Controversies and new trends in staging vulval and vaginal carcinoma

DONALD E. MARSDEN, M.D., NEVILLE F. HACKER M.D.

Gynaecological Cancer Centre, Royal Hospital for Women, Randwick

ABSTRACT The current surgical staging system for vulval carcinoma has a number of limitations in practical use, and does not provide a good spread of prognostic groupings. In this respect it has not actually improved on the previous clinical staging system. In particular, the significance of the number and morphology of involved lymph nodes needs to be taken into account in the system, and recognition given to the fact that in the absence of positive nodes, lesion size is of little significance. On the other hand, despite the problems of clinical assessment, the staging system in use for vaginal cancer is both practical and useful.

Key words vaginal neoplasms, vulval neoplasms, clinical staging, surgical staging

STAGING OF CARCINOMA OF THE VULVA In 1969, the International Federation of Obstetrics and Gynaecology (FIGO) introduced a staging system for vulvar cancer based on the TNM classification utilising the clinical assessment of tumour size, tumour site, the regional lymph nodes and a limited search for distant metastases. The most serious problem with this staging system was the inaccuracy of clinical assessment in determining groin node status. Not only may microscopic metastases be present in clinically normal nodes, but nodes may be enlarged by inflammation rather than tumour involvement.

Rutledge and colleagues (1) reported that 88% of patients with palpable groin nodes had nodal metastases. *Morley* (2) found a 25% error rate in detection of metastases by clinical examination. *Cavanagh and colleagues* (3) detected nodal metastases in about 50% of patients with palpable nodes, compared to only 8% where nodes were not palpable.

Address correspondence to:

Donald E. Marsden, M.D.
Gynaecological Cancer Centre
Royal Hospital for Women
Barker Street, Randwick, NSW, 2031, Australia
Phone (61 2) 9382 6291 Fax (61 2) 9382 6200
Email d.marsden@unsw.edu.au

Although *Iversen* (4) demonstrated that only 64% of involved groin nodes were detected by clinical palpation, and that 16% of clinically suspicious nodes were in fact negative, he found a statistically significant difference in survival between those patients with palpably involved nodes and those where the metastases were not clinically suspected, and he therefore supported the continuation of the clinical staging system arguing "enlarged suspicious lymph nodes gave valuable preoperative information about the prognosis. This information is lost if one relies upon a postoperative staging system only."

When one examines the outcome of over 1000 patients treated with curative intent in a total of seven studies, it is apparent that the clinical staging system provided a quite good differentiation of prognostic groups with five-year survivals of about 90% for stage I disease, 77 for stage II, 51 for stage III and 18 for stage IV *(Table 1)*. The main reason for this was that regardless of the problems associated with the clinical assessment of lymph nodes, the clinical stages correlated well with the incidence of positive nodes, which was about 11% for stage I, 26 for stage II, 64 for stage III and 89 for stage IV *(Table 2)*.

Table 1. Survival rates for patients treated for vulval cancer with curative intent by FIGO clinical stage (1, 9, 15-19)

Clinical stage	Number	Dead of disease	5-year survival
Stage I	376	36	90%
Stage II	310	71	77%
Stage III	238	116	51%
Stage IV	111	91	18%
Total	1035	314	70%

In 1988, the FIGO staging system for vulvar cancer was revised to include surgico-pathologic findings in accordance with the TNM system (5) *(Table 3)*. *Creasman* (6) commented that the staging had only been changed "modestly" with respect to tumour site and nodal status. Location of a tumour on the perineum no longer placed it in stage III. Nodal status was categorised as negative (N0), unilaterally positive (N1) or bilaterally positive (N2), and all patients with N1 disease were

Table 2. Proportion of patients with positive nodes by FIGO clinical stage (9, 20-21)

Clinical stage	Number	Positive nodes	Percentage
Stage I	140	15	11%
Stage II	145	38	26%
Stage III	137	88	64%
Stage IV	18	16	89%

Table 3. The FIGO staging of vulval cancer, 1994

Stage	TNM	Clinical/pathologic findings
Stage 0	Tis	Carcinoma in situ, intraepithelial carcinoma
Stage I	T1 N0 M0	Tumour 2 cm or less in greatest dimension and confined to the vulva. Nodes are negative
Stage IA	T1a N0 M0	As above with stromal invasion of up to 1 mm
Stage IB	T1b N0 M0	As above with stromal invasion greater than 1 mm
Stage II	T2 N0 M0	Tumour confined to the vulva and/or the perineum, greater than 2 cm in maximum dimension; nodes negative
Stage III	T3 N0 M0 T3 N1 M0 T1 N1 M0 T2 N1 M0	Tumour of any size with 1. Spread to the lower urethra and/or vagina and/or anus 2. Unilateral regional lymph node metastases
Stage IVA	T1 N2 M0 T2 N2 M0 T3 N2 M0 T4, any N, M0	Tumour invades any of the following: upper urethra, bladder mucosa, rectal mucosa, pelvic bone or bilateral regional lymph node metastases
Stage IVB	Any T, any N, M1	Any distant metastasis including pelvic lymph nodes

T primary tumour N regional lymph nodes (regional lymph nodes are the inguinal and femoral nodes) Tx primary tumour cannot be assessed T0 no evidence of primary tumour Nx regional lymph nodes cannot be assessed Tis carcinoma in situ N0 no lymph node metastasis T1 tumour confined to the vulva and/or perineum, 2 cm or less in maximum dimension N1 unilateral regional lymph node metastasis T2 tumour confined to the vulva and/or perineum, more than 2 cm in maximum dimension N2 bilateral regional lymph node metastasis T3 tumour involves any of the following: lower urethra, vagina, anus M distant metastasis Mx presence of distant metastases cannot be assessed T4 tumour involves any of the following: bladder mucosa, rectal mucosa, upper urethra, pelvic bone M0 no distant metastasis M1 distant metastasis (pelvic lymph node metastasis is M1)

categorised as stage III, while those with N2 disease were assigned to stage IV.

Homesley and associates (7) assessed the new FIGO staging system using data obtained from a Gynecologic Oncology Group study which included 588 patients treated between 1977 and 1984, making it by far the largest series in the literature. They confirmed the differences between the new staging system and clinical staging and noted that the new system restaged 18% of clinical stage I disease and 44% of clinical stage IV disease. In their analysis, the new staging system provided 5-year survival rates of 98% for surgical stage I disease, 85 for stage II, 74 for stage III, and 31 for stage IV.

They also identified a major problem with the new staging, in that they were able to identify low-, intermediate- and high-risk groups within stage III, with relative survivals of 95, 74 and 34% respectively. Thus there was not a reasonable spread of prognostic groupings. Patients with stage I disease had almost 100% survival while even those with stage III disease had a very good chance of 5-year survival.

A multiple regression analysis of the study group explains these findings. The most important prognostic variable for vulvar cancer was the number of positive groin nodes, and the second most important was the tumour diameter. The significance of the number of positive groin nodes on the prognosis of patients with vulvar cancer has been repeatedly demonstrated (8-10). The size of the lesion was highly relevant to groin node status, but if groin nodes were negative the size of the lesion was not an independent prognostic factor unless it was 8 cm or greater. The site of the lesion did not affect survival.

A smaller study designed to compare the merits of clinical and surgical staging was reported by *Shanbour et al.* (11) in 1992. They examined the charts of 106 patients treated between 1971 and 1990. Surgical staging clearly had greater prognostic power. Stage I disease using either system had a 100% five-year actuarial survival, a figure which appears extremely high, but where the clinical staging system was used survivals for stage II, III and IV disease were 50, 58 and 40% respectively. Utilising surgical staging gave 5-year survivals of 82% for stage II disease, 51 for stage III, 33 for stage IVA and 0 for stage IVB. As in the previous study, nodal metastasis was the most important prognostic factor. A single nodal metastasis in association with a T1 tumour was of little significance, but the presence of two or more positive nodes regardless of tumour size led to a highly significant reduction in survival. Tumour size was an independent prognostic factor with 100% survival for node-negative women with T1 tumours and 82% for those with T2 lesions. The site of the tumour had no prognostic significance.

Ndubisi and colleagues (12) performed a retrospective chart review of 135 patients treated according to a uniform protocol over a 17-year interval. They analysed disease-free survival rather than actual survival. Once again, the only two factors which were significant predictors of disease-free survival were the lesion size and the surgical status of the groin nodes. Unfortunately, they did not quantify the number of involved nodes in their analysis.

It is therefore apparent that in the current staging system, FIGO stage III disease represents a heterogenous group of patients ranging from those with involvement of the distal urethra or

vagina with negative nodes, who have an excellent prognosis, to those with multiple positive groin nodes, and a very poor prognosis. This problem needs to be addressed.

Homesley et al. (7) on the basis of the study already cited, developed what they termed the "Gynecologic Oncology Group" risk groups for vulvar cancer. The "minimal risk" group had tumours less than 2 cm in diameter and negative nodes, with a relative 5-year survival of 98%. The "low-risk" group consisted of patients with tumours between 2 and 8 cm in maximum dimension and negative nodes, or those with tumours less than 2 cm and one positive node. This group had a relative 5-year survival of 87%. An "intermediate risk" group consisted of patients with tumours over 8 cm in size and negative nodes, tumour greater than 2 cm and one positive node, and tumours less than 8 cm with two unilaterally positive nodes, and this group had a 75% relative 5-year survival. Patients with tumours over 8 cm and two unilaterally involved nodes, those with tumours of any size and 3 or more positive nodes and those with bilaterally positive nodes formed a "high-risk" group with a relative 5-year survival of only 29%.

This approach is still unsatisfactory as it fails to give an even spread of prognostic groupings. Ideally, patients with stage I disease should have about an 80-85% survival, stage II about 60-70, stage III about 35-50 and stage IV less than 30%.

Several studies in the last decade have demonstrated that it is not only the number of positive lymph nodes that is relevant to prognosis, but also the morphology of the nodes. In a study of 53 patients with stage III and IVA vulvar cancer, Origoni et al. (13) demonstrated the importance of both the size of the involved nodes and the presence or absence of extracapsular spread of tumour. For patients with involved nodes of less than 5 mm in diameter, the 5-year survival rate was 91% whereas when the involved nodes were between 5 and 15 mm in diameter it was 42%. Where the involved nodes were over 15 mm in diameter the 5-year survival fell to only 21%. Where the involvement of the nodes was intracapsular, the 5-year survival rate was 86%, but where there was extracapsular spread of tumour it was only 25%.

A similar study of 75 patients with positive lymph nodes reported by *Paladini and associates* (14) in 1994 demonstrated that, on multivariate analysis, extracapsular spread was the single most important prognostic factor, followed by the FIGO stage (III, IVA or IVB.) But all node-related parameters had an important bearing on prognosis in univariate analysis. For patients whose metastases occupied less than 5% of the node the 5-year survival was 83 compared to 17% where the metastases involved over 50% of the node. In patients with only intracapsular metastases the 5-year survival was 51% whereas even with only one node with extracapsular spread it was 15%.

More recently, van der *Velden et al.* (15) looked at the morphology of positive lymph nodes and its effect on survival in 71 patients. Extracapsular growth, two or more positive nodes and greater than 50% replacement of nodes by tumour were associated with poor outcome. The most important predictor of poor outcome was extracapsular spread, and even in patients with only one positive node, the presence of extracapsular spread reduced the 5-year survival rate from 88 to 44%.

It is apparent that there are several major problems with the current staging system for vulvar cancer. In particular, there is still a poor distribution of prognostic groupings, with survival rates for stage I disease too high. There are several other problems as well. The first is the fact that while increasing tumour size is associated with higher rates of nodal involvement, tumour size up to 8 cm in the absence of positive nodes has minimal effect on prognosis. The second problem is the heterogeneity of stage III. Finally, no account is taken of the number or morphology of excised nodes. The Gynecologic Oncology Group risk groups do not fully incorporate our understanding of the importance of nodal morphology in prognosis, and nor do they give an even spread of prognostic groupings.

It is possible that complete groin node dissections will be replaced by sentinel node biopsy in the future. Although some false negatives may occur, which would make a surgical staging system inaccurate, this situation could be considered comparable to the present situation with endometrial cancer, where the status of the lymph nodes is part of the surgical staging system but not all patients have a complete (or even partial) lymphadenectomy.

STAGING OF CARCINOMA OF THE VAGINA Primary cancer of the vagina is an uncommon condition. The staging used by FIGO is clinical, utilising physical examination, vaginal examination, cystoscopy, proctoscopy and chest radiographs, with skeletal radiographs if there is a suspicion of bone metastases *(Table 4)*. Surgery has a limited role in treating the disease, partly because of the close proximity of the bladder and rectum which mean that extremely radical surgery is required to elim-

Table 4. FIGO staging for vaginal cancer

Stage 0	Carcinoma in situ, intraepithelial neoplasia grade 3
Stage I	The carcinoma is limited to the vaginal wall
Stage II	The carcinoma has involved the subvaginal tissue but has not extended to the pelvic wall
Stage III	The carcinoma has extended to the pelvic wall
Stage IV	The carcinoma has extended beyond the true pelvis or has involved the mucosa of the bladder or rectum; bullous oedema as such does not allow a case to be allocated to stage IV
IVA	Tumour invades bladder and/or rectal mucosa and/or direct extension beyond the true pelvis.
IVB	Spread to distant organs

Table 5. Distribution of vaginal cancers by stage (22-32)

Stage	Number	Percentage
Stage I	358	26 %
Stage II	511	37%
Stage III	331	24%
Stage IV	175	13%

Table 6. Five-year survival rates for vaginal cancer by stage (23-24, 26-29, 33)

Stage	Number	5-year survival
Stage I	212	69%
Stage II	274	48%
Stage III	245	33%
Stage IV	132	18%

inate the disease and partly because of the fact that many cases present with disease beyond the vagina. These facts make surgico-pathological staging inappropriate.

The only major problem with the staging system lies in the difficulty of accurately determining the extent of spread into subvaginal tissues, and this is reflected in the wide range of stage distributions and the wide range of survivals reported within each stage. Despite this, an examination of *Table 5* shows that, with pooled results from many studies, the staging system provides what would be considered a reasonable proportion of patients in the various stages of the disease, and as shown in *Table 6,* the clinical stage correlates well with prognosis.

REFERENCES

1. Rutledge F, Smith JP, Franklin EW III. Carcinoma of the vulva. Am J Obstet Gynecol 1970; 106:1117-1129.

2. Morley GW. Infiltrative carcinoma of the vulva: Results of surgical treatment. Am J Obstet Gynecol 1976; 124:874.

3. Cavanagh D, Hovadhanakul P, Taylor H. Carcinoma of the vulva. Missouri Med 1976; 73:129.

4. Iversen T. The value of groin palpation in epidermoid carcinoma of the vulva. Gynecol Oncol 1981; 12:291-295.

5. FIGO stages - 1998 revision (Announcements). Gynecol Oncol 1989; 35:125-127.

6. Creasman WT. New gynecologic cancer staging. Obstet Gynecol 1990; 75:287-288.

7. Homesley HD, Bundy BN, Sedlis A, Yordan E, Berek JS, Jahshan A, et al. Assessment of current International Federation of Gynecology and Obstetrics staging of vulvar carcinoma relative to prognostic factors for survival. (A Gynecologic Oncology Group Study). Am J Obstet Gynecol 1991; 164:997-1004.

8. Curry SL, Wharton JT, Rutledge F. Positive groin nodes in vulvar squamous carcinoma. Gynecol Oncol 1980; 9:63-67.

9. Hacker NF, Berek JS, Lagasse LD, Leuchter RS, Moore JG. Management of regional lymph nodes and their prognostic significance in vulvar cancer. Obstet Gynecol 1983; 61:408-412.

10. Podratz KC, Symmonds RE, Taylor WF, Williams TJ. Carcinoma of the vulva: analysis of treatment and survival. Obstet Gynecol 1983; 61:63-74.

11. Shanbour KA, Mannel, RS, Morris PC, Yadack A, Walker JL. Comparison of clinical versus surgical staging systems in vulvar cancer. Obstet Gynecol 1992; 80:927-930.

12. Ndubisi B, Kaminski PF, Olt G, Sorosky J, Singapuri K, Hackett T, et al. Staging and recurrence of disease in squamous cell carcinoma of the vulva. Gynecol Oncol 1995; 59:34-37.

13. Origoni M, Sideri M, Garsia S, Carinelli SG, Ferrari AG. Prognostic value of pathological patterns of lymph node positivity in squamous cell carcinoma of the vulva stage III and IVA FIGO. Gynecol Oncol 1992; 45:313-316.

14. van der Velden J, van Lindert ACM, Lammes FB, ten Kate FJW, Sie-Go DMD, Oosting H, et al. Extracapsular growth of lymph node metastases in squamous cell carcinoma of the vulva. Cancer 1995; 75:2885-2890.

15. Boutselis JG. Radical vulvectomy for invasive squamous cell carcinoma of the vulva. Obstet Gynecol 1972; 39:827.

16. Morley GW. Infiltrative carcinoma of the vulva; results of surgical treatment. Am J Obstet Gynecol 1976; 124:874-880.

17. Japeze H, Garcia-Buneul R, Woodruffe JD. Primary vulvar neoplasia. A review of in situ and invasive carcinoma, 1935 - 1972. Obstet Gynecol 1977; 49:404.

18. Benedet JL, Turko M, Fairey RN, Boyes DA. Squamous carcinoma of the vulva. Results of treatment 1938 to 1976. Am J Obstet Gynecol 1979; 134:201-206.

19. Cavanagh D, Roberts WS, Bryson SCP, Marsden DE, Ingram JM, Anderson WR. Changing trends in the surgical treatment of carcinoma of the vulva. Surg Gynecol Obstet 1986; 162:164-168.

20. Green TH Jr. Carcinoma of the vulva: a reassesment. Obstet Gynecol 1978; 52:462-468.

21. Iversen T, Aaalders JG, Christensen A, Kolstad P. Squamous cell carcinoma of the vulva: a review of 424 patients, 1956 - 1974. Gynecol Oncol 1980; 9:271-279.

22. Ball HG, Berman ML. Management of primary vaginal carcinoma. Gynecol Oncol 1982; 14:154-163.

23. Houghton CRS, Iversen T. Squamous cell carcinoma of the vagina: a clinical study of the location of the tumor. Gynecol Oncol 1982; 13:365-372.

24. Benedet JL, Murphy KJ, Fairey RN, Boyes DA. Primary invasive carcinoma of the vagina. Obstet Gynecol 1983; 62:715-719.

25. PetersWA, Kumar NB, Morley GW. Carcinoma of the vagina. Cancer 1985; 55:892-897.

26. Rubin SC, Young J, Mikuta JJ. Squamous carcinoma of the vagina: treatment, complications and long term follow up. Gynecol Oncol 1985; 20:346-353.

27. Kucera H, Langer M, Smekal G, Weghaupt K. Radiotherapy for primary carcinoma of the vagina: management and results of different therapeutic schemes. Gynecol Oncol 1985; 21:87-93.

28. Eddy GL, Marks RD, Miller MC, Underwood PB. Primary invasive vaginal carcinoma. Am J Obstet Gynecol 1991; 165:292-298.

29. Kirkbridge P, Fyles A, Rawlings GA, Manchul L, Levin W, Murphy KJ. Carcinoma of the vagina: experience at the Princess Margaret Hospital (1974-1989). Gynecol Oncol 1995; 56:435-443.

30. Stock RG, Chen ASJ, Seski J. A 30-year experience in the management of primary carcinoma of the vagina: analysis of prognostic factors and treatment modalities. Gynecol Oncol 1995; 56:45-52.

31. Chyle V, Zagars GK, Wheeler JA, Wharton JT, Delclos L. Definitive radiotherapy for carcinoma of the vagina: outcome and prognostic factors. Int J Radiat Oncol Biol Phys 1996; 35:891-905.

32. Ali MM, Huang DT, Goplerud DR, Howells R, Lu JD. Radiation alone for carcinoma of the vagina: variation in response related to location of the primary tumor. Cancer 1996; 77:1934-1939.

33. Pride GL, Schultz AE, Chuprevich TW, Buchler DA. Primary invasive squamous cell carcinoma of the vagina. Obstet Gynecol 1979; 149:233-237.