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Prognostic factors for local recurrence of squamous cell carcinoma of the vulva: A systematic review

Nienke C. te Grootenhuis [a,1], Anne-Floor W. Pouwer [b,1], Geertruida H. de Bock [c], Harry Hollema [d], Johan Bulten [e], Ate G.J. van der Zee [a], Joanne A. de Hullu [b], Maaike H.M. Oonk [a,*]

[a] University of Groningen, University Medical Center Groningen, Department of Obstetrics and Gynaecology, Groningen, The Netherlands
[b] Department of Obstetrics and Gynaecology, Radboud university medical center, Nijmegen, The Netherlands
[c] University of Groningen, University Medical Center Groningen, Department of Epidemiology, Groningen, The Netherlands
[d] University of Groningen, University Medical Center Groningen, Department of Pathology Groningen, The Netherlands
[e] Department of Pathology, Radboud university medical center, Nijmegen, The Netherlands

HIGHLIGHTS

- We estimated a local recurrence rate of 4% per year without plateauing.
- Prognostic relevance of a pathological free margin of <8 mm remains questionable.
- For all other variables analyzed, prognostic relevance remains equivocal.

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ABSTRACT

Background. In patients treated for early-stage squamous cell vulvar carcinoma local recurrence is reported in up to 40% after ten years. Knowledge on prognostic factors related to local recurrences should be helpful to select high risk patients and/or to develop strategies to prevent local recurrences.

Objective. This systematic review aims to evaluate the current knowledge on the incidence of local recurrences in vulvar carcinoma related to clinicopathologic and cell biologic variables.

Data sources. Relevant studies were identified by an extensive online electronic search in July 2017.

Study eligibility criteria. Studies reporting prognostic factors specific for local recurrences of vulvar carcinoma were included.

Study appraisal and synthesis methods. Two review authors independently performed data selection, extraction and assessment of study quality. The risk difference was calculated for each prognostic factor when described in two or more studies.

Results. Twenty-two studies were included; most of all were retrospective and mainly reported pathologic prognostic factors. Our review indicates an estimated annual local recurrence rate of 4% without plateauing. The prognostic relevance for local recurrence of vulvar carcinoma of all analyzed variables remains equivocal, including pathologic tumor free margin distance <8 mm, presence of lichen sclerosus, groin lymph node metastases and a variety of primary tumor characteristics (grade of differentiation, tumor size, tumor focality, depth of invasion, lymphovascular space invasion, tumor localization and presence of human papillomavirus).

Conclusions. Current quality of data on prognostic factors for local recurrences in vulvar carcinoma patients does not allow evidence-based clinical decision making. Further research on prognostic factors, applying state of the art methodology is needed to identify high-risk patients and to develop alternative primary and secondary prevention strategies.

1. Introduction

Vulvar cancer accounts for 5% of all gynecologic cancers with an incidence of 2.5 per 100,000 women [1]. It mostly affects elderly women, with more than half of the patients above the age of 70 years at time of diagnosis. The most common histological type of vulvar

* Corresponding author at: University of Groningen, University Medical Center Groningen, Department of Obstetrics and Gynaecology, CB20, Hanzeplein 1, 9700RB Groningen, The Netherlands.
E-mail address: m.h.m.oonk@umcg.nl (M.H.M. Oonk).
[1] Equally contributed.

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cancer is squamous cell carcinoma [2]. There are two different preneoplastic lesions known for vulvar carcinoma; differentiated vulvar intraepithelial neoplasia (dVIN) and high-grade squamous intraepithelial lesion (HSIL) [3]. The dVIN pathway is associated with lichen sclerosus, the second pathway is related to HSIL which is caused by infection with human papillomavirus (HPV) and associated with immunosuppressive state and smoking [4]. Over the past few decades, the incidence of vulvar carcinoma has increased slowly, but steadily [1].

Standard treatment for early-stage vulvar carcinoma entails wide local excision of the primary tumor and, if the tumor is macro-invasive (depth of invasion >1 mm), either a sentinel node (SN) procedure or an elective inguinofemoral lymphadenectomy, depending on tumor size, focality or the presence of suspected metastatic groin lymph nodes [5]. Despite radical treatment, local recurrences on the vulva are reported in up to 40% of the patients [6]. Of these patients 43–72% will develop a second local recurrence and subsequently 57% will have a third or even more local recurrences. It has been shown that disease-specific survival decreases from 90% to 69% in patients after a local recurrence, as was observed both in SN-positive as well as in SN-negative patients [6].

In patients with a local recurrence, first choice of treatment is wide local excision of the tumor. An inguinofemoral lymphadenectomy is indicated if a macro-invasive recurrent tumor is present and no inguinofemoral lymphadenectomy was performed previously. As a consequence, patients who previously had a negative SN will now suffer from significant short and long term morbidity associated with inguinofemoral lymphadenectomy [5]. For these reasons, knowledge on prognostic factors related to local recurrences is of utmost importance. Both clinicopathologic as well as cell biologic markers may be of prognostic value for local recurrences of vulvar carcinoma [7,8].

One of the most debated prognostic factors is the minimal pathologic tumor free margin distance. Worldwide a pathologic tumor free margin of ≥8 mm has been advocated as safe [9,10]. However, the question whether a margin distance <8 mm does really increase the number of patients suffering from a local recurrence has not been answered unequivocally yet. Furthermore, it is unclear why some patients with lichen sclerosus and dVIN develop a primary squamous cell vulvar carcinoma and/or multiple local recurrences, whereas other patients do not.

1.1. Objective

The aim of this systematic review was to summarize the current knowledge on the incidence of local recurrences in patients diagnosed with squamous cell vulvar carcinoma related to clinicopathologic and cell biologic variables.

2. Methods

2.1. Information sources and search strategy

This review was conducted according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines, and in accordance with the principles outlined in the Cochrane Handbook for Systematic Reviews of Interventions [11,12]. Relevant studies were identified by an online electronic search on July 25, 2017 using PubMed, EMBASE, Web of Science and the Cochrane library. The search strategies were developed by two authors (AWP and NCG) in consultation with a librarian using medical subject heading (MeSH) and text words related to vulvar cancer, local recurrence and prognostic factors, see Supplementary 1. To ensure completeness of included references, we scanned the reference lists of the included studies or relevant reviews identified through the search. See Fig. 1 for the PRISMA flow diagram.

2.2. Eligibility criteria and data extraction

Eligible study designs for inclusion were; randomized controlled trials, controlled clinical trials, case-control studies, cross-sectional studies and cohort studies. The eligibility criteria were: studies evaluating (1) the association between clinicopathologic and cell biologic variables and local recurrence of squamous cell vulvar carcinoma (2) including patients above the age of 18 years and (3) written in English. Two review authors (AWP and NCG) independently screened the titles and abstracts retrieved by the search. Two review authors (AWP and NCG) independently decided whether these articles met our inclusion criteria.

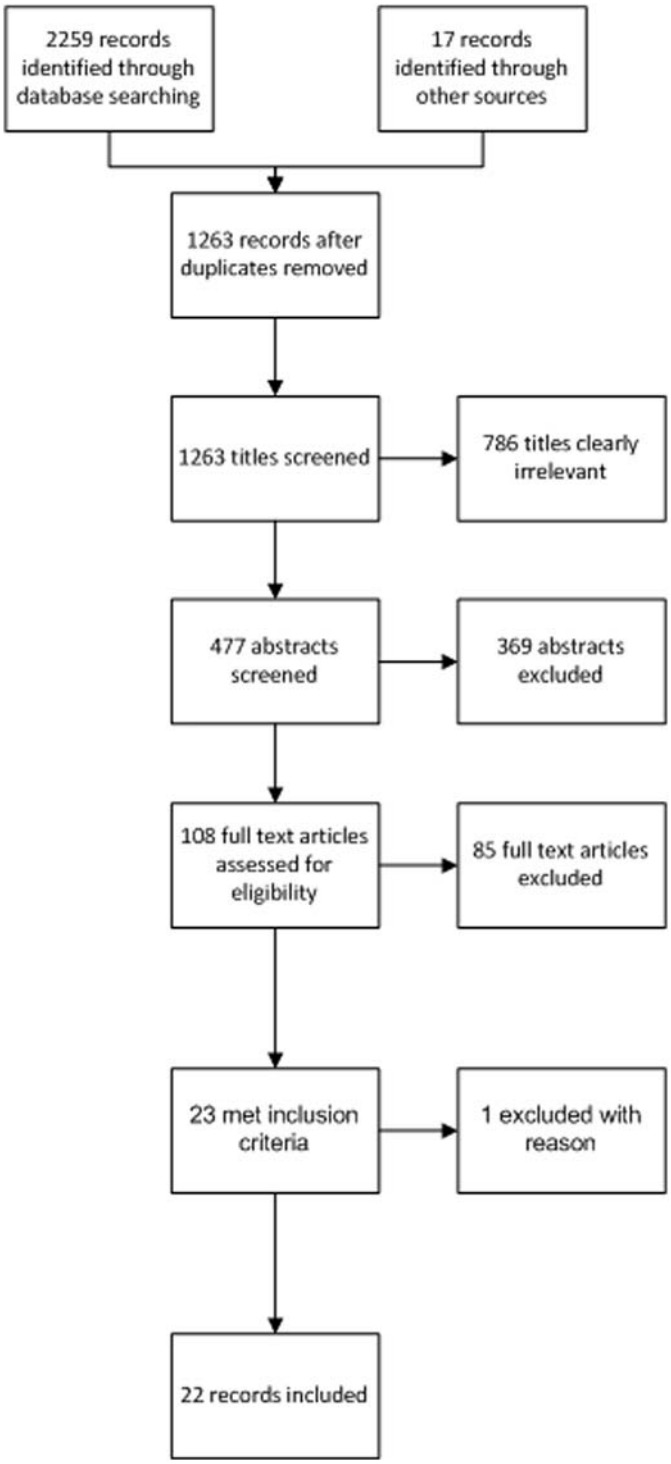

Fig. 1. PRISMA flow diagram.

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