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Relationship of margin status and radiation dose to recurrence in post-operative vulvar carcinoma

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HIGHLIGHTS

- This is the largest series to date to evaluate the role of margin status in postoperative vulvar cancer.
- Positive or close margins <5mm have a significant risk of vulvar recurrence after vulvar cancer resection.
- A radiation dose ≥56Gy may reduce the risk of vulvar recurrence.

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ABSTRACT

Objective. To evaluate the effect of margin status and radiation dose in patients treated with radiation therapy (RT) for vulvar cancer. Clinical outcomes included vulvar recurrence (VR), relapse-free survival (RFS) and overall survival (OS).

Methods. We retrospectively reviewed the records of 300 patients with Stage I–IVA vulvar cancer treated between 1988 and 2009. Slides were reviewed and margin status was scored as negative (≥1 cm), close (<1 cm) or positive after formalin fixation. Cox proportional hazards models were constructed to determine significant prognostic factors for vulvar relapse.

Results. Of 205 eligible patients, 69 (34%) had negative surgical margins, 116 (56%) had close margins and 20 (10%) had positive margins. Median follow-up time was 49 months. The 4-year RFS rate was 53% and OS was 73%. Of 78 recurrences, 62 had the vulva as the first site of recurrence. The 4-year rates of freedom from vulvar recurrence were 82%, 63% and 37% for those with negative, close and positive margins, respectively (p for trend = 0.005). On multivariate analysis, close margins (HR = 3.03, 95% CI 1.46–6.26) and positive margins (HR = 7.02, 95% CI 2.66–18.54) were associated with a significantly increased risk of vulvar relapse. Those who received a dose ≥56 Gy had a lower risk of relapse than those who received ≤50.4 Gy ($p < 0.05$). Though recurrences were noted with margins up to 9 mm, the highest risk of vulvar recurrence was associated with margins ≤5 mm ($p = 0.002$).

Conclusions. Close or positive margins were associated with a significantly increased risk of vulvar recurrence. Radiation with a dose ≥56 Gy may decrease the risk of vulvar recurrence.

Introduction

Vulvar carcinoma is a rare gynecologic malignancy. In 2012, 4490 new cases and 950 estimated deaths occurred in the U.S. [1]. Radical vulvectomy, the surgical resection of the vulva with inguinofemoral lymphadenectomy, represents the 'classic' standard treatment for invasive disease, resulting in 5-year survival rates of 80–90% [2,3]. However, complications from radical surgery including leg edema, wound breakdown, pelvic organ prolapse, urinary incontinence and psychosexual impairment may occur [4,5]. Radical local excision, or the removal of the tumor with an adequate margin, has become a much more common form of vulvar surgery [6–8]. More limited resections such as wide local excision or partial vulvectomy are acceptable in cases with early, less extensive disease resulting in fewer side effects [9–13]. However, assuring that adequate margins have been obtained is imperative. Wide local excision with adequate resection margins can be as effective as a radical vulvectomy, without compromising the function of the vulva.

Local recurrence has been observed in patients when microscopic margins are less than 8 mm [14–16]. Though one series has shown

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that radiation appeared to reduce the risk of recurrence in vulvar cancer patients with close margins, no dose threshold was identified [8]. This 8-mm, pathologic, formalin-fixed tissue margin correlates with a 1-cm margin on fresh tissue postoperatively. Therefore, the standard recommendation is that surgical resection for primary invasive tumors should include a margin of at least 1 to 2 cm [7,17].

Radiation therapy (RT) is accepted as an important part of the postoperative treatment of early-stage lesions with high-risk features, with the goal of reducing local recurrence without substantial increase in morbidity [18]. Patients with high-risk features, such as lymph-node involvement, close or positive margins, tumor size >4 cm and lymphovascular invasion [19], may be considered for postoperative RT to eradicate micrometastasis. In retrospective studies, postoperative RT was associated with improvements in local control [8]. Concurrent chemotherapy may be considered in some cases [20].

To date, it is not known what dose of radiation may reduce the risk of vulvar recurrence in patients with close or positive margins. Our objectives in this report were to evaluate the effect of margin status on local vulvar recurrence and to analyze the relation between radiation dose to the vulva and vulvar recurrence (VR) with the corresponding rates of freedom from vulvar relapse (FFVR), relapse-free survival (RFS), and overall survival (OS) when stratified by margin status.

Materials and methods

We retrospectively reviewed the records of 300 patients with Stages I–IVA invasive vulvar squamous cell carcinoma or adenocarcinoma treated at Brigham and Women's Hospital between 1988 and 2009 with Institutional Review Board approval and a waiver of consent. Information about patient characteristics, treatment, follow-up and disease status were obtained from hospital records. Patients treated without surgery (n = 12), with unknown margin status (n = 7), with non-squamous or non-adenocarcinoma histologies (n = 69) or with Paget's disease (n = 7) were excluded. Baseline characteristics of the remaining 205 included patients are listed in Table 1.

Two pathologists (APP and CPC) reviewed the vulvar tumor on hematoxylin- and eosin-stained slides. The margin was defined as the distance from the tumor edge to the edge of the specimen as measured after formalin fixation. Distances from tumor to deep and peripheral margins were recorded. Margin status was defined as negative if ≥1 cm, close if <1 cm or positive if coincident with the edge of the tumor.

Adjuvant RT was delivered with 6–15 MV photon fields to the vulva +/− inguinal nodal regions. Most commonly, a two-field technique (anterior–posterior/posterior–anterior [APPA]) was used to treat the vulva and the inguinal nodes were covered primarily only by the anterior field; 6 MV energy was used for the anterior field and 15 MV energy for the posterior field. The dose was prescribed to the midplane for the pelvis and at depth for the inguinal nodes based on computed tomography (CT) simulation.

The following potential factors associated with vulvar recurrence were evaluated: race; stage; grade; histology; tumor size; depth of invasion; presence of positive lymph nodes; lymphovascular invasion; use of radiation; chemotherapy; type of surgical resection and smoking status. Frequency distributions of categorical variables by margin status were compared using the chi-square test or chi-square trend test. Sites of relapse were recorded.

RFS was defined as the interval from diagnosis of primary or recurrent disease to the date of first evidence of disease recurrence or progression or death from any cause. OS was defined from the date of diagnosis or documented recurrence until death from any cause. Survival time was calculated at the date of last follow-up for censored patients. Vulvar failure was defined as recurrent disease in the vulvar tissues documented by clinical examination, biopsy, or radiologic imaging. Kaplan–Meier estimates for OS and RFS were calculated. Log-rank analysis was performed on the potential factors to examine their unadjusted association with margin status. Multivariable Cox proportional hazards regression analysis was performed with stepwise selection ($p > 0.15$) to identify factors independently associated with VR, RFS and OS. Cox model results were reported using hazard ratios (HR) with 95% confidence intervals (CI). Secondary analyses were performed to analyze rates of VR by radiation dose. All data were analyzed using SAS (version 9.0; SAS, Inc., Cary, NC).

Table 1
Patient, tumor, and treatment characteristics.

	Negative margins (n = 69)	Close margins (n = 116)	Positive margins (n = 20)	p-Value
Patient characteristics				
Race				p = 0.20
White	88% (35)	90% (77)	93% (13)	
Black	10% (4)	2% (2)	0% (0)	
Hispanic	3% (1)	8% (7)	7% (1)	
Smoking history				p = 0.11
Current smoker	29% (18)	30% (32)	19% (3)	
Nonsmoker	53% (33)	46% (49)	31% (5)	
Prior smoker	18% (11)	24% (25)	50% (8)	
Tumor characteristics				
FIGO stage				p = 0.31
I	49% (34)	35% (40)	50% (10)	
II	29% (20)	37% (43)	35% (7)	
III	16% (11)	25% (29)	10% (2)	
IV	6% (4)	4% (4)	5% (1)	
Grade				p = 0.39
1	52% (29)	38% (42)	43% (6)	
2	36% (20)	45% (50)	50% (7)	
3	13% (7)	18% (20)	7% (1)	
Size				p = 0.17
≤2 cm	56% (34)	43% (49)	61% (11)	
>2 cm	44% (27)	57% (64)	39% (7)	
Positive inguinal lymph nodes				p = 0.20
0	83% (57)	74% (86)	90% (18)	
1	7% (5)	16% (18)	0% (0)	
2+	10% (7)	10% (12)	10% (2)	
Histology				p = 0.42
Squamous cell carcinoma	88% (61)	96% (111)	90% (18)	
Adenocarcinoma	2% (1)	2% (2)	5% (1)	
Adenosquamous carcinoma	2% (1)	0% (0)	0% (0)	
Basal cell carcinoma	6% (4)	1% (1)	5% (1)	
Verrucous carcinoma	0% (0)	1% (1)	0% (0)	
Papillary squamous	3% (2)	1% (1)	0% (0)	
Depth of nodal dissection				p = 0.14
Superficial	77% (46)	62% (66)	73% (11)	
Deep	23% (14)	38% (40)	27% (4)	
Lymphovascular invasion				p = 0.53
No	93% (64)	89% (103)	95% (19)	
Yes	7% (5)	11% (13)	5% (1)	
Treatment characteristics				
Any radiation				p = 0.19
No	78% (54)	66% (76)	70% (14)	
Yes	22% (15)	35% (40)	30% (6)	
Vulvar radiation				p = 0.72
No	84% (58)	79% (92)	80% (16)	
Yes	16% (11)	21% (24)	20% (4)	
Chemotherapy				p = 0.76
No	87% (60)	90% (104)	85% (17)	
Yes	13% (9)	10% (12)	15% (3)	
Surgery type				p = 0.33
Wide local excision[a]	32% (22)	37% (42)	50% (10)	
Vulvectomy[b]	68% (47)	64% (73)	50% (10)	

Note: patients not included in the table had unknown status.
[a] Includes partial and skinning vulvectomy.
[b] Includes simple vulvectomy, and modified radical vulvectomy (hemivulvectomy).

Results

Baseline characteristics are described in Table 1. The median patient age was 73 years (range, 34–101). The median follow-up time was 49.1 months (range, 0–260). After pathology review, 69 patients (34%) had negative surgical margins, 116 (56%) had close margins and 20 (10%) had positive margins. Adjuvant treatment consisted of RT alone in 40 (20%), RT and chemotherapy in 21 (10%) or chemotherapy alone in 3 women (1%); 141 (69%) had neither chemotherapy nor RT. Of 61 patients treated with RT, 15 (25%) had negative, 40 (66%) had close and 6 (10%) had positive margins. The median vulvar RT dose was 50.4 Gy in patients with negative margins, 47.4 Gy in patients with close margins and 47.6 Gy in patients with positive margins.

A total of 78 recurrences (34%) were recorded with a median time to recurrence of 17.8 months (range, 2–124). The 4-year RFS rate for all patients was 53%. Predictors of RFS on Cox multivariate analysis included nodal involvement, positive margins (HR = 2.5, 95% CI 1.14–5.5) and smoking status but not depth of invasion. The actuarial 4-year OS rate for all patients was 73%. Only nodal status and tumor size predicted OS in the final Cox model. Fig. 1 shows RFS and OS by margin status.

In 62/78 women (79%), the vulva was the first site of recurrence; for 2 others, it was a subsequent site of recurrence. Initial stages of disease in patients who had any VR were IA (4/28, 14%), IB (20/56, 36%), II (22/70, 31%), III (14/42, 33%) and IVA (2/8, 25%). There was a significant association of VR with margin status (chi-square p =0.0006). The 4-year rates of FFVR were 82%, 63% and 37% among those with negative, close and positive margins, respectively (p = 0.005). The crude rate of VR was 21% (4/19) in women treated with ≥56 Gy and was 34% (11/32) in those treated with ≤50.4 Gy. The log-rank p value for VR by RT dose (< versus ≥56 Gy) was p = 0.046. VR was not associated with clinical stage, vulvar RT, lymphovascular invasion, tumor size, depth of invasion, smoking status or lymph-node status. In the final Cox analysis, VR was significantly increased in women with close (HR = 3.03, 95% CI 1.46–6.26) or positive (HR = 7.02, 95% CI 2.66–18.54) margins. Fig. 2 shows the Kaplan–Meier curves of freedom from vulvar recurrence by margin status and by radiation dose.

There was no interaction between positive margins, radiation, radiation dose, and local recurrence.

Among the 166 patients treated without vulvar RT, the overall crude rate of first VR was 14% (8/58) for those with negative margins, 37% (34/92) with close margins and 56% (9/16) with positive

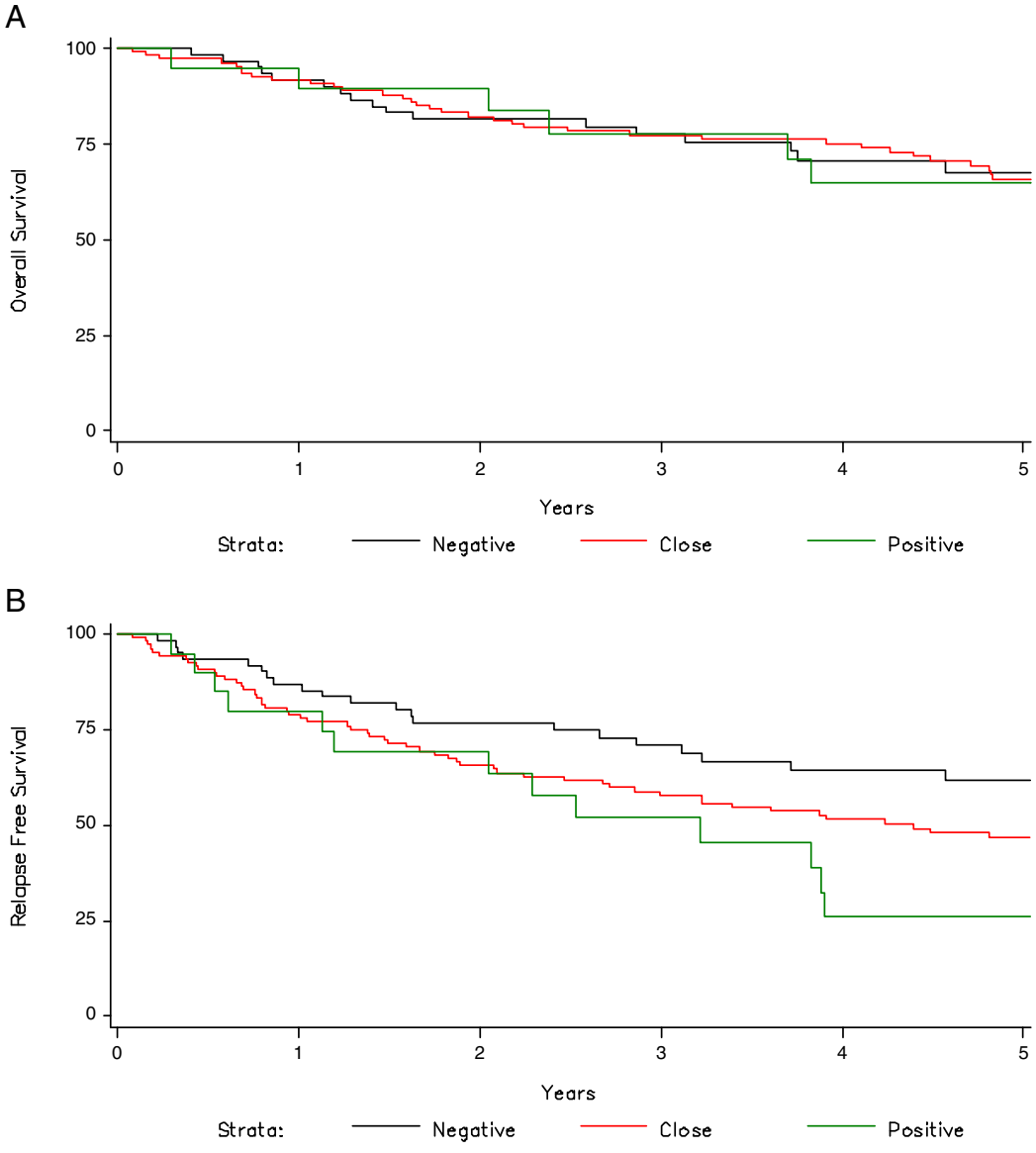

Fig. 1. Overall survival (A) and relapse-free survival (B) by margin status.

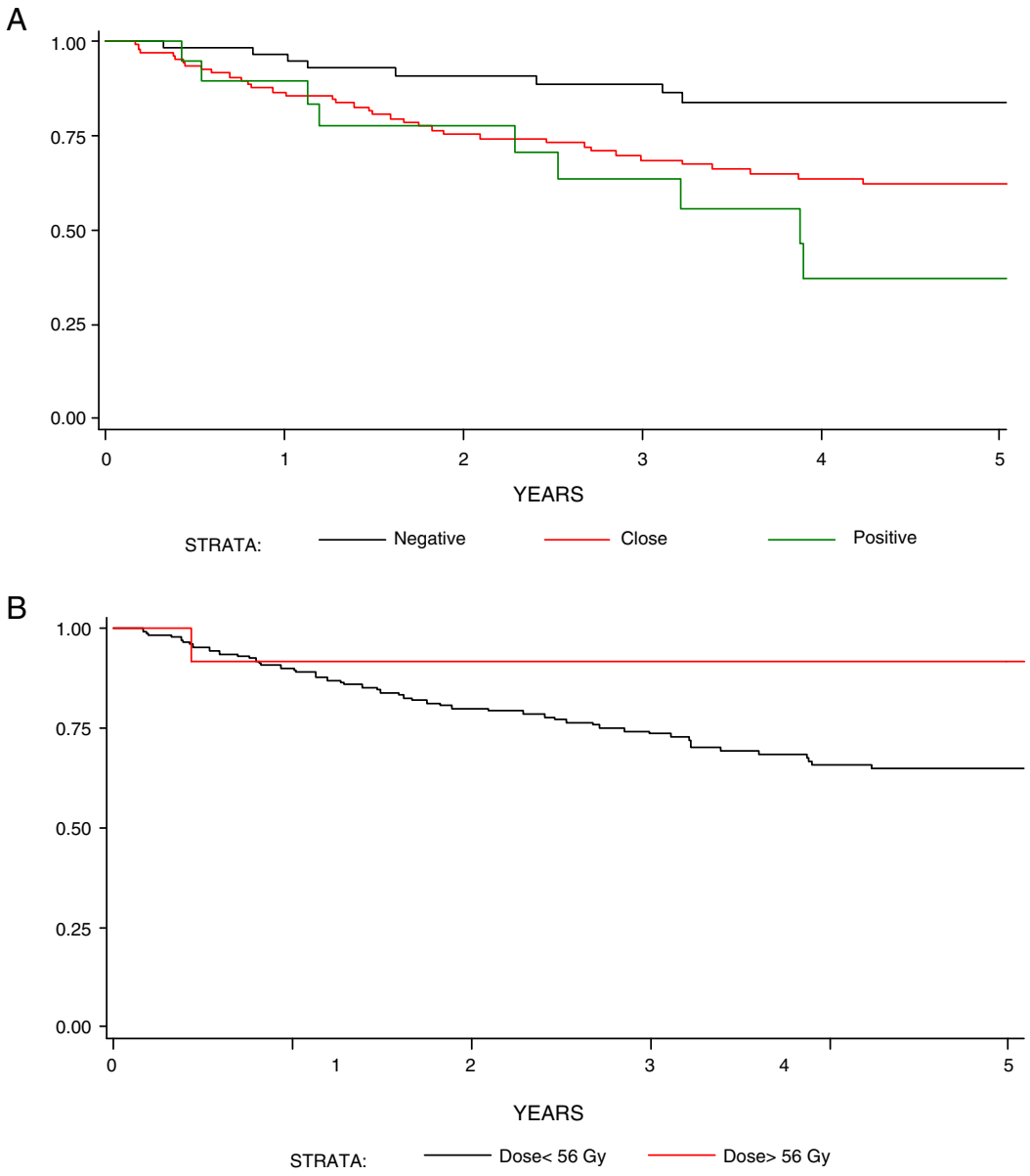

Fig. 2. Freedom from vulvar relapse by margin status (A) and radiation dose (B).

margins. For the 39 patients treated with RT to the vulva, the corresponding rates were 9% (1/11) with negative margins, 42% (10/24) with close margins and 0% (0/4) with positive margins. Among the 62 patients who had any RT (vulvar and/or nodal), VR rates were 13% (2/16) with negative margins, 35% (14/40) with close margins and 17% (1/6) with positive margins.

In secondary analyses for the patients with close and positive margins, 45 vulvar recurrences were identified among 116 patients in the close-margin cohort. Of the 116, 92 (79%) did not receive RT and of those, 34 (37%) had a vulvar recurrence. Of the 24 patients who did receive RT, 10 (42%) had a vulvar recurrence. The median dose to the vulva was 45 Gy for women with recurrence and was 50.4 Gy for those without. Of the 20 patients with positive margins, 16 did not receive RT and 9 (56%) of these had a VR. Of the 4 patients treated with vulvar RT in the positive margin group, none relapsed.

Margin distance and the number of recurrences by mm margin increment are shown in Fig. 3. For the entire study cohort, the risk of VR by mm increase in margin distance as a continuous variable was HR = 0.73 (95% CI, 0.53–1.01). The median distance to the closest margin for all 116 close-margin patients was 4 mm. A total of 55 patients had margins of 1–1.5 cm; 7 of these had a recurrence. However, margins ≥5 mm were associated with a significantly reduced risk of VR (HR = 0.53, 95% CI 0.31–0.9).

Discussion

This analysis, the largest series to date, confirms the importance of margin status in predicting vulvar recurrence. Though relapses did occur with margins up to 9 mm, margins ≥5 mm were associated with a significantly reduced risk of VR. The study also indicates that a radiation dose ≥56 Gy may reduce the risk of VR.

Three series have assessed the impact of close margins in postoperative vulvar-cancer patients. Heaps et al. reported on 135 patients not treated with RT, 21 of whom developed a vulvar recurrence [14]. None of the 91 patients with a tumor-free margin >8 mm on tissue section had a local recurrence whereas 21/44 patients with a margin <8 mm had a local recurrence [14]. Faul et al. [8] reported on 62 patients with either positive or close margins; 31 were observed

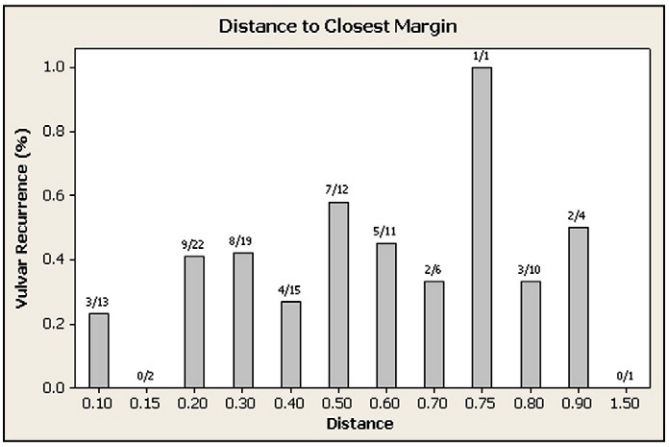

Fig. 3. Number of relapses by distance (in cm) for patients with close (<1 cm) margins.

and 31 were treated with vulvar radiation. The crude local recurrence rate was 58% in the observation group and 16% in the irradiated group. RT was associated with a significantly reduced rate of recurrence, but the dose of RT was not reported. Chan et al. [7] reported on 90 patients, 19 of whom received adjuvant RT, although the dose and the selection criteria for the use of RT were not described (including the use of margin status). Nevertheless, 30 patients had negative margins and none had a local recurrence. Of the 53 patients with close margins, 12 (23%) had a local recurrence. These studies confirm the high risk of local recurrence conferred by the presence of close margins, with the highest risk in patients with <5 mm margins.

In the current analysis, the use of RT was associated with a significantly lower risk of vulvar recurrence. The Heaps et al. [14] and Faul et al. [8] studies also showed lower vulvar recurrence rates in patients treated with RT; however, neither reported a potential dose threshold required for risk reduction. In our analysis, a dose ≥56 Gy was associated with a lower crude VR rate than was ≤50.4 Gy.

Strengths of this study include the higher number of patients compared to previously published series, the re-review of pathology to confirm margin size, and the detailed radiation information available allowing analysis of dose effect. Limitations include the retrospective nature of single-institutional series.

In conclusion, histopathologic determination of margin status by measuring the distance between the border of the tumor and the closest surgical resection margin is an important component of vulvar carcinoma management. For patients with close or positive margins, a radiation dose ≥56 Gy should be administered to the vulva in order to prevent a subsequent local recurrence.

Conflict of interest statement

The authors declare that actual or potential conflicts of interest do not exist.

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