Primary Malignant Melanoma of the Vagina: Long-Term Remission Following Radiation Therapy

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Objective. To describe the characteristics and clinical course of patients with primary vaginal melanoma treated at three large Austrian institutions.

Methods. The medical records of 14 patients treated at the Departments of Obstetrics and Gynecology of the Universities of Graz and Vienna and the Salzburg Women’s Hospital between 1982 and 1996 were reviewed.

Results. The median age at diagnosis was 73 years. Presenting symptoms included vaginal bleeding in all patients. Three of seven patients (43%) with tumors <3 cm survived longer than 5 years compared to none of seven patients with a tumor size >3 cm. Three of nine patients (33%) who received radiotherapy either in addition to surgical excision or as primary treatment, survived for 5 years. Other potential prognostic factors such as age, location, FIGO stage, depth of invasion, Chung level, histology, cell type, mitotic count, vessel involvement, ulceration, p53 accumulation, type of surgery, type of radiotherapy, or chemotherapy did not seem to correlate with the patients’ outcome. The median overall survival was 10 months (range 1–153). The 5-year disease-free and overall survival rates were 14 and 21%, respectively. All three long-term survivors recurred locally.

Conclusion. All three patients who had long-term survival had lesions <3 cm and received either primary radiotherapy (n = 2) or adjuvant radiotherapy after complete excision of the primary lesion (n = 1). In view of the poor overall survival rates, regardless of treatment, radiotherapy may be a limited valuable alternative or adjunct to surgery in patients with primary malignant melanoma of the vagina <3 cm in diameter.

INTRODUCTION

Ninety-three percent of malignant melanomas are of cutaneous nongenital origin and 6% are of ocular origin [1]. Malignant melanomas are rare in areas of the body not exposed to ultraviolet radiation. The incidence of primary vaginal melanoma is about 0.026/100,000 women per year [1]. Primary melanomas of the vulva are four [1] to nine times [2] as frequent as those of the vagina. Vaginal melanomas account for less than 3% of all vaginal malignancies [3]. Less than 170 cases have been reported to date and only three studies [2, 4, 5] are based on 15 or more patients. We reviewed the experience of two university hospitals and one large urban hospital in Austria in the treatment of this disease.

MATERIAL AND METHODS

We reviewed the medical records of 14 previously unreported patients with primary vaginal melanoma treated at the Departments of Obstetrics and Gynecology of the Universities of Graz and Vienna and the Salzburg Women’s Hospital between 1982 and 1996. Melanomas from locations other than the vagina and particularly the vulva were excluded. All histologic slides were reviewed. The thickness of each primary melanoma was determined as described by Breslow [6] and Chung [7]. The thickness was measured from the outermost epithelial layer of the mucosa to the point of deepest penetration by melanoma cells into the vaginal wall with an optical micrometer [4, 7].

The histologic diagnosis was confirmed by positive immunostaining for S100 and HMB 45 and negative immunostaining for cytokeratin in all cases. Eleven specimens were studied for p53 accumulation with immunohistochemistry. Dепaraffinized tissue sections were pretreated with 0.1% trypsin and incubated overnight at 4°C using the mouse monoclonal p53 antibody Ab-6 (Calbiochem-Novabiochem, La Jolla, CA). The signal was visualized in DAB/imidazol solution and counterstained with hematoxylin. This antibody is specific for an epitope located near the amino end of p53. The proportion of nuclear staining was scored as described [8]. p53-positive cervical carcinomas served as positive controls. Tumors were retrospectively staged according to the FIGO recommendations for primary epithelial carcinoma of the vagina.

Radiotherapeutic modalities were not uniform over the study period. In the majority of patients, pelvic radiotherapy con-
sisted of 50 Gray administered percutaneously over 5 weeks. Patients with tumors of the lower vagina received additional radiation to the inguinal regions (54–60 Gy). In most patients who received brachytherapy, $^{226}$Ra was used.

### RESULTS

Characteristics of the 14 consecutive white patients are shown in Table 1. The median age at diagnosis was 73 years.

#### TABLE 1

Characteristics of the 14 Patients with Primary Malignant Melanoma of the Vagina$^a$

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age (years)</th>
<th>Location</th>
<th>FIGO stage</th>
<th>Size (cm)</th>
<th>Invasion (mm)</th>
<th>✓ Chung level $^b$</th>
<th>Histology</th>
<th>Cell type</th>
<th>Surgery</th>
<th>Radiation, chemotherapy</th>
<th>Disease status</th>
<th>Follow-up (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>44</td>
<td>Lateral lower</td>
<td>I</td>
<td>1.5</td>
<td>6</td>
<td>IV</td>
<td>NM$^c$</td>
<td>Mixed</td>
<td>Excision$^d$</td>
<td>ERT$^e$ + ICRT$^e$ + Dacarbazin + Vindesine + Bleomycin</td>
<td>DOD$^f$ (Progressive disease)</td>
<td>10</td>
</tr>
<tr>
<td>2</td>
<td>73</td>
<td>Anterior lower</td>
<td>I</td>
<td>1.5</td>
<td>6</td>
<td>IV</td>
<td>NM</td>
<td>Mixed</td>
<td>12</td>
<td>None</td>
<td>Lost, NED$^f$</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>65</td>
<td>Anterior middle</td>
<td>II</td>
<td>2</td>
<td>5</td>
<td>IV</td>
<td>NM</td>
<td>Spindle</td>
<td>Biopsy</td>
<td>ERT + ICRT</td>
<td>DOD (Local recurrence$^g$)</td>
<td>153</td>
</tr>
<tr>
<td>4</td>
<td>82</td>
<td>Anterior lower</td>
<td>I</td>
<td>2</td>
<td>8</td>
<td>V</td>
<td>NM</td>
<td>Mixed</td>
<td>15</td>
<td>None</td>
<td>Intercurrent death</td>
<td>1</td>
</tr>
<tr>
<td>5</td>
<td>54</td>
<td>Posterior upper</td>
<td>II</td>
<td>2.5</td>
<td>15</td>
<td>V</td>
<td>NM</td>
<td>Epithelioid</td>
<td>RAH + partial colpectomy$^y$</td>
<td>None</td>
<td>DOD (Progressive disease)</td>
<td>4</td>
</tr>
<tr>
<td>6</td>
<td>54</td>
<td>Anterior lower</td>
<td>II</td>
<td>3</td>
<td>5</td>
<td>IV</td>
<td>NM</td>
<td>Spindle</td>
<td>Excision$^d$</td>
<td>ERT</td>
<td>AWD$^j$ (Local recurrence 93 months)</td>
<td>100</td>
</tr>
<tr>
<td>7</td>
<td>69</td>
<td>Lateral lower</td>
<td>III</td>
<td>3</td>
<td>6</td>
<td>IV</td>
<td>NM</td>
<td>Spindle</td>
<td>Biopsy</td>
<td>ERT + ICRT</td>
<td>DOD (Local recurrence$^h$)</td>
<td>65</td>
</tr>
<tr>
<td>8</td>
<td>68</td>
<td>Anterior upper</td>
<td>I</td>
<td>4</td>
<td>0.6</td>
<td>II</td>
<td>SSM$^k$</td>
<td>Pagetoid</td>
<td>Biopsy</td>
<td>ERT + Carboplatin</td>
<td>DOD (Progressive disease)</td>
<td>33</td>
</tr>
<tr>
<td>9</td>
<td>85</td>
<td>Lateral middle</td>
<td>IVB$^l$</td>
<td>4</td>
<td>—</td>
<td>IV</td>
<td>NM</td>
<td>Epithelioid</td>
<td>4</td>
<td>Biopsy</td>
<td>DOD (Progressive disease)</td>
<td>2</td>
</tr>
<tr>
<td>10</td>
<td>81</td>
<td>Lateral lower</td>
<td>II</td>
<td>4.5</td>
<td>5</td>
<td>IV</td>
<td>NM</td>
<td>Mixed</td>
<td>7</td>
<td>None</td>
<td>AWD (Progressive disease)</td>
<td>2</td>
</tr>
<tr>
<td>11</td>
<td>78</td>
<td>Posterior lower</td>
<td>I</td>
<td>5</td>
<td>7</td>
<td>IV</td>
<td>NM</td>
<td>Mixed</td>
<td>13</td>
<td>Excision$^d$</td>
<td>ERT + ICRT</td>
<td>AWD (Inguinal recurrence 7 months)</td>
</tr>
<tr>
<td>12</td>
<td>81</td>
<td>Posterior upper</td>
<td>III</td>
<td>5</td>
<td>5</td>
<td>IV</td>
<td>NM</td>
<td>Spindle</td>
<td>8</td>
<td>Biopsy</td>
<td>ERT + ICRT</td>
<td>DOD (Local recurrence 23 months)</td>
</tr>
<tr>
<td>13</td>
<td>75</td>
<td>Anterior lower</td>
<td>III</td>
<td>5</td>
<td>6</td>
<td>IV</td>
<td>NM</td>
<td>Spindle</td>
<td>Biopsy</td>
<td>ERT + ICRT</td>
<td>AWD (Progressive disease)</td>
<td>2</td>
</tr>
<tr>
<td>14</td>
<td>73</td>
<td>Anterior middle</td>
<td>IVa</td>
<td>6</td>
<td>7</td>
<td>IV</td>
<td>NM</td>
<td>Mixed</td>
<td>11</td>
<td>Anterior exenteration$^m$</td>
<td>Dacarbazin</td>
<td>AWD (Progressive disease)</td>
</tr>
</tbody>
</table>

$^a$ Tumor ulceration was present in patients 3, 4, 5, 6, 7, 9, 10, 11, 12, 13, and 14. In patients 1, 2, and 8, no ulceration was found. Patients 1, 2, 3, 5, 6, 7, 9, 10, 11, 12, and 13 had lymph vessel as well as blood vessel involvement while patients 4 and 8 had no involvement. p53 overexpression was found in patients 1, 8, and 14 and was not found in patients 2, 5, 6, 7, 10, 11, 12, and 13.

$^b$ Chung et al. [7].

$^c$ NM, nodular melanoma; SSM, superficially spread melanoma.

$^d$ Free surgical margins.

$^e$ ERT, external radiotherapy; ICRT, intracavitary radiotherapy.

$^f$ DOD, dead of disease; NED, no evidence of disease; AWD, alive with disease.

$^g$ Radical abdominal hysterectomy.

$^h$ Therapy of recurrence: Interstitial radiotherapy + hyperthermia.

$^i$ Therapy of recurrence: partial tumor excision + external radiotherapy + brachytherapy.

$^j$ Therapy of recurrence: colpectomy.

$^k$ Lung metastasis.

$^l$ Involved surgical margins.

$^m$ Ileum perforation and peritonitis led to relaparotomy, ileum resection, and the placement of an ileostoma on the 28th postoperative day.
Presenting symptoms included vaginal bleeding in all patients, urinary incontinence in three, a vaginal mass in two, and vaginal discharge, pain, and cachexia in one. Four of the 14 melanomas were amelanotic (29%).

Three of seven patients (43%) with tumors ≤3 cm survived longer than 5 years compared to none of seven patients with a tumor size >3 cm. Three of nine patients (33%) who received radiotherapy either as primary treatment (n = 2) or in addition to surgical excision (n = 1), survived for 5 years. Other potential prognostic factors such as age, location, FIGO stage, depth of invasion, Chung level, histology, cell type, mitotic count, vessel involvement, ulceration, p53 accumulation, type of surgery, type of radiotherapy, or chemotherapy did not seem to correlate with the patients’ outcome (Table 1).

The median overall survival was 10 months (range 1–153). The 5-year disease-free survival and overall survival rates were 14 and 21%, respectively. All three long-term survivors (Table 1, patients 3, 6, 7) received the planned dose of radiotherapy and all of them recurred locally 44, 72, and 93 months after initial diagnosis, respectively. In patient 3, secondary radiotherapy led to a temporary remission of a recurrence. This patient ultimately died 153 months after diagnosis. By April 1, 1998, only one of the three long-term survivors is alive with disease at 100 months.

Both patients who underwent radical surgery (Table 1, patients 5 and 14) developed distant metastases shortly after diagnosis.

Three patients received cytotoxic regimens without obvious clinical benefit. Six patients developed progressive disease in the vagina (n = 3), dissemination to the lung and brain (n = 1), the peritoneal cavity (n = 1), and the vulva (n = 1).

DISCUSSION

Eight of the 14 vaginal melanomas (57%) were located in the lower third of the vagina (Table 1). The majority of patients were older than 60 years, presented with vaginal bleeding, and had primary lesions at Chung level IV. These data correlate well with previous reports [2–4, 9–12].

Eleven patients in this study (79%) were treated with local excision with or without radiotherapy or primary radiotherapy. The high rate of local recurrences or local disease progression may be due to the conservative treatment approach. The tendency of primary vaginal melanoma to recur locally [4, 5, 10, 13] underlines the value of careful gynecologic follow-up.

In our study, tumor size and radiotherapy appeared to be prognostically important, although the small number of patients precluded statistical analysis. All three 5-year-survivors had lesions ≤3 cm and all three underwent radiotherapy (Table 1). Tumor size has been found to be prognostically important in two earlier reports [3, 5].

There are no general recommendations for the treatment of primary vaginal melanoma [3, 5, 14]. Most reports favor limited radical surgery (wide surgical excision plus dissection of the regional lymph nodes) over extensive radical surgery (e.g., exenteration) or primary radiotherapy [3, 11, 12, 15]. Surgery has been shown to lead to better local control than radiotherapy [4, 16, 17].

The 21% 5-year overall survival in the present series is in the upper range reported. Previous studies revealed survival rates between 0 and 21% [1, 2, 4, 5, 10, 11, 14, 15, 18]. Five-year survival has been reported in less than 25 patients with primary vaginal melanoma [4, 5, 10, 12–14, 16–20]. The majority of these patients underwent primary surgery [4, 12–14, 16, 17, 20]. However, some of these long-term survivors additionally received radiotherapy or chemotherapy [12, 17, 20].

In our series, all three long-term survivors received either primary radiotherapy (n = 2) or adjuvant radiotherapy after complete excision of the primary lesion (n = 1). The pelvic radiation dose administered to the four patients with lesions ≤3 cm and a minimum follow-up of 2 months was 50 Gy in the three 5-year survivors compared to 45 Gy in the remaining patient who died earlier. Two of the long-term survivors were disease-free at 5 years. Radiotherapy has been reported to lead to “5-year-cures” in a minority of patients [4, 5, 10, 19].

In conclusion, the prognosis of patients with primary malignant melanoma of the vagina is poor. Radiotherapy may be of value as an alternative to surgery or an adjunct modality in patients with lesions ≤3 cm in diameter. Although there are only anecdotal reports on the efficacy of chemotherapy in vaginal melanoma [4, 10, 19, 20], the administration of chemoradiotherapy in this disease would seem justified.

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REFERENCES