Tissue microarray in prognostic studies on vulva cancer
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Chapter 6

Prognostic value of bilateral positive nodes in squamous cell cancer of the vulva

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Objectives
The aim of the current study was, first, to determine whether laterality of lymph node metastases has prognostic significance, independent of the number of lymph node metastases. Second, to determine the prognostic significance of extracapsular spread irrespective of the number of lymph node metastases.

Methods
Data on 134 patients with stage III/IVA vulva cancer from 1982 till 2004 and treated with curative intent in either the Academic Medical Centre in Amsterdam or the Mercy Hospital for Women in Melbourne were reviewed. The impact of the number of lymph node metastases, extracapsular spread and bilateral existence of lymph node metastases on survival was determined.

Results
The bilateral presence of lymph node metastases is not a significant predictor for survival if a correction is made for the number of lymph node metastases (hazards ratio, 1.31, 95% confidence interval, 0.68 - 2.51; \( P = 0.420 \)). If extracapsular spread is put into the model as well, this is the only parameter of prognostic significance in multivariate analysis (hazards ratio, 5.27; 95% confidence interval, 2.60 - 10.67; \( P < 0.001 \)). The five-year survival of patients with extracapsular spread is only 31%, which is considerably lower than the 80% survival of patients with only intracapsular metastases.

Conclusions
In conclusion, there is growing evidence that bilateral existence of lymph node metastases is not a sufficient variable to qualify stage. Extracapsular spread, however, seems to be the most valuable lymph node-associated prognostic factor for survival.
Introduction

Vulva cancer is a rare disease with an incidence of two per 100,000 women per year. The most frequent histologic subtype is squamous cell cancer with a frequency of 70%. (1) A clinical staging system was used until 1988. The recognition of the importance of pathologic lymph node status for survival and the inability to predict lymph node status accurately by physical examination urged the International Federation of Gynecology and Obstetrics (FIGO) to convert the staging system into a surgical pathologic system.(2;3) Based on this staging system, approximately 40% of patients have stage III/IV disease at first presentation.(4) The presence of unilateral nodal involvement was introduced into stage III, whereas the presence of bilateral positive groin nodes was introduced into stage IVA. Stage III entails both patients with unilateral positive nodes irrespective of local tumor extension and patients with negative nodes but with locally advanced tumors with adjacent spread into the lower urethra, vagina, or anus. Stage IVA entails both patients with bilateral positive nodes irrespective of local tumor extension and patients with negative nodes but with extension into the upper urethra, vagina, bladder mucosa, rectum or pelvic bones.

It is not clear whether the variable “bilateral positive lymph nodes” has independent prognostic value or just reflects the presence of multiple positive nodes. For example, in the only existing prospective study on prognostic factors in vulva cancer based on a large number of patients, the number of positive nodes proved to be a powerful predictor for survival.(5) Other studies came to the same conclusion.(6-15) Although, in the study by Homesley et al., the variable “bilateral positive nodes” was a significant prognostic factor in the univariate analysis, in the multivariate analysis, only the number of positive nodes, tumor diameter and clinical node status showed prognostic significance.

The conclusion of an analysis of 55 patients with stage III/IVA vulva cancer has been that the prognosis of patients with bilateral positive nodes (stage IVA) is similar to patients with 2 or more unilateral positive nodes (stage III).(16) These results suggest that the unfavorable prognosis of the bilateral presence of lymph node metastases is not caused by the mere bilateral existence of the metastases but by the presence of multiple lymph node metastases.

Although extracapsular spread is an independent factor for survival in the majority of studies on this issue, it is not included in the FIGO staging system.(9;10;12;15) The aim of the current study was, first, to determine whether laterality of lymph node metastases has prognostic significance, independent of the number of lymph node metastases. Second was to determine the prognostic significance of extracapsular spread irrespective of the number of lymph node metastases.
Materials and methods

The databases of the Department of Gynecologic Oncology of the Academic Medical Centre, Amsterdam, The Netherlands, and of the Department of Gynecologic Oncology of the Mercy Hospital for Women, Melbourne, Australia, were reviewed retrospectively. Data on patients with stage III/IVA vulva cancer from 1982 till 2004 and treated with curative intent were reviewed. In this period, the 1988 FIGO staging system was used. One hundred and sixty consecutive patients with stage III or IVA disease were treated. Twenty-five patients with stage III and IVA of the disease based on local tumor extension into vagina, urethra and/or anus, irrespective of nodal status, were excluded. One patient was lost to follow-up and excluded as well. Therefore, the study group comprised 134 patients. Data on age, treatment, tumor diameter, number of positive nodes, bilateral presence of lymph node metastases, stage, and extracapsular extension were retrieved. Extracapsular spread of tumor was defined as squamous cell carcinoma extending through the nodal capsule into the perinodal fatty tissue. Deposits inside afferent lymph vessels were not assessed as extracapsular spread. The impact on survival of the number of lymph node metastases and extracapsular spread was determined.

The analysis of the impact of bilateral existence of lymph node metastases was also performed on the data of patients with more than one lymph node metastasis (n=80). This selection was made because patients with one lymph node metastasis have unilateral disease par definition.

Patients from 1982 till 1988 initially staged according to the 1971 staging system were retrospectively restaged according to the 1988 staging system. All patients were treated with curative intent. In this study, treatment of patients usually entailed radical vulvectomy with bilateral inguinofemoral lymphadenectomy. Until 1993, all the patients from Amsterdam underwent an en bloc resection and adjuvant inguinal and pelvic radiotherapy. All the patients from Melbourne and those from Amsterdam after 1994, having more than one positive node or extracapsular tumor extension, had adjuvant radiotherapy. Seventy-two percent (96/134) of patients had adjuvant radiotherapy.

Statistical analysis

Outcome was defined as no clinical evidence of disease, dead of disease and inter-current death. Patients were usually followed up every 3 months during the first year, every 6 months the second and third year, and yearly thereafter.

Survival was defined from the date of surgery to the date of death or last seen. Survival function was estimated by the Kaplan-Meier method (inter-current deaths were censored). Univariate and multivariate analyses were performed in the entire study group (N=134) to calculate the predictive value for disease-specific survival of number of positive nodes,
extracapsular spread of tumor, and bilateral presence of lymph node metastases. Calculations were performed with SPSS for Windows (version 14.02, SPPS Inc, United Kingdom). 

P values were calculated by a 2-sided test, and a P value < 0.05 was considered to be significant. No correction was made for multiple testing.

Results

The disease-specific survivals at 5 and 10 years were 53% and 46%, respectively. The median follow-up of patients not dying was 52 months (range, 4 – 188 months). Forty-five patients (40%) died of recurrent or progressive disease. Twenty-five patients (19%) died of inter-current diseases. Patient characteristics are shown in Table 1. In the entire group of patients, 71% (95/134) had unilateral lymph node metastases and 29% (39/134) had bilateral nodes. Of those with unilateral nodes, 57% (54/95) had 1 positive lymph node, 26% (25/95) had 2 positive lymph nodes, and the remaining 17% had 3 or more lymph node metastases. The maximum number was 6 positive nodes in 2 patients. In the group of patients with bilateral nodes, 26% (10/39) had 2 and 74% (29/39) had 3 or more lymph node metastases. The maximum number was 17 in one patient. Extracapsular spread was present in 43% (41/95) of the patients with unilateral and in 74% (29/39) of the patients with bilateral lymph node metastases.

Table 1. Patient characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Unilateral Lymph Node Metastases, n (%)/(Range)</th>
<th>Bilateral Lymph Node Metastases, n (%)/(Range)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. patients</td>
<td>95 (71)</td>
<td>39 (29)</td>
<td>134</td>
</tr>
<tr>
<td>Age (distribution), y</td>
<td>72 (34-92)</td>
<td>75 (55-92)</td>
<td>75 (34-92)</td>
</tr>
<tr>
<td>5-y DSS, %</td>
<td>56</td>
<td>41</td>
<td>53</td>
</tr>
<tr>
<td>No. lymph node metastases</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>54 (57)</td>
<td></td>
<td>54 (40)</td>
</tr>
<tr>
<td>2</td>
<td>25 (26)</td>
<td>10 (26)</td>
<td>35 (26)</td>
</tr>
<tr>
<td>≥3</td>
<td>16 (17)</td>
<td>29 (74)</td>
<td>45 (34)</td>
</tr>
<tr>
<td>Extracapsular spread</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>54 (57)</td>
<td>10 (26)</td>
<td>64 (48)</td>
</tr>
<tr>
<td>Present</td>
<td>41 (43)</td>
<td>29 (74)</td>
<td>70 (52)</td>
</tr>
<tr>
<td>Tumor size</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;4 cm</td>
<td>50 (53)</td>
<td>20 (53)</td>
<td>70 (52)</td>
</tr>
<tr>
<td>≥4 cm</td>
<td>45 (47)</td>
<td>19 (47)</td>
<td>64 (48)</td>
</tr>
</tbody>
</table>

DSS indicates disease-specific survival
The impact of laterality, the number of lymph node metastases, and extracapsular spread were calculated for the whole group of patients with positive nodes (N=134). In univariate analysis, all these parameters are significant for survival (Table 2).

The number of lymph node metastases in patients with bilateral nodes is significantly higher than in patients with unilateral nodes (P < 0.001), and the number of lymph node metastases in patients with extracapsular growth is significantly higher than that in patients with only intracapsular metastases (P = 0.004).

Disease-specific survival decreases significantly in patients with 3 or more lymph node metastases (Fig. 1). The bilateral presence of lymph node metastases is not a significant predictor for survival if a correction is made for the number of lymph node metastases (hazards ratio [HR], 1.31; 95% confidence interval [CI], 0.68 - 2.51; P = 0.420). If extracapsular spread is put into the model as well, this is the only parameter of prognostic significance in multivariate analysis (HR, 5.27; 95% CI, 2.60 - 10.67; P < 0.001) (Table 2). The 5-year survival of patients with extracapsular spread is only 31%, which is considerably lower than the 80% survival of patients with only intracapsular metastases (P < 0.001). The importance of extracapsular growth versus intracapsular growth is shown in Figure 2.

### Table 2. The impact of characteristics on the survival of patients in univariate and multivariate analyses

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate analysis</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Proportional Hazard</td>
<td>P</td>
<td>Proportional Hazard</td>
<td>P</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(With Limits of 95%CI)</td>
<td></td>
<td>(With Limits of 95%CI)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. lymph node metastases</td>
<td>1.14 (1.06-1.22)</td>
<td>&lt;0.001</td>
<td>1.08 (0.99-1.18)</td>
<td>0.071</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bilateral nodes</td>
<td>1.86 (1.07-3.21)</td>
<td>0.027</td>
<td>1.01 (0.53-1.93)</td>
<td>0.971</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extracapsular spread</td>
<td>5.80 (2.91-11.57)</td>
<td>&lt;0.001</td>
<td>5.27 (2.60-10.68)</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

N=134.
Patients with two or more lymph node metastases

To analyze further whether bilateral existence of lymph node metastases has prognostic significance on its own regardless the number of nodes, the impact on survival of bilateral presence of lymph node metastases is calculated for the group of patients with 2 or more positive nodes (n=80). In this subgroup, no significant difference between the impact of bilateral node metastases and unilateral metastases on survival can be demonstrated (HR, 1.55; 95% CI, 0.81-2.97; \( P=0.189 \)). Patients with unilateral and bilateral lymph node metastases had a 5-year survival of 58% and 46%, respectively.

Discussion

This study shows that bilateral presence of lymph node metastases is not an independent factor for survival when the number of lymph node metastases is taken into account. Moreover, it confirms the results of earlier studies that the presence of extracapsular growth is the single, poorest prognostic marker of lymph node metastases.

The strength of the study is both in the uniformity and the size of the study group. It is the second largest study on this subject in the literature. In contrast to many other studies on this subject, only patients with T1 and T2 tumors were included, thus eliminating any negative influence of local extension on survival.

When the literature on this subject is reviewed, it is clear that our finding regarding the prognostic value of bilateral presence of nodal metastases is contradictory to the results of some other researchers (Table 3). In 3 studies, bilateral presence of lymph node metastases was an independent factor for survival.(6;7;13)

In the study by Burger et al, the relative risk of dying within a given period for patients with bilateral lymph node metastases was estimated to be 2.65 (95% CI, 1.03 – 6.84), compared with patients with unilateral lymph node metastases. In this study, however,
51% (26/51) of the patients with lymph node metastases had one positive node. These patients had a unilateral metastasis par definition. In our opinion, the analysis of the impact of laterality of nodes on survival has to be confined to the group of patients who are at risk for bilateral nodes and have 2 or more lymph node metastases. Besides this, the worse prognosis of patients with bilateral nodes in this study was probably also influenced by differences in number of lymph node metastases in both groups. Of 11 patients with bilateral nodes, 10 (90%) had 3 or more lymph node metastases. On the other hand, only 5 of 40 patients (13%) with unilateral lymph node metastases had three or more positive nodes. Although the authors concluded that bilateral metastases were associated with a large number of involved lymph nodes, any association between number of nodes and prognosis could not be demonstrated. It was suggested that this could be an effect of insufficient statistical power.

The conclusion in the study by Boyce et al was that patients with bilateral groin node metastases had a significantly worse outcome. The 5-year survival of patients with bilateral lymph node metastases was 39% compared with the 62% of the patients with unilateral nodes. However, this survival benefit for patients with unilateral nodes did not exist anymore after correction for the number of metastases. Six patients with 3 or more
unilateral positive nodes had a 54% 2-year survival comparable to the 52% 2-year survival of the patients with bilateral lymph node metastases.

In the study by Rutledge et al., the HR within a given period was estimated to be 6.9 (95% CI, 3.5 – 13.3) and 20.3 (95% CI, 10.1 – 40.9) for patients with unilateral lymph node metastases and patients with bilateral lymph node metastases, respectively, compared with patients without lymph node metastases. Patients with one lymph node metastasis were included in the group of patients with unilateral nodes as well. Neither the number of lymph node metastases nor whether the numbers of positive nodes were equally divided between the groups of patients with unilateral and bilateral nodes were mentioned in the report.

As is shown in Results, we found in our study bilateral existence of lymph node metastases to be significant for survival when data of patients with one positive node were included in the analysis. The conclusion of the multivariate analysis was, however, that as soon as a correction for number of lymph node metastases was made, laterality was not significant anymore.

In 3 other studies, laterality is not an independent factor for survival. (4;12;16) In the study by Lataifeh et al, patients had T3 or T4 tumors. Whether these were equally distributed among the groups with unilateral and bilateral lymph node metastases cannot be deducted from the report, which makes it difficult to draw any conclusions on the impact of bilateral existence of lymph node metastases. To eliminate the local extension of the disease as confounder, all patients with T3 and T4 tumors were excluded in our study.

In summary, the evidence found for the impact of bilateral presence of lymph node metastases on prognosis is questionable and reflects most likely the poor prognostic effect of multiple lymph node metastases, independent of laterality.

Extracapsular spread is an independent factor for survival of patients with positive lymph nodes. This result is in agreement with most of the results in former studies. (9;10;12;15) In the study by Burger et al, extracapsular spread is not an independent factor for survival. (7) In this study, survival of patients with extracapsular spread is 51% after 5 years. This is considerably better than the survival mentioned in other studies. It approaches the 5-year survival of 57% of patients with only intracapsular growth. In the other studies mentioned, survival after 5 years differed from 15% to 33% for patients with extracapsular spread and from 51% to 86% for patients with only intracapsular metastases. The difference between the study of Burger et al and the other studies might be related to 2 factors. First, the way extracapsular spread is defined could influence the result. In none of the reports of former studies is the definition of extracapsular spread mentioned. No reports are available on the issue of interobserver variability of extracapsular spread of tumor. Second, in the study by Burger et al but also in the study by Paladini et al, overall survival is used instead of disease-specific survival. This could explain the relatively low 5-year
survival rate of patients with intra-capsular metastases in both studies (57% and 51% respectively).
In conclusion, there is growing evidence that bilateral existence of lymph node metastases is not a sufficient variable to qualify stage. Extracapsular spread, however, seems to be the most valuable lymph node-associated prognostic factor for survival. A main drawback of this factor as a qualifying variable for prognosis is the lack of insight in the reproducibility of this parameter. Before the introduction of extracapsular spread in the staging system, it is of utmost importance to establish unequivocal histopathologic criteria.
References


