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Low yield of residual vulvar carcinoma and dysplasia upon re-excision for close or positive margins

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HIGHLIGHTS

- Low yield of carcinoma upon vulvar re-excision
- Relatively low overall local recurrence rate

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ABSTRACT

Objectives. The objectives of this study are to determine the utility of re-excision after a primary diagnosis of vulvar carcinoma by assessing the frequency of residual carcinoma found upon re-excision and to quantitate the wound breakdown and carcinoma recurrence rates.

Methods. We reviewed 1122 cases of VIN or vulvar carcinoma. Women who underwent re-excisional procedures, as part of their initial surgical treatment were identified. Associations between the margin status of the original excisional sample and histology of re-excision, as well as association between the depth of invasion upon initial excision and histology of re-excision were analyzed with Chi-square tests.

Results. We identified 84 evaluable patients, 72 with stage I disease, 4 with stage II, and 7 with stage III disease. Upon the initial excisional procedure, 33 patients (39%) had carcinoma-positive margins, 27 patients had VIN-positive margins (32%) and 24 patients (28%) had negative margins (>1 mm). Upon re-excision, 1/24 (4%) patients with negative margins, 2/27 (7%) patients with VIN-positive margins, and 11/33 (33%) patients with carcinoma-positive margins were found to have carcinoma in the re-excision specimens ($p < 0.0001$, $\chi^2 = 31$). Deeper tumor invasion of the initial excisional specimen (1–12 mm) was associated with a higher chance of finding carcinoma upon re-excision (range 18–42%, depending on depth of invasion) ($p = 0.015$, $\chi^2 = 19$). Nineteen patients (23%) had vulvar wound breakdown post re-excision. Twelve patients (15%) experienced recurrences.

Conclusions. The yield of micro- or invasive carcinoma at re-excision is low, with a high wound breakdown rate. Re-excision should be considered for patients with margins positive for carcinoma, especially for women with deep invasion, while women with VIN or close but clear margins may be followed.

Introduction

Malignant tumors of the vulva account for approximately 5% of all the cancers of the female genital tract. In 2012, there were estimated to be 4490 new cases diagnosed in the United States. Approximately 90% are of squamous histology [1–3].

Historically, vulvar cancer has been considered a disease of older women, but the mean age of diagnosis has decreased over the last 50 years [4]. There has been a significant increase in the incidence of vulvar intraepithelial neoplasia (VIN) and VIN-associated cancer in young women in recent decades [2,5–7]. This has been partially attributed to an increase in infection rates by oncogenic genital human papilloma viruses (HPVs) [8].

Proper initial evaluation is crucial in establishing the diagnosis of vulvar cancer. Because vulvar cancer is a rare disease, clinicians may be unfamiliar with gross appearance of vulvar carcinoma and thus inadequately sample lesions prior to vulvectomy. This may explain the relatively high rate of invasive disease found after vulvectomy for presumed VIN. Spencer et al. highlighted the importance of performing excisional procedures in establishing the

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diagnosis of carcinoma in women with persistent vulvar ulcerations and preceding negative punch biopsies [9]. Similarly, Husseinzadeh and colleagues reported that 21% of patients with VIN 3 on a punch biopsy were found to have invasive vulvar carcinoma upon surgical excision [10].

Although in-office punch biopsies are usually sufficient to diagnose an invasive disease, often larger operative excisional procedures may be necessary to establish the diagnosis, and are critical to staging and adjuvant therapy decisions. In many cases, margins following diagnostic excisional procedures are negative, but within 1 cm. Managing these close margins can be problematic, as margin status is a powerful predictor of recurrence for women with vulvar cancer. Patients with invasive cancer within 8 mm of surgical margins after fixation (equivalent to approximately 1 cm in vivo) have an increased risk for recurrence [11]. This had led several gynecologic oncology groups to advocate the utilization of radical re-resection for women with margins within this threshold [12–14]. However, wound breakdown is common after radical resection of vulvar cancer, and larger excisions may cause scarring that interferes with sexual function and may affect body image. Furthermore, local recurrences of excisions with close margins may be curable with re-excision, allowing women who are observed and do not recur to avoid further procedures [13,15].

Currently, there is a paucity of literature describing the yield of VIN or carcinoma in surgical specimens obtained by re-excision, especially when gross or pathologic margins are clear but are less than 10 mm. This study aimed to determine the frequency of residual VIN and carcinoma identified in re-excision specimens obtained after initial diagnosis of microinvasive or frank carcinoma. Re-excisions were carried out for negative, yet close margins (<10 mm), or VIN/carcinoma present at margins. As a secondary objective of this study, we aimed to quantitate the wound breakdown and recurrence rates and to ascertain the relationship between depth of invasion of the initial excisional specimen and the histology of the re-excisional specimen.

Materials and methods

After obtaining approval from the Washington University Medical Center Human Research Protection Office and the University of Alabama at Birmingham Institutional Review Board, 1122 cases of VIN or vulvar squamous cell carcinoma treated between 1998 and 2011 at the Washington University School of Medicine and the University of Alabama at Birmingham Medical Center were identified by ICD-9 billing codes from institutional databases and reviewed. Patients with invasive or micro-invasive vulvar carcinoma on the excisional biopsy or local excision who subsequently underwent a radical re-excisional procedure were selected for further review.

Once patients were identified, charts were reviewed for clinical and pathologic data. Clinical data included patients' age, ethnicity, BMI, smoking history, medical co-morbidities, including immunodeficiency (i.e. HIV, lupus), type of re-excisional procedures, as well as disease stage, recurrence, and wound break down post re-excision. All patients were surgically treated by a gynecologic oncologist and all re-excisional specimens were reviewed by pathologists at Washington University or University of Alabama at Birmingham. Central review for this study was not conducted. Pathologic data included the histology of the initial excisional and re-excisional specimens, depth of invasion of the initial specimen, and status and histology of margins. Margins were considered positive for invasive carcinoma when disease was found within 1 mm, and negative yet close margins were less than 10 mm. Duration of follow-up and status at last follow-up were recorded, as well as post-surgical treatment modalities and outcomes.

Statistical analysis

The demographics of the cohort were summarized with descriptive statistics. The incidences of residual VIN and carcinoma upon re-excisional procedures were calculated for the entire cohort, and associations were assessed with the Chi-square test. The correlation between the depth of invasion and re-excisional histology was also analyzed with the Chi-square test. A Kaplan–Meier plot was constructed to describe the recurrence pattern of the cohort. Statistical analyses were conducted utilizing GraphPad Prism Software®, Version 6.0 (San Diego, California).

Results

We identified 87 patients who met the inclusion criteria for this study. Of these, 84 (97%) had detailed pathology reports describing histology, margin status, as well as recurrence patterns. Demographic characteristics of the evaluable patients are summarized in Table 1a. Median age at diagnosis for this cohort was 53; the majority of patients were Caucasian, and most were diagnosed with stage I disease according to the FIGO 2009 vulvar cancer staging system. Approximately half of the cohort had never smoked, and 38% were current smokers. Eight patients (10%) had a history of immunodeficiency or autoimmune disorders (i.e. HIV, systemic lupus erythematosus, rheumatoid arthritis, non-Hodgkin's lymphoma). Five patients, all with stage III vulvar cancer, underwent adjuvant post-operative radiation therapy. The median length of follow-up for the entire cohort was 28 months (range 1–139 months).

Pathologic characteristics of the initial excision specimens are shown in Table 1b. Upon the initial excisional procedure, 22 patients had microinvasion, and 65 patients had frankly invasive squamous cell carcinoma. Also, upon the initial excisional procedure, 33 of the 84 evaluable patients (39%) had margins positive for micro-invasive or invasive carcinoma, 27 patients had VIN-positive margins (32%), and 24 patients (28%) had negative margins (more than 1 mm but less than 10 mm, in cases where precise measurements of negative margins were available on the reports from original excisions). Upon re-excision, only one of twenty-four (4%) patients with negative margins, two of twenty-seven (7%) patients with VIN-positive margins, and 11 of 33 (33%) patients with margins positive for micro- or invasive carcinoma were found to have carcinoma or micro-invasive carcinoma upon re-excision ($p < 0.0001$, $\chi^2 = 31$, Table 2). Seventy of 82 evaluable patients had negative re-excisional margins (85%), with the remaining 12 patients (15%) having VIN-positive margins. None of the patients were found to have microinvasion or carcinoma at re-excisional margins. When specifically evaluating the seven patients with stage III disease, it is notable that none had residual carcinoma in their re-excisional specimens, two of the seven had VIN, and five of the seven had negative histology. Greater depth of tumor invasion (mm) in the initial excisional sample was associated with finding VIN or carcinoma in the re-excision specimen, as opposed to negative pathology

Table 1a
Patient characteristics. The majority of patients in the group were of Caucasian descent, had stage I disease, and never smoked.

Number of patients	n = 84 (100%)
Median age (years)	53 (range 20–98)
Race	Number of patients (%)
White	73 (87%)
Black	11 (13%)
Stage (FIGO 2009)	
I	73 (87%)
II	4 (5%)
III	7 (8%)
IV	0 (0%)
Smoker	
Never	41 (49%)
Former	8 (10%)
Current	32 (38%)
Unknown	3 (4%)
Immunocompromised	8 (10%)