvar carcinoma: further experience with radical wide excision and selective inguinal lymphadenectomy. *Gynecol Oncol* 1995;**57**(2):215–20.
20. Chan JK, Sugiyama V, Pham H, et al. Margin distance and other clinico-pathologic prognostic factors in vulvar carcinoma: a multivariate analysis. *Gynecol Oncol* 2007;**104**(3):636–41.
21. Groenen SM, Timmers PJ, Burger CW. Recurrence rate in vulvar carcinoma in relation to pathological margin distance. *Int J Gynecol Cancer* 2010;**20**(5):869–73.
22. Heaps JM, Fu YS, Montz FJ, Hacker NF, Berek JS. Surgical-pathologic variables predictive of local recurrence in squamous cell carcinoma of the vulva. *Gynecol Oncol* 1990;**38**(3):309–14.
23. Rouzier R, Haddad B, Plantier F, et al. Local relapse in patients treated for squamous cell vulvar carcinoma: incidence and prognostic value. *Obstet Gynecol* 2002;**100**(6):1159–67.
24. Woelber L, Choschzick M, Eulenburg C, et al. Prognostic value of pathological resection margin distance in squamous cell cancer of the vulva. *Ann Surg Oncol* 2011.
25. Micheletti L, Borgno G, Barbero M, et al. Deep femoral lymphadenectomy with preservation of the fascia lata. Preliminary report on 42 invasive vulvar carcinomas. *J Reprod Med* 1990;**35**(12):1130–3.
26. Courtney-Brooks M, Sukumvanich P, Beriwal S, et al. Does the number of nodes removed impact survival in vulvar cancer patients with node-negative disease. *Gynecol Oncol* 2010;**117**(2):308–11.
27. Wittekind C, Meyer HJ, Bootz F. TNM Klassifikation maligner Tumoren. Springer; 2002.
28. Gaarenstroom KN, Kenter GG, Trimbos JB, et al. Postoperative complications after vulvectomy and inguinofemoral lymphadenectomy using separate groin incisions. *Int J Gynecol Cancer* 2003;**13**(4):522–7.
29. Rouzier R, Haddad B, Plantier F, et al. Local relapse in patients treated for squamous cell vulvar carcinoma: incidence and prognostic value. *Obstet Gynecol* 2002;**100**(6):1159–67.
30. Woelber L, Mahner S, Voelker C, et al. Clinicopathological prognostic factors and patterns of recurrence in vulvar cancer. *Anticancer Res* 2009;**29**(2):545–52.
31. Bell JG, Jayanthi CL, Reid GC. Complete groin lymphadenectomy with preservation of the fascia lata in the treatment of vulvar carcinoma. *Gynecol Oncol* 2000;**77**:314–8.
32. Levenback C, Burke TW, Gershenson DM, et al. Intraoperative lymphatic mapping for vulvar cancer. *Obstet Gynecol* 1994;**84**(2):163–7.
33. Decesare SL, Fiorica JV, Roberts WS, et al. A pilot study utilizing intraoperative lymphoscintigraphy for identification of the sentinel lymph nodes in vulvar cancer. *Gynecol Oncol* 1997;**66**(3):425–8.
34. de Hullu JA, Doting E, Piers DA, et al. Sentinel lymph node identification with technetium-99m-labeled nanocolloid in squamous cell cancer of the vulva. *J Nucl Med* 1998;**39**(8):1381–5.
35. Sliutz G, Reinthaller A, Lantzsch T, et al. Lymphatic mapping of sentinel nodes in early vulvar cancer. *Gynecol Oncol* 2002;**84**(3):449–52.
36. Cicco C, Sideri M, Bartolomei M, et al. Sentinel node biopsy in early vulvar cancer. *Br J Cancer* 2000;**82**(2):295–9.
37. Moore DH, Thomas GM, Montana GS, et al. Preoperative chemoradiation for advanced vulvar cancer: a phase II study of the Gynecologic Oncology Group. *Int J Radiat Oncol Biol Phys* 1998;**42**(1):79–85.
38. Hampl M, Hantschmann P, Michels W, Hillemanns P. Validation of the accuracy of the sentinel lymph node procedure in patients with vulvar cancer: results of a multicenter study in Germany. *Gynecol Oncol* 2008;**111**(2):282–8.
39. van Zee AG, Oonk MH, Hullu JA, et al. Sentinel node dissection is safe in the treatment of early-stage vulvar cancer. *J Clin Oncol* 2008;**26**(6):884–9.
40. Rodolakis A, Diakomanolis E, Voulgaris Z, et al. Squamous vulvar cancer: a clinically based individualization of treatment. *Gynecol Oncol* 2000;**78**(3 Pt 1):346–51.
41. Bell JG, Lea JS, Reid GC. Complete groin lymphadenectomy with preservation of the fascia lata in the treatment of vulvar carcinoma. *Gynecol Oncol* 2000;**77**(2):314–8.
42. Hacker NF, Berek JS, Lagasse LD, Leuchter RS, Moore JG. Management of regional lymph nodes and their prognostic influence in vulvar cancer. *Obstet Gynecol* 1983;**61**(4):408–12.

43. Hyde SE, Valmadre S, Hacker NF, et al. Squamous cell carcinoma of the vulva with bulky positive groin nodes-nodal debulking versus full groin dissection prior to radiation therapy. *Int J Gynecol Cancer* 2007;**17**(1):154–8.
44. Gadducci A, Cionini L, Romanini A, Fanucchi A, Genazzani AR. Old and new perspectives in the management of high-risk, locally advanced or recurrent, and metastatic vulvar cancer. *Crit Rev Oncol Hematol* 2006;**60**(3):227–41.
45. Homesley HD, Bundy BN, Sedlis A, Adcock L. Radiation therapy versus pelvic node resection for carcinoma of the vulva with positive groin nodes. *Obstet Gynecol* 1986;**68**(6):733–40.
46. van der Velden J, van Lindert AC, Lammes FB, et al. Extracapsular growth of lymph node metastases in squamous cell carcinoma of the vulva. The impact on recurrence and survival. *Cancer* 1995;**75**(12):2885–90.
47. Lataifeh I, Carraro Nascimento M, Nicklin JL, et al. Patterns of recurrence and disease-free survival in advanced squamous cell carcinoma of the vulva. *Gynecol Oncol* 2004;**95**(3):701–5.
48. Paladini D, Cross P, Lopes A, Monaghan JM. Prognostic significance of lymph node variables in squamous cell carcinoma of the vulva. *Cancer* 1994;**74**(9):2491–6.
49. Origoni M, Sideri M, Garsia S, Carinelli SG, Ferrari AG. Prognostic value of pathological patterns of lymph node positivity in squamous cell carcinoma of the vulva stage III and IVA FIGO. *Gynecol Oncol* 1992;**45**(3):313–6.
50. Oonk MH, de Hullu JA, van der Zee AG. Current controversies in the management of patients with early-stage vulvar cancer. *Curr Opin Oncol* 2010;**22**(5):481–6.
51. Oonk MH, van Hemel BM, Hollema H, et al. Size of sentinel-node metastasis and chances of non-sentinel-node involvement and survival in early stage vulvar cancer: results from GROINSS-V, a multicentre observational study. *Lancet Oncol* 2010;**11**(7):646–52.
52. Fons G, Groenen SMA, Oonk MHM, et al. Adjuvant radiotherapy in patients with vulvar cancer and one intra capsular lymph node metastasis is not beneficial. *Gynecol Oncol* 2009;**114**(2):343–5.
53. Parthasarathy A, Cheung MK, Osann K, et al. The benefit of adjuvant radiation therapy in single-node-positive squamous cell vulvar carcinoma. *Gynecol Oncol* 2006;**103**(3):1095–9.
54. Hacker NF, Berek JS, Lagasse LD, Leuchter RS, Moore JG. Management of regional lymph nodes and their prognostic influence in vulvar cancer. *Obstet Gynecol* 1983;**61**(4):408–12.
55. Curry SL, Wharton Taylor J, Felix R. Positive lymph nodes in vulvar squamous carcinoma. *Gynecol Oncol* 1980;**9**(1):63–7.
56. Kunos C, Simpkins F, Gibbons H, Tian C, Homesley H. Radiation therapy compared with pelvic node resection for node-positive vulvar cancer: a randomized controlled trial. *Obstet Gynecol* 2009;**114**(3):537–46.
57. de Hullu JA, VdZ AGJ. Surgery and radiotherapy in vulvar cancer. *Crit Rev Oncol/Hematol* 2006;**60**:38–58.
58. Burger MP, Hollema H, Emanuels AG, et al. The importance of the groin node status for the survival of T1 and T2 vulval carcinoma patients. *Gynecol Oncol* 1995;**57**(3):327–34.
59. Woelber L, Mahner S, Voelker K, et al. Clinicopathological prognostic factors and patterns of recurrence in vulvar cancer. *Anticancer Res* 2009;**29**(2):545–52.
60. Hoffman MS. Squamous-cell carcinoma of the vulva: locally advanced disease. *Best Practice Res Clin Obstet Gynaecol* 2003;**17**(4):635–47.
61. Tans L, Ansink AC, van Rooij PH, Kleijnen C, Mens JW. The role of chemo-radiotherapy in the management of locally advanced carcinoma of the vulva: single institutional experience and review of literature. *Am J Clin Oncol* 2010;**34**(1):22–6.
62. van Doorn HC, Ansink A, Verhaar-Langereis M, Stalperis L. Neoadjuvant chemoradiation for advanced primary vulvar cancer. *Cochrane Database Syst Rev* 2006;(3):CD003752.
63. Shylasree TS, Bryant A, Howells RE. Chemoradiation for advanced primary vulval cancer. *Cochrane Database Syst Rev* 2011;4:CD003752.
64. Han SC, Kim DH, Higgins SA, Carcangiu ML, Kaciriski BM. Chemoradiation as primary or adjuvant treatment for locally advanced carcinoma of the vulva. *Int J Radiat Oncol Biol Phys* 2000;**47**(5):1235–44.
65. Moore DH, Koh WJ, McGuire WP, Wilkinson EJ. Vulva. In: Hoskins WJ, Perez CA, Young RC, Barakat RR, Markman M, Randall ME, editors. *Principles and practices of gynecologic cancers*. Philadelphia, PA: Lippincott Williams and Wilkins; 2005.
66. Bellati F, Angioli R, Manci N, et al. Single agent cisplatin chemotherapy in surgically resected vulvar cancer patients with multiple inguinal lymph node metastases. *Gynecol Oncol* 2005;**96**(1):227–31.
67. Cormio G, Loizzi V, Gissi F, et al. Cisplatin and vinorelbine chemotherapy in recurrent vulvar carcinoma. *Oncology* 2009;**77**(5):281–4.
68. Wagenaar HC, Colombo N, Vergote I, et al. Bleomycin, methotrexate, and CCNU in locally advanced or recurrent, inoperable, squamous-cell carcinoma of the vulva: an EORTC Gynaecological Cancer Cooperative Group Study. *Gynecol Oncol* 2001;**81**(3):348–54.
69. Witteveen PO, van der Velden J, Vergote I, et al. Phase II study on paclitaxel in patients with recurrent, metastatic or locally advanced vulvar cancer not amenable to surgery or radiotherapy: a study of the EORTC-GCG (European Organisation for Research and Treatment of Cancer Gynaecological Cancer Group). *Ann Oncol* 2009;**20**(9):1511–6.
70. Olawaiye Alexander, Lee LM, Krasner Carolyn, Neil H. Treatment of squamous cell vulvar cancer with the anti-EGFR tyrosine kinase inhibitor tarceva. *Gynecol Oncol* 2007;**106**(3):628–30.