Malignant Melanoma of Cervical and Parotid Lymph Nodes With an Unknown Primary Site

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Forty-six patients with malignant melanoma metastatic to cervical or parotid lymph nodes with an unknown primary site were treated at UCLA Medical Center from 1964 through 1991. Treatment consisted of parotidectomy and/or neck dissection with or without adjuvant therapy. The initial presentation was a cervical mass in 74% and a parotid mass in 26% of patients. Metastasis distal to the head and neck nodal basins developed in 22% of patients.

Involvement of more than four cervical or parotid nodes resulted in a significant increase in distant metastasis ($P<.01$). Adjuvant therapy was found to have no significant effect on survival rates. However, age at the time of diagnosis influenced the survival rates. The significance of the improved survival of these patients as compared to those with a known primary melanoma is discussed.

INTRODUCTION

Malignant melanoma comprises 1% of all malignancies of the human body and 0.9% of deaths from cancer.[1,2] Although most melanomas involve the epidermis, involvement of rare locations such as the choroid of the eye and mucous membranes of the nasopharynx has also been documented.[3] It has been estimated that 20% of melanomas occur in the head and neck region.[4,5] The factor deemed most responsible for a worsened prognosis of cutaneous melanoma is the appearance of regional lymph node metastasis, referred to as stage II disease.[6] Table I summarizes staging of the malignant melanoma.[7]

An unusual and distinct entity is melanoma involving an area where melanocytes do not normally reside. The incidence of these melanomas with an unknown primary site ranges from 2% to 16% of all melanomas.[2,7–12] When strict criteria are used for diagnosis as described by Das Gupta, *et al.*, most authorities find the incidence to be closer to 5%.[13] Stage II disease is the most common site of secondary presentation for primary melanoma.[2] Up to 60% of unknown primary melanomas have been reported to have regional lymph node metastasis.[7,8,14] The remainder have metastasis involving more than one nodal basin, visceral, or subcutaneous tissue.[7] The cervical and parotid lymph nodes are not uncommonly involved in stage II melanoma. Cascinelli, *et al.* demonstrated that 13% of all stage II melanomas involve the head and neck region.[6] An extensive review of the literature indicates that of all stage II melanomas with an unknown primary site, 20% to 30% involve the cervical lymph nodes.[2,7,11]

The relative prognosis of melanomas with unknown primary and stage II melanomas with the primary site known is disputed.[15] Some authors have suggested that in a specific subgroup of patients, host-tumor interactions lead to spontaneous regression of the primary tumor site after it has metastasized to the regional lymph nodes.[16] It has been theorized that, due to this antitumor immune response, disease is contained and suppressed within the regional lymph nodes.[1] The question therefore rises as to whether unknown primary melanomas have a different natural progression and prognosis as compared to those with a known primary site.

The purpose of this study is to present 46 patients with malignant melanoma of unknown primary origin metastasized to the cervical and parotid lymph nodes. The clinical and pathologic data of this rare presentation of melanoma are analyzed.

MATERIALS AND METHODS

Forty-six patients were treated at UCLA Medical Center from 1964 through 1991 with melanoma metastatic to the parotid or cervical lymph nodes without evidence of primary cutaneous, mucosal, or ocular melanoma. No distant metastasis was identified. The evaluation of each patient included a thorough history and physical examination, accompanied by an intense dermatologic investigation of cutaneous lesions and biopsy of any suspicious area. Chest roentgenograms, sinus films or, in recent years, CT scans of the head and neck region were also obtained. The diagnosis of melanoma was established by lymph node biopsy or fine-needle aspiration. The tissue was examined and verified as melanoma by a pathologist.

Treatment consisted of surgery with or without adjuvant therapy. All patients were operated on with curative intent. Surgery included superficial parotidectomy, neck dissection, superficial parotidectomy along with neck dissection, and excisional biopsy. For patients undergoing neck dissections, the site and number of nodes containing melanoma were recorded. Adjuvant therapy included radiotherapy, chemotherapy, and immunotherapy. The chemotherapeutic agents used were dacarbazine, carmustine, hydroxyurea, cyclophosphamide (Cytoxan®), bleomycin, and vincristine. A group of patients received bacille Calmette-Guérin (BCG) and/or interleukin-1 (IL-1) and/or tumor cell vaccine (TCV) singly or in combination with the aforementioned chemotherapeutic agents. Of those treated with radiation therapy, aproximately 40 to 60 Gy was delivered to the cervical or parotid nodal beds. After treatment, reappearance of disease in the original or adjacent nodal basins was regarded as a relapse. Lesions that reappeared elsewhere were all regarded as distant metastasis. The survival values were calculated based on the life-table method and were determined from the time of diagnosis of the cervical or parotid nodal metastatic disease. The chi-squared test was used when appropriate for statistical analysis.

TABLE I.
Memorial Sloan-Kettering Cancer Center Staging of Malignant Melanoma.

Stage I	Localized melanoma without metastasis to distant/regional lymph nodes
	Primary melanoma untreated or removed by excisional biopsy.
	Locally recurrent melanoma within 4 cm from primary site.
	Multiple primary melanomas.
Stage II	Metastasis limited to regional lymph nodes
	Primary melanoma present or removed with simultaneous metastasis.
	Primary melanoma controlled with subsequent metastasis.
	Locally recurrent melanoma with metastasis.
	Intransit metastasis beyond 4 cm from primary site.
Stage III	Disseminated melanoma
	Visceral and/or multiple lymphatic metastasis.
	Multiple cutaneous and/or subcutaneous metastasis.

RESULTS

Fifteen percent (7/46) of the patients were females and 85% (39/46) males. The age range was 15 to 83 years with a median age at the time of diagnosis of 43 years. All patients presented with a mass in the parotid or cervical area. Seventy-four percent (34/46) initially presented with cervical nodal metastasis and 26% (12/46) with parotid nodal metastasis. Once a node biopsy was performed, the median time to definitive treatment was 3 weeks.

TABLE II.
Type of Treatment.

Treatment	n	Percentage
Parotidectomy	5	11%
Neck dissection	27	59%
Radical	15	
Modified	12	
Parotidectomy and neck dissection	8	17%
Radical	5	
Modified	3	
Excisional biopsy	6	13%
Total	46	100%

Of the 46 patients, all were surgically treated. Five patients had a parotidectomy, 8 had a parotidectomy and neck dissection, 27 had a neck dissection alone, and 6 had an excisional biopsy. Of the patients treated with a neck dissection, 15 underwent a modified and 20 radical neck dissection (Table II).

Overall, 54% (25/46) of patients remain alive and well. The remaining 46% (21/46) died of progression of disease. Twenty-four percent of all patients had a recurrence in the parotid or cervical nodes. Of the patients treated with a modified radical neck dissection, 27% (4/15) experienced a recurrence compared to 20% (4/20) of patients treated with a radical neck dissection. This difference was not statistically significant. No significant difference in survival was noted when modified neck dissection was compared to radical neck dissection at 2, 5, and 10 years postoperatively. At 2 years, patients with a modified neck dissection had a 77% survival rate. At 5 and 10 years, their survival rates fell to 55% and 50%. The respective 2-, 5-, and 10-year survival for patients with a radical neck dissection were 71%, 62%, and 54%. Of those who died after treatment, the median survival of patients with a radical neck dissection was 22 months. Patients who underwent modified radical neck dissection had a median survival time of 23 months.

The location of the lymph node metastasis did not significantly affect survival. The 5-year survival of patients presenting with a cervical metastasis was 58% (18/31), as compared to 50% (4/8) for those with a parotid metastasis (Table III).

Sixty-seven percent (31/46) of patients received

TABLE III.
Survival Rates of Patients With Cervical or Parotid Metastasis.

Location of Metastasis	2-Year	5-Year	10-Year
Cervical	76% (26/34)	58% (18/31)	46% (12/26)
Parotid	80% (8/10)	50% (4/8)	17% (1/6)

TABLE IV.
Survival Rates With and Without Adjuvant Treatment.

Adjuvant Therapy	2-Year	5-Year	10-Year
With	77% (24/31)	54% (14/26)	36% (8/22)
Without	77% (10/13)	62% (8/13)	50% (5/10)

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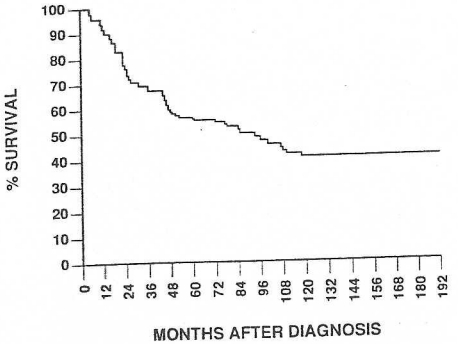

Fig. 1. Survival of stage II patients with metastatic melanoma of unknown origin to the cervical and parotid nodes.

postoperative adjuvant therapy. Of these, 90% received chemotherapy and/or immunotherapy. The remaining 10% received radiation treatment. There was no significant difference in the survival rate for patients treated with and without adjuvant therapy (Table IV). In fact, the survival rate of patients not receiving adjuvant treatment demonstrated a slight improvement over those receiving such therapy. The respective 5-year survival rates were 62% and 54%. This difference was not statistically significant.

Distant metastasis occurred in 22% (10/46) of the patients. In this group, the median time between completion of treatment and appearance of distant metastasis was 7 months. Of the patients who developed distant metastasis, 20% (2/10) had a modified radical neck dissection compared to 30% (3/10) who underwent a radical neck dissection. Statistical significance was not achieved. The median survival time of patients with distant metastasis was 18 months. Eighty percent of these patients were dead within 2 years. Ninety percent were dead within 5 years and no one lived longer than 6 years. Involvement of 4 or more cervical or parotid nodes demonstrated an association with distal metastasis. Eighty percent of patients with 4 or more diseased cervical and/or parotid lymph nodes had distant metastasis compared to only 20% for fewer than 4 nodes ($P<.01$).

The 5-year survival of patients with 4 or more lymph nodes involved was 33% (3/9). Patients with fewer than 4 lymph nodes involved had a 5-year survival of 55% (16/29). This difference was not statistically significant. Age at the time of diagnosis influenced 5- and 10-year survival rates. Of those under 30 years of age at the time of diagnosis (13 patients), 83% were alive at 5 years and 78% at 10 years. The 5- and 10-year survival rates for patients over 50 (16 patients) were 47% and 31%, respectively ($P<.05$).

Overall, the median survival was 24 months with an average survival of 44 months and an average follow-up of 71 months. At 2 years, 77% remained alive. The respective 5- and 10-year survivals in this series were 56% and 41% (Fig. 1).

DISCUSSION

Malignant melanoma demonstrates extreme variation in behavior. An uncommon form of this disease is nodal involvement where no primary cutaneous site can be identified. The incidence of this presentation is approximately 5%.[2,7,9] In this series, the male predominance and a peak incidence in the decade 40 to 49 is in agreement with previous studies.[9,11] One possible explanation for the male predominance in this series is that, in females, the most common site of primary cutaneous melanoma is the thighs as compared to the trunk for males.[6] Given the assumption that the primary site undergoes regression, males would have a greater chance of presenting with axillary and cervical nodal involvement.

Most authors have advocated radical neck dissection where cervical lymph nodes are involved.[17] More recently, modified neck dissections have been proposed.[18] Some authors have obtained results suggesting higher survival in patients after a modified neck dissection versus those with a radical neck dissection.[15] In this series, a statistically significant difference in survival rates was not noted when modified and radical neck dissections were compared. Following therapeutic neck dissections, recurrence rates have been reported to range from 26% to 50%.[17–19] Our recurrence rate of 23% after neck dissection is slightly lower than that reported in the literature. There was no significant difference between modified and radical neck dissections in terms of recurrence. Thus the best surgical choice is the one that removes all involved lymph nodes, yet preserves maximal function.

Some investigators have found that the level of nodal involvement is an important prognostic variable in stage II melanoma.[6,20,21] Other authors studying stage II melanoma of unknown primary origin have not been able to demonstrate a significant survival difference between patients with various degrees of nodal involvement.[7,12] Milton, *et al.* have demonstrated that, for patients with a single lymph node involved with melanoma, the 5-year survival is significantly better than those with more than one lymph node involved.[21] Our findings corroborate this previous study; however, statistical significance was not achieved, possibly due to our small sample size.

Wong, *et al.* have suggested that lymph node involvement in patients with cutaneous melanoma places them at a high risk for future development of metastatic disease.[12] In this series, patients with 4 or more cervical or parotid nodes involved had a significantly higher likelihood of distant metastasis compared to those with fewer than 4 nodes. This suggests that the degree of lymph node involvement in unknown primary melanoma is a prognostic factor in the development of future metastasis. As expected, with appearance of distant metastasis, the patients had an extremely poor prognosis. The median survival of 7 months and a 2-year survival rate of 20% in this series are comparable to the report by Chang and Knapper for disseminated melanoma with an unknown primary site.[7] Similarly Velez and coworkers described a 7-month median survival and a 10% 5-year survival rate for this group of patients.[22]

There was no significant difference in the survival of patients treated with adjuvant therapy compared to the survival of those who did not receive such treatment. This finding is consistent with that of other investigators.[1,22,23] In fact, patients receiving adjuvant therapy had a slightly worse prognosis in this series. However, a selection bias was involved as patients with a worse prognosis were more likely to receive adjuvant treatment.

Malignant melanoma has traditionally been considered a radioresistant neoplasm.[24] Some studies have suggested that meaningful palliation may be obtained in some patients with metastatic or locally recurrent disease.[25] In a randomized prospective clinical trial comparing lymphadenectomy along with postoperative radiation treatment versus lymphadenectomy alone, Creagan, *et al.* found that postoperative radiation treatment did not have a significant effect on survival or disease-free interval.[26] Clearly, the role of radiation therapy as a surgical adjuvant after therapeutic node dissection in the treatment of regional metastatic melanoma has not been well defined. Further experience is required before radiation therapy can be recommended beyond the confines of a clinical trial in the treatment of metastatic melanoma of regional lymph nodes.

The overall 5-year survival rate (56%) in this series of patients with cervical or parotid lymph node metastasis of unknown primary origin is better than that reported in adequately treated stage II melanoma of the head and neck region.[27] Conley and Hamaker demonstrated that, in all patients with stage II melanoma of the head and neck, the 5-year survival rate was 12.6%.[27] Caldwell and Spiro reported a 5-year survival rate of 36% for patients with cervical node metastasis and known cutaneous melanoma.[28]

Several authors have suggested that the prognosis of patients with stage II melanoma of unknown primary origin is improved when compared to those with a known primary site.[7,14] In patients with known cutaneous melanoma and palpable involvement of the regional lymph nodes, the 5-year survival rate in the literature is commonly less than 30%.[6,20,27,28] In comparison, others have reported 5-year survival rates of 33% to 65% for patients with stage II unknown primary melanoma.[1,7,14,22] Lopez, *et al.* demonstrated a 5-year survival of 58% for this group of patients after radical lymphadenectomy.[23] However, less favorable 5-year survival rates (29.7% and 33%) were found in two other reports.[14,21]

The reasons for the possible survival advantage of stage II melanoma of unknown primary origin as compared to melanoma with a known primary site remain obscure. Two theories on the etiology of unknown primary melanomas have been proposed. The less favored theory is that melanoma cells arise de novo within the lymph nodes or that there are ectopic melanocytes that undergo malignant degeneration.[7,13] McCarthy, *et al.* found nevus cells in 8 of 129 axillary lymph node dissections.[29] Greene and Bernier demonstrated the existence of melanoblasts in the parotid gland and reported 5 cases of primary melanoma of the parotid.[30] Based on this theory, patients with unknown primary melanoma may have an improved survival because, in effect, the occult primary is removed during lymphadenectomy.[7]

The more widely accepted theory is that, due to the host immune response, the primary melanoma lesion spontaneously regresses after metastasizing to the regional lymph nodes.[7,12,22] Melanoma accounts for 11% of all instances of spontaneous tumor regression.[31] Giuliano, *et al.* presented 5 cases of spontaneous regression of melanoma.[8] Bulkley, *et al.* theorized that regression occurs in association with an immune stimulating effect.[16] Other investigators have demonstrated an augmented humoral and cellular immunity in patients with unknown primary melanoma.[23,32] Serum from a patient who had spontaneous regression of metastatic melanoma was found to induce regression in another patient.[33] Specifically, a circulating factor was identified that potentiated lymphocytic cytotoxic activity in patients with a regressing melanoma.[34]

Given this evidence, it is possible to suggest that a strong antitumor immune response can cause the containment of micrometastases within the regional lymph nodes. This increased protection against subsequent spread may translate into prolonged survival times. Some investigators. however, have suggested that the level of antitumor immunity actually falls with the occurrence of metastasis.[8] Clearly, further studies need to be conducted in order to explain the possible survival advantage of patients with stage II melanoma of unknown primary origin as compared to those with a known primary site.

CONCLUSION

Forty-six cases of metastatic melanoma of cervical and parotid lymph nodes with an unknown primary site were presented. These patients appear to have a better prognosis compared to the patients with a known primary site. Surgical intervention is the treatment of choice, including removal of all diseased neck and parotid lymph nodes without sacrificing function. Adjuvant therapy was not effective in prolonging survival in this study.

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