Vulval cancer: what is an adequate surgical margin?

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Summary

Objective: To determine the accuracy of naked eye assessment of surgical margins after formalin fixation in vulval cancer in comparison with microscopic assessment. *Design:* Retrospective review. *Setting:* The Gynaecological Cancer Centre, St Bartholomew's Hospital, London, UK. *Population:* Patients with primary vulval cancer who underwent surgery from 1997 to 2006. *Methods:* Histopathology reports were reviewed and data on surgical margins were analysed. After formalin fixation, pathologists analysed surgical margins and measured them with a ruler. This measurement was compared with microscopic measurement. Other clinicopathologic variables were also recorded and compared. *Main outcome measure:* Comparison between macroscopic and microscopic measurement, and the relation to clinicopathological variables. *Results:* Naked eye assessment of surgical margins was within 2 mm of correlated microscopic measurement in 29 patients *(Group 1).* In ten patients the macroscopic measurement of clear margins was less than the microscopic (Group 2). In the remaining 11 cases (22%) naked eye observation overestimated the normal skin margins (Group 3). Seven patients from this group eventually fell into the unfavourable prognostic category of surgical margins < 8 mm. The presence of LVSI was significantly more frequent in Group 3 than in the other two groups (p = 0.01). The difference between other variables of the study groups was statistically non-significant. *Conclusion:* Our study demonstrates that naked eye assessment of surgical margins after formalin fixation is inaccurate and that surgical margins are often inadequate. We conclude that tumours with LVSI should be considered for a wider surgical excision.

Key words: Vulval cancer; Surgical margin; LVSI.

Introduction

Vulval cancer constitutes only 4% of female genital tract cancers but represents major clinical dilemmas. Although the majority of patients are over 70, often with multiple medical comorbidities, 20% of patients are under the age of 50. In the United Kingdom, the incidence of vulval cancer has shown an increasing trend since the mid-1990s and has now reached a similar level to that of 1975 with approximately 1,000 diagnoses each year and 380 deaths from disease [1]. In the United States the incidence of vulval carcinoma has increased by 20% since 1973 and the incidence of in situ vulval cancer by a striking 411% [2].

Radical excision of the primary lesion with unilateral or bilateral inguinofemoral lymph node dissection continues to be the standard of care for patients with vulval cancer. The traditional butterfly en-bloc resection of the vulva and groins described by Antoine Basset in 1912 and promoted by Stanley Way in the 1940s, was associated with high cure rates but significant morbidity [3]. A reduction in radicality was achieved during the last century to preserve sexual function and to reduce postoperative morbidity including wound dehiscence, infection, and disfiguration. Radical wide local excision with separate groin incision(s) eventually became the standard of surgical care by reducing morbidity without compromising survival [4-7]. Further reduction in morbidity in the groins has more recently been proposed using sentinel node techniques or ultrasound-guided fine needle aspiration cytology [8, 9].

Reducing the extent of surgical resection is not without risk. In spite of clear surgical margins, recurrence of vulval cancer is frequent (12-37%) with more than half of cases having a local component [10]. Surgical margin status, depth of invasion, size of tumour, pattern of infiltration (pushing vs spray pattern), and lymphovascular space invasion (LVSI) have been established for some time as the most important prognostic factors for local recurrence [11]. Tumour-free surgical margins < 8 mm measured in a formalin-fixed pathology specimen are clearly associated with significant risk for local recurrence, while margins ≥ 8 mm are not [12, 13]. On the basis of these findings, many clinical guidelines and textbooks recommend that a surgical margin of 1-1.5 cm be removed with the tumour at the time of surgery [8, 14, 15]. However, others have criticised this practice as there is a high rate (50%) of pathological margins < 8 mm in spite of removing 1 cm of an apparent clear surgical margin intraoperatively [8].

Naked eye estimation of surgical margins is the most important step in planning resection of vulval cancer. However, to date there are no data on the correlation of macroscopic assessment and the microscopic measurement of surgical margins. The aim of this study was to determine the accuracy of naked eye assessment of surgical margins after formalin fixation in comparison with microscopic measurement.

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Patients and Methods

A retrospective analysis of hospital notes of patients who underwent surgical treatment for primary vulval cancer at St Bartholomew's Hospital during the period 1997-2006 was performed. The departmental policy of removing an apparently tumour-free surgical margin at least 1 cm during the operative procedure was applied to all patients. Histopathology reports were reviewed and data on surgical margins analysed. Patients with incomplete data on surgical margins were excluded from the study.

After formalin fixation, pathologists analysed the lateral surgical margins and measured them with a ruler in the course of routine macroscopic examination of the specimen. This macroscopic assessment of the lateral surgical margins was compared with microscopic measurement which was taken by an ocular micrometer. Data on deep surgical margins were not included in this study. Other clinicopathologic variables, including age, stage, grade, tumour diameter, presence of LSVI, site of tumour, and type of operation were also recorded. For statistical analysis, Fisher's exact test, the chi-square test, and unpaired t-test were performed using GraphPad Prism version 5.00 for Windows (GraphPad Software, San Diego CA, USA).

Results

Data of 50 consecutive patients with primary vulval cancer were available for analysis. The mean age of patients was 70 years (24-89 years). Thirty-one patients were staged as FIGO Stage II, 12 as Stage III and seven as Stage IVA. Thirty-eight patients (76%) underwent some form of radical vulvectomy (total or hemi-vulvectomy, anterior or posterior horseshoe vulvectomy) and the rest of the patients (24%) received wide local excision (WLE). Forty-five patients underwent bilateral groin node dissection, three received unilateral lymphadenectomy, and two patients did not undergo this procedure due to the palliative nature of their surgical procedure. All cancers were squamous in type: 34% were grade 1, 40% grade 2, and 26% grade 3.

Naked eye assessment of surgical margins after formalin fixation was within 2 mm of microscopic measurement in 29 of the 50 patients (58% - *Group 1*). In ten patients (20%) the pathologist estimated the margins closer than under the microscope *(Group 2)*. In the remaining 11 cases (22%), naked eye observation overestimated the normal skin margin, *(Group 3)*. The difference between the naked eye and microscopic measurement ranged from 2.5-15 mm (40 to 70%). Seven of these 11 patients from Group 2 (14% of all 50 cases) had an inadequate microscopic margin less than 8 mm.

The presence of LVSI was significantly more common in Group 3 than in the other two groups (*Group 3* - 5/11 pts vs *Groups 1&2* – 2/30 pts; p = 0.01) (Table 1). The difference between other variables of the study groups was statistically non-significant: tumours in Group 3 (closer microscopic margins) were more likely to be

Table 1. — *Clinicopathologic characteristics of the study groups.*

	Adequate assessment (Group 1+2)	Inadequate assessment (Group 3)	p value	Statistical test
Stage				
II	23	7	0.87	Chi square
III	10	3		
IVA	6	1		
Grade				
1	12	5	0.25	Chi square
2	18	2		
3	9	4		
Central tumour				
Yes	17	7	0.49	Fisher's exact
No	19	4		
Presence of LVSI				
Yes	2	5	0.01	Fisher's exact
No	28	6		
Presence of LS				
Yes	9	5	0.28	Fisher's exact
No	21	5		
Presence of VIN				
Yes	19	4	0.13	Fisher's exact
No	8	6		

LVSI = lymphovascular space invasion; LS = lichen sclerosus; VIN = vulval intraepithelial neoplasia.

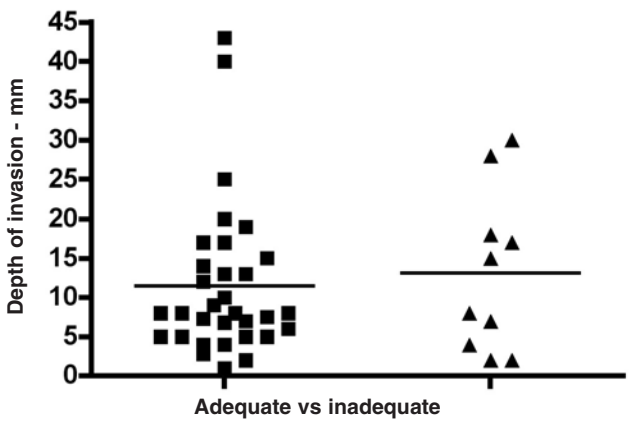

Table 2. — Difference between the means of depth of invasion in the study groups (unpaired t-test, p = 0.6518).

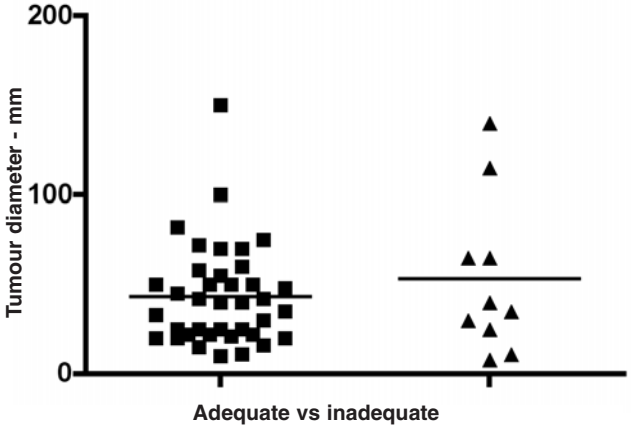

Table 3. — Difference between the means of tumour diameter in the study groups (unpaired t-test, p = 0.3762).

central than those in Groups 1 or 2 (7/11 vs 14/28 and 3/8); grade 1 and 3 tumours were more common in tumours in Group 3 than in Groups 1 or 2. In terms of skin abnormalities around the cancer, the presence of lichen sclerosus was more common in Group 3 (5/10) than in Groups 1 and 2 (7/22 and 2/8). In contrast, vulval intraepithelial neoplasia (VIN) was least frequent in Group 3 (4/10) than Groups 1 and 2 (14/22 and 5/8). The difference between the means of depth of invasion and tumour diameter in the study groups was not statistically significant (Tables 2 and 3).

Discussion

Local recurrence is by far the most common site of treatment failure in vulval cancer, with 53-86% of all recurrences developing in the vulva [10]. In spite of clear surgical margins approximately 20% of patients develop local recurrence after primary surgical treatment [10, 11]. There are three different patterns of local recurrence described: primary tumour site recurrence (within 2 cm of the previous incision), distant local recurrence (more than 2 cm from the scar), and skin bridge recurrence [11]. Rouzier *et al.* found that a close or positive margin was significantly more common in patients with primary tumour site recurrence than in more distant local recurrences. Using microscopic measurement of surgical margins in formalin-fixed specimens, Heaps *et al.* reported that 21 of the 44 patients with microscopic margins < 8 mm developed local recurrence (47.7%), as opposed to none of the 91 patients with margins ≥ 8 mm [12]. More recently their results have been supported by other publications [8, 13]. De Hullu *et al.* however found that in spite of their policy to remove a clear surgical margin of at least 1 cm, the pathological evaluation of the specimens revealed that only 50% of patients had clear margins > 8 mm, resulting in significant undertreatment [8]. To date there is a dearth of evidence in the literature on the exact accuracy of naked eye assessment of surgical margins. Interestingly, we expected that depth of tumour invasion and diameter of tumour would correlate with the inaccuracy of naked eye assessment, but the correlation was not statistically significant.

Marking the surgical margins on the vulva prior to surgical excision is an important but not always straightforward step of the operation. Tumour size, the patient's age, comorbidity and patient's wishes together with proximity to the urethra, rectum, and clitoris may compromise clear surgical margins. On the other hand, an adequate tumour-free surgical margin must be removed to reduce the risk of local recurrence. Difficulties in correctly planning surgical margins prior to surgical incision may include positional stretching of vulval skin in the lithotomy position and tissue retraction of surgical specimens after surgical excision. Misinterpretation of the surrounding epithelial changes, e.g., inflammation, lichen sclerosus, and VIN3 by the surgeon can also result in undertreatment or overtreatment. Shrinkage of surgical specimens during formalin fixation has been well documented and up to 50% shrinkage has been recorded [16]. Microscopic subcuticular invasive tumour foci or tumour emboli in lymphovascular spaces under the apparent normal margin may also alter the efficacy of naked eye assessment [16].

In our study we analysed the accuracy of naked eye assessment of surgical margins after formalin fixation, therefore positional retraction of skin and shrinkage of specimens in formalin did not alter our results. We found that in 58% of the cases there was a strong correlation between macroscopic and microscopic measurement. In 20% of the cases the naked eye method measured surgical margins even smaller than microscopic measurement. However, in 22% of cases surgical margins were inadequately assessed and were overestimated by the naked eye. In seven of these 11 patients, the closest microscopic margin was measured < 8 mm. Although these seven patients (14% of all patients) were thought to have an adequate surgical margin at the time of surgery, they eventually fell into an unfavourable prognostic group with a high risk of local recurrence. We found that the presence of LVSI in inadequately assessed tumours was significantly more frequent than in tumours with adequate margin assessment.

Our study demonstrates that macroscopic assessment of surgical margins is inaccurate and surgical margins are often inadequate when aiming for a 1 cm apparently tumour-free surgical margin. We think that as general principle, the 1 cm clear margin is inadequate when planning a vulval excision. As part of the preoperative assessment mapping biopsies around the tumour in the apparent normal surgical margin may play a role in individual surgical planning. Our results demonstrate that tumours with LVSI should be considered for a wider surgical excision than 1 cm. Prospective studies on preoperative assessment of surgical margins of vulval cancer are required to determine an adequate surgical margin.

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