Melanomas of the Vulva and Vagina

ABSTRACT: Melanomas of the vulva and vagina comprise less than 2% of melanomas in women. Although their biologic behavior appears to be similar to that of cutaneous melanoma, vulvar and vaginal melanomas appear to have a different etiology. Women presenting with pigmented vulvar lesions should undergo expedited examination and full-thickness biopsy. Vulvar and vaginal melanomas should be staged surgically using the AJCC system, which incorporates Breslow and Clark microstaging. Adverse prognostic factors include advanced age at diagnosis, central location of tumor, capillary lymphatic space involvement, ulceration, high mitotic rate, and aneuploidy. Primary surgery should include radical local excision with 1-cm skin margins for melanomas less than 1 mm thick and 2-cm margins for melanomas 1 to 4 mm thick. Deep margins should be at least 1 to 2 cm. Femoral inguinal lymphadenectomy should be performed in patients at increased risk of lymph node metastases on the basis of primary tumor characteristics. Adjuvant interferon-alfa appears to confer survival benefits in patients with regional nodal disease. Effective salvage therapy has not yet been identified. [ONCOLOGY 10(7):1017-1023, 1996]

Introduction

Melanomas of the vulva and vagina are rare, accounting for no more that 2% of melanomas among women. Population-based studies of vulvar and vaginal melanomas have recently been reported from the United States and Sweden [1,2]. In the United States, information was derived from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program, which collects data from cancer registries covering about 10% of the US population. Over a 15-year period from 1973 to 1987, 30,295 melanomas were diagnosed among men and women. Among these were 203 vulvar melanomas and 51 vaginal melanomas, which comprised 1.3% and 0.3%, respectively, of all melanomas among women. The annual incidence rates were .108 per 100,000 women for vulvar melanoma and .026 per 100,000 women for vaginal melanoma.

The Swedish study looked at melanomas of the vulva and vagina diagnosed over a 25-year period between 1960 and 1984, using the Swedish National Cancer Registry. Since 1958, Swedish law has required that all neoplasms be reported to their national cancer registry linked to a national death registry. The study identified 219 patients with vulvar melanoma and 26 patients with vaginal melanoma. A decline in the incidence of vulvar melanoma was noted, from .27 per 100,000 women per year between 1960 and 1964 to .14 per 100,000 women per year between 1980 and 1984. In contrast, the incidence of cutaneous melanoma rose in Sweden by 6% per year between 1960 and 1982, suggesting that vulvar melanoma may have a different etiology than cutaneous melanoma.

Epidemiology

In both the United States and Sweden, vulvar and vaginal melanomas tended to occur among older women, as opposed to cutaneous melanomas, which were more common among younger women. The median age at diagnosis among US women was 66 years for vulvar melanoma and 70 years for vaginal melanoma. Among Swedish women, the mean age at diagnosis was 67.7 years for vulvar melanoma and 66.3 years for vaginal melanoma.

In the United States, vulvar melanoma appeared to be more common among white women than among black women (relative risk, 2.6; 95% confidence interval [CI], 1.2 to 6.0). No such racial difference was noted for vaginal melanoma.

In the United States, women with vulvar melanoma had a median survival of 61 months, with a 60%
adjusted (for expected mortality) survival rate at 5 years and a 50% rate at 10 years. Survival for US women with vaginal melanoma was markedly worse than for those with vulvar melanoma. Women with vaginal melanoma experienced a median survival of 19 months and had a 5-year relative survival rate of 25%.

Similar survival rates were noted in Sweden. Swedish women with vulvar melanoma had a 47% relative survival rate at 5 years and a 44% rate at 10 years. Among Swedish women with vaginal melanoma, the 5-year relative survival rate was 18%.

Among US patients with vulvar melanoma, age and race were significant independent predictors of survival. The hazard ratio for black race, adjusted for age, was 5.1 (95% CI, 2.0 to 13.1). The hazard ratio for age was 1.4 per 10 years of age (95% CI, 1.3 to 1.6).

In the one prospective trial evaluating outcome in patients with vulvar melanoma, conducted by the Gynecologic Oncology Group (GOG), older patients were at significantly increased risk for recurrence, with a 26% increase for each decade (P = .02) [3]; this is consistent with SEER findings. Retrospective studies conducted by Podratz et al, Rose et al, Bradgate et al, Trimble et al, and Scheistroen et al also found a worse prognosis conferred by advanced age at diagnosis [4-8].

**Diagnosis**

Women should be instructed in routine surveillance of all skin, including that of the vulva. A hand-held mirror may facilitate examination of the vulva. Any pigmented lesions, particularly those which appear to be growing rapidly or seem irregularly irregular--with varying colors, thickness, and borders--should be reported immediately.

In retrospective series, women with vulvar melanomas present with signs and symptoms similar to those of other vulvar malignancies. They note a lump or mass on the vulva; bleeding or itching also are frequent complaints. Such reports should prompt immediate inspection of the vulva with excisional biopsy of suspicious lesions. Colposcopy with acetic acid may be helpful. Excisions should not be "shave" biopsies. Rather, small lesions should be circumferentially resected with the underlying subcutaneous tissue so that the thickness of the lesion may be measured. For larger lesions, full-thickness biopsies should be performed, such as those obtained with a Keyes punch. Benign pigmented lesions of the vulva include lentigo simplex; vulvar melanosis; junctional, compound, and intradermal nevi; dysplastic nevi; acanthosis nigricans; and seborrheic keratosis. Pigmented vulvar neoplasia may include vulvar intraepithelial neoplasia, squamous carcinoma, and Paget's disease, in addition to melanoma. Immunohistochemical studies and electron microscopy may be helpful in making the differential diagnosis. Melanomas are usually immunoreactive for S-100 protein and HMB-45. On electron microscopy, melanoma cells contain melanosomes and other ultrastructural features not present in Paget's cells.

**Staging**

In the past, cutaneous melanomas were staged using a clinical staging system, as well as microstaging systems based on tumor thickness or depth of invasion [9]. In 1983, the American Joint Committee on Cancer (AJCC) recommended the use of a new staging system that incorporates surgical staging, as well as tumor thickness or depth of invasion [10].

**Vulvar Melanomas**

Vulvar melanomas have been staged using two macrostaging systems--the AJCC staging system for cutaneous melanomas and the International Federation of Obstetrics and Gynecology (FIGO) system for squamous vulvar carcinoma (Table 1) [11]. Both of these staging systems now correlate with the TNM system [12]. In addition, a variety of microstaging systems have been used, including the Clark and Breslow systems for cutaneous melanomas and the Chung modification of the Clark system for vulvar melanoma (Table 2) [13-15]. The Clark system of levels is based on the depth of invasion relative to papillary dermis, reticular dermis, and subcutaneous fat. The Breslow system of levels is based on melanoma thickness as a multiple of 0.75 mm.

Both the Clark and Breslow systems have been shown to correlate with prognosis in patients with cutaneous melanoma. Chung and colleagues argued that Clark microstaging was inappropriate for the vulva and labia, which lack a well-defined papillary dermis, and substituted measurement of tumor thickness as a multiple of 1 mm for the middle three Clark levels.

In the predominantly retrospective literature on women with vulvar and vaginal melanoma, there has been little consistency in the use of macrostaging or microstaging systems. In addition, older series
of patients with vulvar melanoma often used the older FIGO staging, in which regional lymph nodes were assessed clinically, not surgically. Several patterns emerge from this literature, however: Breslow and Chung microstaging systems appear to be more accurate than the Clark system. Also, AJCC staging appears to be more predictive of outcome than FIGO staging.

In the only prospective study of patients with vulvar melanoma, conducted by the GOG, [3] AJCC staging for cutaneous melanoma had the most significant correlation with recurrence-free interval. At 5 years, for example, the GOG noted an 85% survival rate for those with AJCC stage I disease, 40% for those with stage II disease, and 25% for those with stage III disease. FIGO staging was not found to be an important discriminant of recurrence-free interval. The GOG concluded that AJCC staging should be used for patients with vulvar melanomas “for the determination of prognosis and selection of therapies.” In the absence of AJCC stage, Breslow levels were the next most prognostic. Podratz et al identified 48 patients with vulvar melanoma treated at the Mayo Clinic between 1950 and 1980 [4]. They found FIGO stage to be of little value in predicting outcome, whereas both Clark and Breslow microstaging had prognostic significance. Patients with level 5 disease, whether Breslow or Clark, had significantly worse survival than patients with more superficial disease.

Trimble et al [7] analyzed outcome in 80 patients with vulvar melanoma treated at Memorial Sloan-Kettering Cancer Center, including 44 previously reported by Chung et al. Chung microstaging was a more accurate predictor of survival and risk of nodal disease than was Breslow tumor thickness.

Scheistroen et al identified 43 patients with vulvar melanoma treated at the Norwegian Radium Hospital between 1956 and 1987 [8]. Prognosis was related to Breslow tumor thickness, with significantly worse survival observed in patients with tumor thickness more than 5.0 mm (P = .002).

Vaginal Melanoma

No prospective studies have addressed staging in patients with vaginal melanoma. Reid et al compiled data on 115 patients reported retrospectively from a variety of institutions [16]. FIGO stage, reported for only 42 patients, was not found to affect survival or time to recurrence. Tumor size was important; patients with lesions less than 3 cm experienced significantly better survival than those with lesions equal to or more than 3 cm (P = .024). Tumor thickness, reported in only 31 patients, was a significant prognostic variable for disease-free interval but not survival.

In light of the prospective data from the GOG study in vulvar melanoma, it would seem reasonable to use AJCC staging in vaginal melanoma.

Histopathology

Three histopathologic subtypes of vulvar melanoma have been described: superficial spreading melanoma, nodular melanoma, and acral lentiginous melanoma. Acral lentiginous melanoma appears to be the least common subtype found in the vulva. Superficial spreading melanoma is characterized by radial growth, nodular melanoma by vertical growth, and acral lentiginous melanoma by both growth patterns. All three subtypes may consist predominantly of epithelioid, dendritic, or spindle-type cells. Melanin content may range from none to large amounts. In the Mayo Clinic experience, nodular melanomas conveyed a worse prognosis than superficial spreading melanoma, while the Norwegian Radium Hospital study found no difference in outcome between these two histologies [4,8].

In a small series of 15 patients with vaginal melanoma from the University of Michigan and Bowman Gray, all were nodular melanomas [16].

Primary Site

Primary site appears to affect prognosis in patients with vulvar melanoma. In the GOG trial, patients with a central primary lesion were at significantly higher risk for groin node involvement (P = .006) and recurrence (P = .03) than were those with lateralized disease [3]. In a retrospective series from the Mayo Clinic, patients with central tumors had a 37% 10-year survival rate, which was significantly lower than the 61% rate observed in patients with lateral lesions (P = .027) [4]. The Norwegian Radium Hospital investigators found that survival was significantly better in patients with lateralized tumors than in those with clitoral or multifocal tumors (P less than .001) [8].

Other Risk Factors

Several other histopathologic risk factors have been identified. In the GOG study, capillary lymphatic space involvement correlated significantly with positive groin nodes (P = .0001) and approached
significance in discriminating recurrence-free interval (P = .08) [3]. In a study of 30 women from the Netherlands by Tasseron et al, ulceration was a significant prognosticator for poor survival (P = .046) [17]. Ulceration and high mitotic rate were associated with a high risk of recurrent disease in Bradgate et al's retrospective study of 50 women in the English Midlands [6]. Among the 75 patients in the series from the Norwegian Radium Hospital, significant histopathologic factors associated with a worse prognosis were angio-invasion (P less than .0001) and aneuploidy (P = .009) [7].

**Treatment**

**Primary Surgery**

**Studies on Vulvar Melanoma**--In the past, vulvar melanoma was treated in the same manner as squamous vulvar carcinoma, namely, by radical vulvectomy with en bloc bilateral inguinofemoral lymphadenectomy. As surgery for carcinoma of the vulva has become more conservative, less radical primary surgery has been performed for vulvar melanomas. This more conservative approach has also paralleled the surgical treatment of cutaneous melanomas elsewhere on the body. In the GOG study, for example, 37 patients underwent radical vulvectomy, while 34 were treated with radical hemivulvectomy [3]. The GOG investigators were unable to draw any conclusions about the extent of surgery necessary for patients with vulvar melanoma. Retrospective studies suggest that radical vulvectomy does not improve survival over more limited resection. Davidson et al, for example, identified 32 patients with vulvar or vaginal melanoma treated at the Royal Marsden Hospital between 1964 and 1984 [18]. Primary surgery consisted of local excision in 14 patients, simple vulvectomy in 7, and radical resection in 11. The authors found that the extent of primary resection had no impact on local control, disease-free interval, or patient survival.

Rose et al reported on 26 patients with vulvar melanoma treated at the Roswell Park Memorial Institute between 1927 and 1986, 12 of whom underwent local excision and 14, radical surgery [5]. The researchers found no difference in survival between the two groups. Bradgate et al identified 50 patients diagnosed with vulvar melanoma in the West Midlands region of England between 1957 and 1982 [6]. Of these, 23 underwent conservative surgery and 23, radical surgery. The authors found no significant difference in survival between the two groups. A report by Trimble et al focused on 80 patients with vulvar melanoma treated at Memorial Sloan-Kettering Cancer Center between 1949 and 1990 [7]. Of the 80 patients, 59 had a radical vulvectomy; 10, a partial vulvectomy; and 9, wide local excision. At a median follow-up of 193 months, no difference in survival was noted among the three groups.

Tasseron et al examined survival among 30 patients with vulvar melanoma treated at the Netherlands Cancer Institute. Of these, 12 had undergone conservative surgery and 17, radical vulvectomy [17]. The investigators found no association between extent of initial surgery and survival. Similarly, in the Norwegian Radium Hospital series, survival did not differ significantly among patients undergoing local excision, simple vulvectomy, or radical vulvectomy with inguinal lymph node dissection [7].

**Studies on Vaginal Melanoma**--Limited data are available on which to base recommendations on primary surgery for patients with vaginal melanoma. Investigators from the University of Michigan and Bowman Gray College of Medicine identified 15 patients with vaginal melanoma from their institutions and pooled their data with 115 patients reported in the literature [16]. They noted four different treatment strategies: surgery only, radiation therapy only, surgery plus radiation therapy, and chemotherapy plus surgery or radiation therapy. There were no significant differences in survival among these treatment regimens.

The investigators then compared survival among the 55 patients who underwent surgery only. In these 55 patients, 24 had undergone conservative procedures (wide local excision, partial vaginectomy) and 31, radical procedures (radical hysterectomy, radical vaginectomy, exenteration). No difference in survival or disease-free interval was observed between the two groups. Van Nostrand et al at the University of California/Irvine subsequently reported on eight patients with vaginal melanoma [19]. They pooled these 8 patients with 111 reported in the literature and divided them into two groups: those treated with radical surgery (50 patients) and those treated with conservative surgery (69 patients). Survival rates at 2 years were 48% for those treated with radical surgery and 20% for these treated with conservative surgery (P less than .005). Van Nostrand et al concluded that radical surgery is recommended for patients with primary vaginal melanomas less than 10 cm².

As these two "meta-analyses" are based largely on the same cases, it is difficult to understand how...
they could have reached such contradictory conclusions. In the absence of more definitive data, it would seem reasonable to offer patients with vaginal melanoma surgery tailored to achieve adequate deep and lateral margins—an approach consistent with the management of cutaneous melanoma (see below).

**Studies on Cutaneous Melanoma**—Large prospective, randomized trials in patients with cutaneous melanoma suggest that limited resection is as effective as radical resection. In a trial conducted by Balch et al, 468 patients with 1- to 4-mm thick melanomas of the trunk or proximal extremities were randomized to undergo resection with either a 2- or 4-cm surgical margin [20]. After a mean follow-up of 6 years, no difference between the two arms was discerned with respect to local recurrence or survival. Patients who received the 2-cm margin were more likely to have primary wound closure, less likely to require skin grafts, and had significantly shorter hospital stays. Veronesi and Cascinelli published 8-year follow-up data on 612 patients with clinical stage I melanomas equal to or less than 2 mm thick who were randomized to receive 1- or 3-cm margins [21]. No difference between the two groups was seen with regard to disease-free or overall survival. The authors concluded that 1-cm skin margins are adequate for melanomas equal to or less than 1 mm in thickness, but cautioned that the excision should be "1 or 2 cm wider in the subcutaneous fat extending to muscular fascia." They did note a 3.3% local recurrence rate after narrow excision for melanomas 1.1 to 2 mm thick compared to 0% after wide excision, but suggested that longer follow-up would be needed before a final statement could be made on the optimal margins for melanomas between 1 and 2 mm thick.

Urist et al performed a retrospective analysis of 3,445 clinical stage I melanoma patients [22]. Among 1,151 patients with melanomas less than 1 mm thick, 62% of whom had resection margins of equal to or less than 2 cm, only one local recurrence was noted. Based on these studies, therefore, it seems reasonable to conclude that 1-cm skin margins are adequate for vulvar melanomas less than 1 mm thick, and that 2 cm margins are adequate for intermediate-thickness melanomas (1 to 4 mm). In all cases, however, the excision should include at least a 1-cm deep margin extending through the subcutaneous fat to the muscular fascia below.

**Elective Lymph Node Dissection**

In the GOG study of vulvar melanoma, capillary lymphatic space involvement and Breslow's depth of invasion correlated significantly with positive groin nodes [3]. In multiple regression analysis, a central primary lesion and capillary lymphatic space involvement were independent predictors of positive lymph nodes. Of 22 patients with positive capillary lymphatic space involvement or a central primary lesion, 7 (31.8%) had positive groin nodes. The risk of positive lymph nodes rose with increased depth of invasion and tumor thickness. The patient numbers are so small, however, that it would be inadvisable to attempt to derive accurate risks of lymph node involvement from this one study.

A large, retrospective, single-institution study of 911 patients with cutaneous melanoma who underwent elective lymph node dissection revealed the following incidence of positive nodes, according to lesion thickness: less than 0.76 mm, 0%; 0.76 to 1.5 mm, 5%; 1.5 to 2.5 mm, 16%; 2.5 to 4.0 mm, 24%; more than 4 mm, 36% [23]. In cutaneous melanoma, several retrospective studies have suggested a survival benefit from elective regional lymph node dissection in patients with intermediate-thickness melanoma (0.76 to 4.0 mm) [24-26]. Two large prospective clinical trials failed to show such a benefit, however. In a World Health Organization study, 267 patients with clinical stage I melanoma underwent wide excisions of the primary lesion and immediate node dissection and 286 underwent wide local excision only, with lymph node dissection reserved for patients in whom clinically evident regional lymph node metastases were noted [27]. At 20 years of follow-up, elective node dissection did not improve the survival of patients with thin (less than 1 mm), intermediate (1 to 4 mm), or thick (more than 4.1 mm) primary lesions.

In the GOG study, 56 of 71 evaluable patients underwent groin node dissection. The authors reached no conclusion about the benefit of groin node dissection in patients with vulvar melanoma [3].

**Sentinel Nodes**—Several methods to identify sentinel nodes draining melanomas have been reported. Patients found to have metastatic disease in the sentinel nodes would then undergo
regional lymphadenectomy; those with no metastatic disease in the sentinel nodes could be spared this procedure. Intraoperative lymphatic mapping using vital dyes was first reported by Fisher et al and Morton et al in patients with cutaneous melanoma [29,30]. Levenbeck et al recently studied this technique in the evaluation of nine patients with vulvar cancer, including two with melanoma [31]. Intraoperative technetium-99m lymphoscintigraphy has also been used to identify sentinel lymph nodes in melanoma patients [32,33]. Recently reported trials have identified effective adjuvant therapy for melanoma patients at high risk for recurrent disease after local excision (discussed below). Identification of patients with positive lymph nodes may help select patients who would potentially benefit from such therapy.

**Adjuvant Therapy**

Several recent trials have shown that adjuvant therapy may be of benefit in preventing recurrence in certain patients with cutaneous melanoma. As yet, no trial have evaluated adjuvant chemotherapy in patients with vulvar or vaginal melanoma.

**Warfarin**—Thornes et al randomized 27 patients with AJCC stage IB or stage II melanoma lesions to a double-blind trial of warfarin (50 mg/d) or placebo for 2 years after primary wide local excision [34]. Recurrences were noted in 10 of 14 patients in the control group but only 2 of 13 in the warfarin group. The trial was halted prematurely when these results reached statistical significance (P less than .01).

**Hyperthermic Perfusion**—Ghussen et al reported on a prospective, randomized trial of hyperthermic perfusion with melphalan (Alkeran) chemotherapy after wide local excision and regional lymph node resection in patients with melanomas of the extremities [35]. Eligible patients were those with a tumor thickness more than 1.5 mm or Clark's level more than III. Of the 107 patients who met these criteria, 53 were randomized to receive hyperthermic perfusion and 54 to the control arm. An intermediate analysis showed a significant difference between the two groups, with 21 recurrences noted in the control group and 4 in the perfusion group (P less than .001). The difference remained significant at the P less than .001 level when the patients were stratified by Breslow tumor thickness (1.5 to 3.0 mm vs more than 3.0 mm). This study was discontinued prematurely as well.

**Interferon-alfa-2b**—Kirkwood et al recently published the results of a randomized controlled Eastern Cooperative Oncology Group (ECOG) trial of adjuvant interferon alfa-2b (Intron A) vs observation in patients with AJCC stage IIB or III melanoma, as well as patients with regional nodal relapse [36]. A total of 137 patients were assigned to the control arm, and 143 patients received interferon, given at a dose of 20 MU/m²/d intravenously 5 days weekly for 4 weeks, followed by 10 MU/m²/d subcutaneously three times weekly for 48 weeks. With a median follow-up time of 6.9 years, there was significant prolongation of relapse-free survival (P = .0023) and of overall survival (P = .0237) in the interferon-treated patients. The benefit of interferon was greatest in patients with positive nodes.

**Recommendations**—Adjuvant radiotherapy, chemotherapy and immunotherapy, including vaccines, have not yet shown a survival advantage in phase III trials. The positive studies described above support a role for adjuvant therapy after primary surgery in patients with melanoma, however. The warfarin study would seem to need confirmation in a large multi-institution trial. Hyperthermia with melphalan perfusion may not be practical or appropriate for a pelvic tumor. On the other hand, patients found to have metastatic disease in inguinofemoral lymph nodes may benefit from interferon as prescribed in the ECOG study. The number of patients with vulvar and vaginal melanoma is so small as to make successful conduct of a randomized trial of adjuvant therapy unlikely. Melanomas of the vulva and vagina appear to have the same biologic behavior and response to treatment as cutaneous melanomas. Consideration should be given to enrolling patients with vulvar and vaginal melanoma who meet other eligibility criteria in cutaneous melanoma trials.

**Salvage Therapy**

Effective salvage therapy for melanoma patients with distant metastatic disease has not yet been identified. The most active chemotherapeutic agent is dacarbazine (DTIC), which engenders response rates ranging from 15% to 25% [37]. The median duration of response is 5 to 6 months. Overall, only 1% to 2% of patients treated with DTIC have long-term complete responses. Palliative radiotherapy and surgery may be useful for controlling symptoms in patients with metastatic disease. Patients with metastatic melanoma should be encouraged to enroll in appropriate phase I and II trials.
to help identify more effective treatment.

References:

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