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Clitoral involvement of squamous cell carcinoma of the vulva: Localization with the worst prognosis

F. Hinten [a,*], L.C.G. van den Einden [a], M. Cissen [a], J. IntHout [b], L.F.A.G. Massuger [a], J.A. de Hullu [a]

[a] *Radboud University Medical Centre, Department of Obstetrics and Gynaecology, PO Box 9101, 6500 HB Nijmegen, The Netherlands*

[b] *Radboud University Medical Centre, Department for Health Evidence, PO Box 9101, 6500 HB Nijmegen, The Netherlands*

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Abstract

Objective: The overall 5-year survival of patients with vulvar squamous cell carcinoma (SCC) is 70%. The clinical impression is that localization of SCC on the clitoris may lead to worse prognosis. The aim of this study is to assess the disease specific survival (DSS) in patients with clitoral SCC compared to patients with SCC without clitoral involvement.

Methods: All consecutive patients with primary vulvar SCC treated with surgery at the Department of Gynaecologic Oncology at the Radboud university medical centre (Radboudumc) between March 1988 and January 2012, were analysed. The clinical and histopathological characteristics and DSS rates of patients with (N = 72) and without clitoral SCC (N = 275) were compared. Furthermore, patients with clitoral involvement were compared to patients with perineal SCCs (N = 52) and other central SCCs without clitoral and/or perineal involvement (N = 117).

Results: Patients with clitoral SCC more often had larger and deeper invaded tumours, lymphovascular space involvement (LVSI), positive surgical margins and a higher percentage of positive lymph nodes. Kaplan–Meier survival analyses showed worse DSS in patients with a clitoral SCC compared to patients without clitoral involvement. Multivariable analysis showed that not clitoral involvement, but invasion depth, differentiation grade and lymph node status are independent prognostic factors.

Conclusions: Patients with clitoral SCC have worse survival compared to patients without clitoral involvement. This is probably caused by unfavourable histopathological characteristics of the tumour rather than the localization itself. Prospective studies are needed to further assess the influence of localization of the vulvar SCC on prognosis.

Keywords: Vulvar cancer; Clitoris; Survival

Introduction

Vulvar cancer is rare with a worldwide incidence of 2–3 per 100,000 women, increasing with age.[1–3] It represents 1% of all malignancies in women and about 3–5% of all gynaecological malignancies.[4] Approximately 80% of vulvar malignancies are squamous cell carcinomas (SCC). Two different types of SCC are described, namely a type caused by an infection with high risk Human Papillomavirus (HPV) via usual vulvar intraepithelial neoplasia (uVIN) that primarily affects younger women and the second type SCC is the most common type, which often occurs in a background of lichen sclerosus (LS) and/or differentiated VIN (dVIN), especially in elderly women.[5] Taking a biopsy for histopathological examination is the gold standard for diagnosing vulvar SCC.

Nowadays, the triple incision technique, consisting of wide local excision (WLE) with uni- or bilateral inguinofemoral lymphadenectomy (IFL) via separate incisions, is the standard treatment for vulvar SCC with >1 mm invasion.[6]

* Corresponding author. Radboud University Medical Centre, Department of Obstetrics and Gynaecology (791), PO Box 9101, 6500 HB Nijmegen, The Netherlands. Tel.: +31 24 3668663; fax: +31 24 3668597.

E-mail address: Floor.Hinten@radboudumc.nl (F. Hinten).

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Early stage vulvar SCC patients can be treated by WLE and a sentinel lymph node (SLN) procedure, preferentially within the protection of a clinical trial such as the GROINSS VII study.[7]

Several studies show that age, tumour size, invasion depth, extranodal growth, and differentiation grade are independent prognostic factors in vulvar SCC[8–11]; lymph node status being the most important prognostic factor.[11–14] The overall 5-year survival rate is 70% and in patients with negative inguinofemoral lymph nodes (stage I and II) this reaches 90%, but diminishes in case of positive inguinofemoral lymph nodes.[15,16]

In several other malignancies, an association between the anatomic localization and the prognosis has been described. For example, patients with cutaneous melanomas have a worse prognosis when the lesions are located on the head, neck and/or trunk compared to lesions on the extremities.[17] It has been hypothesized that the location of the primary tumour in vulvar SCC may also influence prognosis. Magrina et al.[18] showed that invasion of the urethra had a significant disadvantageous impact on the 5-year survival. Boyce et al.[19] and Andreasson et al.[20] showed the unfavourable impact of clitoral involvement on the prognosis, while Masak et al.[21] on the other hand determined that clitoral involvement did not predict poor prognosis. Although the literature does not provide unambiguous evidence, we hypothesize that primary tumour localization on the clitoris correlates with an unfavourable prognosis in patients with vulvar SCC, based on our clinical experience. Therefore, the aim of this study is to assess the disease specific survival (DSS) of clitoral SCC compared to SCC of the vulva without clitoral involvement.

Materials and methods

Patients and data

Data of 385 consecutive patients with primary vulvar SCC who were primarily surgically treated at the Department of Gynaecological Oncology at the Radboud university medical centre (Radboudumc) between March 1988 and January 2012 (follow up until 1st of August 2012), were selected from the local patient registry of vulvar SCC patients. Data were collected after consultation of medical files and pathological reports. A total number of 38 patients were excluded from the analysis; these patients did not receive surgical treatment (N = 30) and/or received incomplete surgical treatment (N = 2) and/or the exact localization of the tumour was unclear (N = 6). The variables extracted from the database included patient characteristics (age at diagnosis and time of follow up) and histopathological characteristics (tumour size, focality, depth of invasion, surgical margin status (positive, ≤8 mm or >8 mm)). Furthermore, lymphovascular space involvement (LVSI), lymph node status, differentiation grade, the FIGO stage at time of diagnosis (staging system of 1988 or 2009), adjuvant radiotherapy and the recurrence rate (vulvar-, groin- and/or distant) were extracted from the database.

Within the total group of 347 vulvar cancer patients, two different groups were defined: the clitoral group consisted of patients with a clitoral SCC (N = 72) and the non-clitoral group (≥1 mm from the clitoris) (N = 275) consisted of patients with tumours without clitoral involvement. The non-clitoral SCC group was divided in three different groups, namely perineal SCCs (all tumours with perineal involvement, except the tumours with simultaneous clitoral involvement) (N = 52), other central SCCs (≤1 cm from the midline[22]) without clitoral and/or perineal involvement (N = 117) and lateral SCCs (>1 cm from the midline) (N = 106).

Statistical methods

Patient and histopathological characteristics and adjuvant radiotherapy were compared between groups using Chi-square tests and t-tests for independent samples. Disease specific survival (DSS) was defined as survival from the date of diagnosis to the date of death due to vulvar SCC or the date of last follow-up. Censoring was applied to patients alive at last follow-up, patients who were lost to follow-up and patients who died of another disease. The DSS and recurrence rates were estimated according to the Kaplan–Meier method and were compared using the log-rank test. Univariate Cox regression was used to assess the prognostic value of patient and histopathological characteristics on the prognosis of vulvar cancer. Based on the subset of statistically significant variables, multivariable Cox regression with a forward stepwise procedure based on likelihood ratio statistics was used to identify those characteristics that independently contributed to the prognosis of vulvar SCC patients. Hazard ratios (HR) with 95% confidence intervals (CIs) are presented. A p-value of <0.05 was considered statistically significant. Analyses were performed using SPSS (PASW statistics, version 20).

Results

Three hundred and forty-seven patients were included in this retrospective study; 72 patients had a clitoral SCC (21%, Group 1) and 275 patients had a tumour without clitoral involvement (79%, Group 2). The median follow up time of the Clitoral group was 32 months (range 0–259) and the median follow up of the Non-clitoral group was 49 months (range 0–276). The baseline characteristics of the study population are listed in Table 1. Patients in the Clitoral group had larger tumours, deeper tumour invasion, more LVSI, more often positive surgical margins and surgical margins <8 mm, a higher percentage of positive lymph nodes, and a higher percentage of a high FIGO stage (FIGO staging valid in year of diagnosis), compared to patients in the Non-clitoral group. Compared to the Perineal group