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NASRI, S, et al.

Abstract

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.

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

Sina Nasri, MD; Ali Namazie, MD; Pavel Dulguerov, MD; Robert Mickel, MD

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 29% 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. It is a relatively uncommon disease, with an unknown primary site ranging from 2% to 16% of all melanomas. Some authorities find the incidence to be closer to 5%. Stage II disease is the most common site of secondary presentation for primary melanoma. Up to 60% of unknown primary melanomas have been reported to have regional lymph node metastasis. The remainder have metastasis involving more than one nodal basin, visceral, or subcutaneous tissue.

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. 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.

The relative prognosis of melanomas with unknown primary and stage II melanomas with the primary site known is disputed. 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. It has been theorized that, due to this antitumor immune response, disease is contained and suppressed within the regional lymph nodes. The question therefore arises 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 with 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 intensive dermatologic investigation of cutaneous lesions and biopsy of any suspicious area. Chest roentgenogram, 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 chemotherapy agents used were dacarbazine, mitomycin, hydrazine, cyclophosphamide (Cytoxan), bleomycin, and vincristine. A group of patients received BCG vaccine and/or interleukin-1 (IL-1) and/or tumor cell vaccine (TCV) singly or in combination with the aforementioned chemotherapy agents. Of those treated with radiation therapy, approximately 40 to 60 Gy was delivered to the cervical or parotid nodal bed. 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.

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.

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 a radical neck dissection (Table II).

Overall, 54% (24/46) 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, 275 (4/15) experienced a recurrence compared to 26% (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. By 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 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

- Parotidectomy 6 11%
- Neck dissection 27 59%
- Modified 15 32%
- Parotidectomy and neck dissection 8 17%
- Radical 5 13%
- Modified 3 13%
- Total 46 100%

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

Malignant melanoma demonstrates extreme variation in behavior. An uncommon form of this disease is nodal involvement where no primary cutaneous site can be identified. Two other forms of this disease have been identified: (1) a primary site with metastatic involvement of lymph nodes that is associated with a good prognosis and (2) a nodal metastasis that is associated with a poor prognosis and a very bad outcome.

Most authors have advocated radical neck dissection where cervical lymph nodes are involved. More recently, modified neck dissections have been proposed. Some authors have obtained results suggesting higher survival in patients after a modified neck dissection versus those with a radical neck dissection. However, in this series, two different surgical procedures were compared. The recurrence rates were not statistically different. Our recurrence rate of 23% after neck dissection is slightly lower than that reported in the literature. There was a significant difference between modified and radical neck dissections in terms of recurrence. Thus, the best surgical option is the one that removes all 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. The incidence of known or unknown primary melanoma, although very rare, is commonly associated with cervical lymph node involvement. In patients with cervical lymph nodes involved, the 5-year survival is significantly better than those with other involved lymph node levels. These findings corroborate previous studies, and statistical significance was achieved, possibly due to case 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. In this study, 10% of patients with cervical lymph node involvement had a longer survival time than those with a known primary.

Some investigators have suggested that the degree of lymph node involvement in 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.22 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.22,22 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 radiosensitive neoplasm. Some studies have suggested that meaningful palliation may be obtained in some patients with metastatic or locally recurrent disease. In a randomized prospective clinical trial comparing lymphadenectomy alone with postoperative radiation therapy versus lymphadenectomy alone, Creagan, et al., found that postoperative radiation treatment did not have a significant effect on survival or disease-free interval. Clearly, the role of radiation therapy as a surgical adjunct to therapeutic node dissection in the treatment of regional metastatic malignant 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.
Distant Metastases From Head and Neck Squamous Cell Carcinomas

Karen H. Calhou, MD; Paul Fulmer, MD; Raymond Weiss, MD, James A. Hokanson, PhD

Distant metastases (DMs) occurred in 83 (11.4%) of 727 retrospectively studied head and neck cancer patients. Primary tumor location and initial treatment did not influence DM development; larger primary (P < .04) or more extensive neck disease (P < .007) more often caused DMs. Initial diagnosis to DMs averaged 11.7 months (range, 0 to 60 months), with 84% diagnosed within 24 months. With the exception of laryngeal primaries, no factor of tumor, host, or initial treatment influenced where or how rapidly DMs developed. Lung was the most common DM site (63.4%), then bone (31.3%) and liver (6.9%). Survival with DMs averaged 4.3 months (range, 1 day to 2.7 years) for 86.7% died within 1 year. This report yields the following conclusions: 1. Initial tumor size and neck disease are the only predictors of DMs. 2. DMs usually occur within 3 years of the initial diagnosis. 3. Lung is the most common DM site, making chest x-ray the most effective DM screen. 4. Survival with DMs is usually less than a year.

INTRODUCTION

As local and regional control of head and neck cancer has improved, distant metastases have become an increasingly common cause of death.1 This retrospective study was undertaken to determine the following: What percentage of head and neck squamous cell carcinoma patients develop DMs? 2. Do any characteristics of initial patient presentation or treatment predict DMs? 3. How soon after initial tumor diagnosis do DMs develop? 4. What factors influence how quickly DMs develop? 5. To what sites do head and neck cancers metastasize? 6. How long do patients with DMs survive?

MATERIALS AND METHODS

Charts of all patients diagnosed with squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx, or larynx from 1976 to 1987 at the University of Texas M

Branch Otolaryngology Service were reviewed. Information abstracted from charts of patients who developed DMs included demographic factors (age, gender, race, weight, weight loss, smoking and drinking history), time to development of DMs and to death, and location of DMs. Details of patient presentation and treatment included primary tumor stage, site, and differentiation, neck stage, whether treatment consisted of radiation therapy, surgery, or both, and whether chemotherapy was administered. Tumor size was classified as oral cavity, oropharyngeal, hypopharyngeal, or laryngeal, and laryngeal tumors were subclassified as glottic, supraglottic, or subglottic. Tumors were staged based on clinical examination using the American Joint Committee on Cancer (AJCC) 1988 staging system. Additional tumors occurring in these patients were tabulated as second primary if they occurred at a head and neck site different from the original tumor (i.e., larynx or oral cavity). Lung tumors were tabulated as metastases if there were multiple nodules of the same cell type as the primary tumor that occurred within 2 years of diagnosis of the primary, otherwise they were tabulated as second primary cancers.

Data were analyzed using microcomputer implementations of the statistical software packages SAS and BMDP. Analysis techniques included correlation, analysis of variance, linear regression, and, where appropriate, nonparametric methods. Because survival data were available on all patients, statistical methods that can accommodate censored observations were not used. Appropriate nonparametric techniques, however, were used for comparison of "time to event" data.

RESULTS

Patient Population

Seven hundred twenty-seven patients with previously untreated squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx, or larynx were seen at the University of Texas Medical Branch from 1976 to 1987, with a mean follow-up time of 56.1 months. Eighty-three (11.4%) developed clinically detected DMs; all of these patients died.

Sixty-four (77.1%) of the patients with DMs were men. Three outcomes for non-smokers (4.8%), pack-years of smoking ranged from 10 to 150 pack-years (mean, 56.9 pack-years).

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Karen H. Calhou, MD; Paul Fulmer, MD; Raymond Weiss, MD, James A. Hokanson, PhD


From the Department of Otolaryngology, University of Texas Medical Branch, Galveston.

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