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Prognostic Indicators in Melanoma of the Vulva

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Background: The aim of this study was to evaluate the prognostic significance of clinical-pathologic variables in melanoma of the vulva.

Methods: From 1979 through 1995, 40 women with a diagnosis of vulvar melanoma underwent radical surgery. Patient age, tumor size and site, histologic type, ulceration, tumor thickness, lymph node status, and number of positive lymph nodes were assessed for prognostic significance by multivariate analysis.

Results: Tumor thickness was a significant predictor of lymph node involvement, but not of survival. The most powerful predictors of survival by multivariate analysis were the lymph node status ($P = .002$) and the number of positive lymph nodes ($P = .00003$).

Conclusions: The number of positive lymph nodes represents the strongest prognostic factor in melanoma of the vulva. Because of the lack of effective adjuvant therapies, such prognostic indicators might be used to define the timing and extent of the surgical approach.

Key Words: Malignant melanoma—Vulvar neoplasm—Prognostic factors—Survival.

Melanoma is the second most common malignancy of the vulva, accounting for 5% to 10% of all primary vulvar malignant neoplasms[1] and 1.3% to 2.3% of all melanoma among women.[1,2] The FIGO clinical staging system has been found to correlate insufficiently with survival.[3,4] Survival of patients with vulvar melanoma varies from 13% to 55%, and has been correlated to the depth of invasion,[5] tumor thickness,[6] tumor growth pattern,[3,7] DNA ploidy,[8] cell mitotic rate,[9] and overall lymph node status,[10] which is strictly dependent on tumor thickness.

Radical vulvectomy with groin node dissection has represented the treatment of choice for decades. In 1983, it was reported that early stage cutaneous melanoma could be treated as effectively with wide local excision as with radical surgery.[11] This concept was then applied to vulvar melanoma, and some authors have reported no differences in survival between patients treated with radical surgery and patients managed conservatively.[12,13] The histologic microstaging system seems to be useful in the identification of high-risk patients.[5,6,10]

The present study was undertaken to evaluate the prognostic significance of clinical and pathologic variables in melanoma of the vulva.

PATIENTS AND METHODS

The retrospective analysis was conducted on 41 consecutive vulvar melanoma patients treated at the Istituto Nazionale Tumori of Milan between 1978 and 1995. One patient, admitted for a large local recurrence after hemivulvectomy performed elsewhere, was excluded from the study, leaving 40 cases for analysis. The analysis included patient characteristics, presenting symptoms, site and size of the primary tumor, ulceration, primary treatment, histologic type, microstaging (assigned according to Breslow tumor thickness), lymph node status, and number of positive inguinal lymph nodes. Institute pathologists reviewed histologic slides. For 2 of the 17 cases, in which the primary tumor had already been excised in another institution, the histologic slides were not available for review. In addition, thickness could not be evaluated in three cases from slides coming from other referring hospitals.

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Primary vulvar melanoma has been treated, according to established local institutional guidelines, with radical vulvectomy and bilateral inguinofemoral lymphadenectomy (i.e., dissection of superficial inguinal nodes and superficial and deep femoral nodes). In cases of inguinal metastases on frozen section, node dissection was extended to the pelvic nodes (common, external, internal iliac, and obturator chains).

Each clinical or pathologic factor first was evaluated according to pathologic lymph node status using the χ^2 test with Yates' correction and Fisher's exact test if necessary. Survival was calculated with the actuarial method, and the log-rank test[14] was used to evaluate differences in survival curves. All variables gave results significant to univariate analysis and were successively subjected to multivariate analysis using the Cox regression model.[15] Significance was defined as $P < .05$.

RESULTS

Clinical Features

The mean age of the patients was 58 years (range, 32–80). Eight were premenopausal and 32 were postmenopausal. In the latter group, the interval from menopause to onset of the disease averaged 15 years. Twenty-nine patients were symptomatic: of these, 7 patients complained of pruritus and 22 of a "lump" on the vulva (associated with bleeding in 8 cases and discharge in 11 cases). Eleven patients were asymptomatic. The mean interval from the beginning of symptoms until seeking medical advice was 4 months (range, 2–48).

Primary Tumor

The tumor involved the labia (minora or majora) in 25 of 40 (62.5%) cases, whereas midline structures (clitoris, urethra) were involved in 12 cases (30%); in 3 cases previously operated elsewhere, the site of the primary was unknown. The diameter of the primary tumor was known in 35 cases (87.5%): it was less than 2 cm in 22 cases, 2 to 4 cm in 9 cases, and greater than 4 cm in 4 cases. The tumor was ulcerated in 22 cases (55%).

Histology

Histologic type was superficial spreading melanoma in 19 cases, nodular melanoma in 13 cases, and mucosal lentiginous melanoma in 4 cases. The lesion could not be classified in 4 cases previously operated elsewhere. Tumor thickness, known in 35 cases, was greater than 3 mm in 20 cases and less than 0.75 in only 2 cases; in 5 cases tumor thickness was between 0.75 and 1.5 mm, and in 8 cases it was between 1.51 and 3 mm. Table 1 lists tumor thickness together with the incidence of lymph node metastases.

TABLE 1. *Lymph node involvement by tumor thickness, according to the Breslow microstaging system*

Tumor thickness (mm)	No. cases	Lymph node involvement
<0.75	2	—
0.76–1.5	5	—
1.51–3.0	8	—
>3.0	20	12

Surgery

All patients underwent radical vulvectomy. Bilateral inguinofemoral lymphadenectomy was performed in 23 patients, bilateral inguinofemoral and pelvic lymphadenectomy in 14 cases, and unilateral inguinofemoral lymphadenectomy in 2 cases. In one of the latter two cases, contralateral node dissection could not be carried out because of anesthesiologic problems. The other of these two cases was a 4-cm, shallow superficial spreading melanoma involving the left labium major in which a unilateral node dissection was deemed sufficient. The only patient who did not undergo node dissection was an 80-year-old woman with a tumor thickness less than 0.75 mm.

Wound breakdown after radical vulvectomy was seen in eight patients (20%), and mild chronic lymphedema of the lower extremities was seen in about 40% of the patients after surgery.

Lymph Node Status

Fourteen of the 39 patients (35.9%) who underwent node dissection had nodal involvement, including 8 with unilateral inguinofemoral node metastases, 3 with bilateral inguinofemoral involvement, and 3 with bilateral inguinofemoral and pelvic involvement. In no cases were pelvic nodes involved in the absence of inguinofemoral disease. In lateral tumors, contralateral lymph nodes were never involved in the absence of ipsilateral nodal metastases. It is noteworthy that 58.3% (7/12) of the central lesions had nodal involvement, compared with 24% (6/25) of the lateral lesions. (The difference was not statistically significant: χ^2 with Yates' correction $P = .094$, probably due to the small numbers.) Lymph node metastases were found only when tumor thickness exceeded 3 mm. The correlation between depth of invasion and lymph node involvement was statistically significant ($P < .002$).

Recurrence

Twenty of the 40 patients relapsed at 7 to 37 months of follow-up. Eleven patients recurred locally, 7 at dis-

tant sites, and 2 locally and at distant sites. All patients with distant relapse (9 patients) and 5 of the 11 patients with local relapse died of cancer. The remaining 6 patients with local recurrences were alive and disease-free 12 to 23 months after the excision of their recurrence. The local recurrence rate was 20% (3 of 15) for tumor thickness less than 3 mm and 40% (8 of 20) for tumor thickness greater than 3 mm ($P = .18$). Moreover, no correlation was found between recurrence rate and lymph node status: the recurrence rate was 71.4% (10 of 14 patients) for patients with lymph node involvement and 40% (10 of 25 patients) for patients without lymph node involvement ($P = .121$, χ^2 with Yates' correction). On the contrary, a higher rate of distant relapse was found in node-positive patients than in node-negative patients (28.5% vs. 12%; $P < .05$).

Survival Analysis

The median follow-up was 48 months (range, 21–220). Of the 40 original patients, 22 were alive and disease-free, 14 had died of cancer, and 4 had died of other causes as of the last follow up in 1999. Actuarial 5-year survival was 48%. Age, size and site of the lesion, ulceration, and histologic type were not significant factors, on univariate and multivariate analysis, in determining survival; tumor thickness was a predictor of survival in univariate analysis but not on multivariate analysis. On multivariate analysis, the most powerful determinants of survival were lymph node status ($P < .002$) and number of positive lymph nodes ($P < .00003$)(Table 2). Actuarial 5-year survival was 26.8% for node-positive patients and 65.2% for node-negative patients ($P < .005$)(Fig. 1). In regard to number of positive nodes, in this analysis we evaluated different cut-off levels and identified the previously mentioned numbers (0, 1–3, >3) as the most significant. No patient with more than three positive lymph nodes was alive at 24 months of follow-up, whereas 5 of 10 patients (50%) with one to three positive nodes and 20 of 26 patients (77%) without nodal disease were alive at that point (Fig. 2).

TABLE 2. *Multivariate analysis by the Cox regression model—step-down procedure*

Variable	P value
Number of positive nodes	.00003*
Lymph node status	.0002*
Thickness	.07
Ulceration	.1

* Statistically significant.

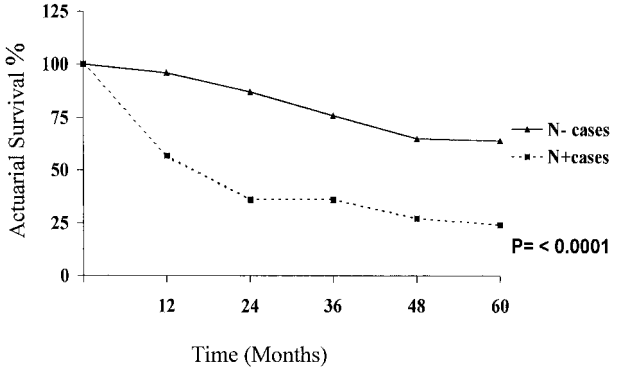

FIG. 1. Actuarial 5-year survival curves that compare patient by lymph node status (positive nodes vs. negative nodes). The difference is statistically significant.

DISCUSSION

In gynecologic oncology, studies dealing with prognostic indicators aim at the identification of subsets of patients at high risk of recurrence whose survival can be significantly improved with an adjuvant therapy. For melanoma of the vulva, identification of a high-risk patient with a poor life expectancy is pointless, because no effective adjuvant therapy is available. Recent studies suggest a survival benefit with adjuvant interferon therapy in patients with cutaneous melanoma,[16] especially when compared to the poor response to chemotherapy. Some authors stated that active, specific immunotherapy with allogenic vaccine may have a role in the postoperative treatment of high-risk vulvar malignant melanoma.[17] However, analysis of the prognostic factors might be useful to differentiate the extent and timing of the surgical approach to the patient.[18] From this point of view, all parameters analyzed for possible prognostic significance can be divided into two classes: those whose importance has been shown by some authors but not by others, such as age,[19] menopausal status,[19] site of the

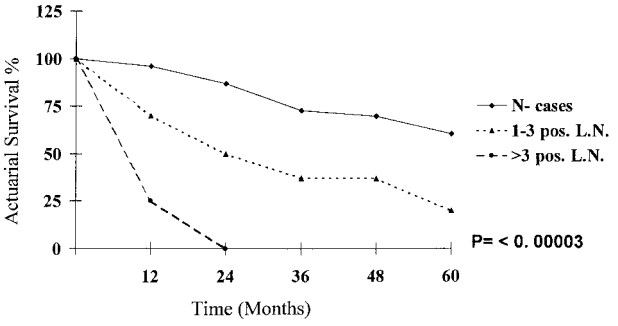

FIG. 2. Actuarial 5-year survival by number of positive lymph nodes (negative nodes vs. 1–3 positive nodes vs. > 3 positive nodes). The differences are statistically significant.

tumor,[4] and histologic type;[4,9] and those for which the real significance is not in doubt, because it has been demonstrated by most studies, such as lymph node status[10] and microstaging.[5,6]

In this series, neither clinical characteristics (e.g., age and menopausal status) nor gross pathologic features (e.g., ulceration, site of tumor, and histologic type) showed any significant correlation with survival. In regard to histology, some reports[4,9] have shown this variable to be of prognostic importance. In one of these series,[9] in which 5-year survival was 38% for nodular melanoma and 75% for superficial spreading melanoma, mean thickness was greater for the nodular type group than for the superficial spreading group. In our series, in which thickness of tumor was evenly distributed between the two histologic types, there were no differences in survival between nodular and superficial spreading melanoma (50% vs. 66.7%), a result that also has been reported by other investigators.[19]

The importance of tumor thickness is limited to the possibility of accurately predicting the presence of nodal involvement, because it was found that the microstaging system did not predict survival reliably, a result also found by Bradgate et al.[19] Most of the patients in our study ($n = 20$) had tumors thicker than 3.0 mm, and lymph node involvement was present in only those patients. This was not a significant factor for survival in multivariate analysis, however, probably because of the small number of patients. Analysis of our data showed that tumor thickness was a predictor of survival in univariate analysis but not in multivariate analysis. In our study the only parameters that acted as reliable predictors of survival were lymph node positivity and number of positive nodes. The importance of the former parameter ($P < .002$) has already been described in other studies.[10,20] Our data show for the first time, to our knowledge, the high prognostic significance of the number of positive lymph nodes, which was the most powerful independent prognostic factor ($P < .00003$) on multivariate analysis. In fact, 5-year survival was 65.2% for node-negative patients and 37.5% for patients with one to three positive nodes; all four patients with more than three positive nodes were dead at 24 months (Fig. 2).

One controversy regards the extension of surgery in primary tumor. Some authors have demonstrated that a conservative approach to melanoma of the vulva is feasible[12,13]; in our series, however, because there is no available adjuvant therapy, we performed radical vulvectomy with systematic inguinofemoral lymphadenectomy to determine whether the radical surgery was beneficial. The local recurrence rate (27.5%) was comparable with that in other series in which a conservative approach was used.[4,11,12]

Because of the small number of patients with vulvar melanoma, there are no randomized trials comparing different methods of treatment . However, as has been shown for cutaneous melanoma, it is doubtful that radical surgery in tumors larger than 3 mm would improve local recurrence rate and outcome. Furthermore, there is no evidence that vulvar melanoma behaves any differently than does cutaneous malignant melanoma.[21,22] Most surgeons have, like us, abandoned radical vulvectomy as the treatment of choice because it is difficult to accept the high complication rate and resulting deformity (which may cause sexual problems and somatopsychic reactions) associated with radical surgery when there is no clear evidence that it provides any improvement in survival.

Another controversy regards the dissection of regional nodes. In cutaneous melanoma, several randomized studies have shown that, in case of clinically negative nodes, there is no difference in survival if the lymphadenectomy is delayed until there is clinical evidence of metastasis in the lymph nodes.[23–25] The question of a prophylactic ipsilateral lymph node dissection has not yet been answered. Undoubtedly, inguinal femoral lymphadenectomy would constitute overtreatment for all patients without palpable or suspicious inguinal nodes. Intraoperative "lymphatic mapping," using Morton's[18] blue dye technique, or the more recent lymphoscintigraphic technique, which has obtained good results in other sites, might be used in vulvar cancer. Several recent studies[26,27] on vulvar cancer patients have found that lymphoscintigraphy and sentinel node biopsy under gamma-detection probe guidance may provide a more accurate assessment of the lymph node status with less aggressive treatment. Whereas Ansink[28] reported in a multicenter study that sentinel lymph node detection with blue dye only is not feasible because its negative predictive value is too low, in melanoma the combination of dynamic and static gamma camera images enables lymph node visualization with identification of the sentinel node in more than 97% of the cases.[29] This would appear to be a rational approach, avoiding unnecessary routine regional lymphadenectomy in those patients with negative sentinel node(s), but should be confirmed.

For melanoma of the vulva, the current trend is to reduce the extent of the primary surgical effort. In this context the previously mentioned prognostic indicators may be used to adjust the timing and the extent of the surgical procedures as follows: systematic radical inguinofemoral lymphadenectomy might be performed at the time of primary surgery only in cases of clinically

positive lymph nodes, to avoid the tumor progression that ultimately results in groin ulceration. Conversely, in the case of negative nodes, a two-step procedure might be suggested: (1) removal of the primary by wide local excision; and (2) in cases with shallow lesions, sentinel node biopsy or lymphadenectomy delayed until lymph node recurrence, as has been suggested for cutaneous melanoma.[23] The same procedure also is justified in cases with deeper invasion (tumor thickness >3 mm). However, in these cases the depth of invasion is strictly correlated with a high risk of nodal diseases, and our data document the strong prognostic importance of number of positive nodes. Although we cannot exclude the possibility that the different survival observed in relation to the number of involved node is an expression of a different biological behavior, we can hypothesize that the removal of metastatic disease in an early fashion, when only 1 or 2 lymph nodes are involved, might have a therapeutic value.

CONCLUSIONS

As with many studies in vulvar melanoma, this is a single-institution, retrospective series. Although such an approach is less optimal than a prospective study, the relative rareness of this tumor type and site makes prospective studies difficult.

In melanoma of the vulva, the current trend is to reduce the extent of the primary surgical effort. Current recommendations include removal of the primary by wide local excision and lymph node assessment by mapping, not complete lymphadenectomy in all patients. Inguinofemoral lymphadenectomy might be performed at the time of primary surgery only in cases of clinically positive lymph nodes.

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