Defining the Clinical Course of Metastatic Skin Cancer in Organ Transplant Recipients

A Multicenter Collaborative Study

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Objective: To evaluate the demographic characteristics, clinical course, and outcome in organ transplant recipients with metastatic skin cancer.

Design and Setting: An international, multicenter, Internet-coordinated collaborative group retrospectively analyzed data from 68 organ transplant recipients with 73 distinct metastatic skin cancers.

Main Outcome Measurements: The Kaplan-Meier method was used to estimate the cumulative incidence of relapse, overall survival, and disease-specific survival after metastatic skin cancer. Univariate Cox proportional hazards models were fit to evaluate factors for an association with survival.

Results: Metastasis from skin cancer in organ transplant recipients most commonly consisted of squamous cell carcinoma in regional nodal basins. It was predominantly treated with a combination of surgery and irradiation. By 1 year after metastasis, the cumulative incidence of relapse was 29%, and the 3-year disease-specific survival was 56%. Patients whose initial metastases were distant or systemic had a significantly poorer disease-specific survival than those whose initial metastases were in-transit or regional (risk ratio, 6.5; P<.001).

Conclusions: Metastatic skin cancer in organ transplant recipients has a poor prognosis. Preventive, early, and aggressive therapeutic interventions are required to minimize this serious complication of transplant-associated immunosuppression.

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Methods

Patient Population

The study was approved by the Mayo Clinic institutional review board. All solid organ transplant patients in whom metastatic cancer developed were identified from the Mayo Clinic Medical Index, and 13 patients were identified who had a history of metastatic skin cancer. Data on 55 similar patients were collected from an international collaborative group.
of physicians involved in the care of organ transplant recipients, either by invitation or in response to an announcement of the study at www.centerspan.org, a transplant Web site.

The patient population consisted of 68 organ transplant recipients who were treated at the collaborating institutions for 73 distinct metastatic skin cancers between 1989 and 2001. At the time of diagnosis of the primary skin tumor, all patients were receiving immunosuppressive therapy to prevent rejection of their allograft.

Data collected included demographic information and details on transplantation, immunosuppression, history of previous nonmetastatic skin cancer, primary tumor and treatment, metastatic disease and treatment, clinical course, and final status. Complete data were not available for all categories in every patient. The data presented represent all available data, and notation is made in the tables when complete data were not available for the entire patient population.

DEFINITIONS

Primary tumor was defined as the primary cutaneous malignant tumor that metastasized. In some cases, the primary tumor was unknown because patients either presented with metastatic disease or had a history of multiple primary tumors, any one of which could have been the source of the metastasis. Recurrence was defined as regrowth of the primary tumor within or adjacent to the treatment scar. Metastatic disease was defined by the presence of disease that was noncontiguous with the primary tumor. Metastases consisted of in-transit, regional nodal, or systemic/distant metastases, which included distant nodal metastases. In-transit metastases were defined as metastatic deposits within the dermis, subcutaneous fat, or other soft tissues. Patients experiencing either in-transit or regional nodal metastases simultaneously with systemic metastases were, for purposes of statistical analysis, grouped with the patients experiencing systemic metastases.

STATISTICAL ANALYSIS

Standard descriptive statistics, frequencies and percentages, medians and interquartile ranges (IQRs), or means±SDs were calculated. Duration of follow-up was calculated from the date of the initial diagnosis of metastasis to the date of death or last follow-up. The Kaplan-Meier method was used to estimate overall survival, disease-specific survival (death due to disease), and cumulative incidence of relapse after treatment of metastatic skin cancer. Associations between various factors (eg, type of treatment) and survival after diagnosis of metastasis were evaluated univariately by fitting separate Cox proportional hazards models and summarized with risk ratios (RRs) and 95% confidence intervals (CIs). All calculated P values were 2-sided, and P values less than .05 were considered statistically significant.

RESULTS

DEMOGRAPHICS

Demographic and clinical characteristics of our patient population are summarized in Table 1. The mean age at transplantation was 44.3 years, and 88% of the patients were men.

COURSE OF NONMETASTATIC SKIN CANCER

Data regarding the course of nonmetastatic skin cancer were not available for all patients. Before experiencing metastatic skin cancer, 39 patients had a median of 11 prior nonmetastatic skin cancers (maximum, 122; IQR, 4-27) over a mean of 10.4 years. After diagnosis of metastatic skin cancer, 31 patients had a median of 8 subsequent nonmetastatic skin cancers (maximum, 192; IQR, 3 to 17) over a mean of 2.7 years.

PRIMARY TUMORS AND THEIR INITIAL TREATMENT

Details regarding primary tumors and their initial treatment are summarized in Table 2. Because not all patients who went on to have metastatic skin cancer had identifiable primary tumors, data regarding primary tumors and initial treatment were unavailable for some patients. The median size of the primary tumor was 120 mm² (IQR, 55-337 mm²; n=32), and the median depth was 3.2 mm (IQR, 2.5-5 mm; n=18).

RECURRENCE AFTER INITIAL TREATMENT

Thirty-four patients had 35 primary tumors that recurred either once or multiple times. No recurrence was reported in 23 cases, and details regarding recurrence were not available in 15 cases. There were 7 cases with a single recurrence after a primary tumor, 9 with 2 recurrences, and 7 with 3 recurrences; 8 patients had 4 or more recurrences (maximum, 6 recurrences). The exact number of recurrences was not noted in 4 other cases. All but 1 of the initial recurrences occurred before or at the time of the initial metastasis. Of note, 2 patients had negative elective lymph node dissection of the parotid region and neck at the time of treatment of the recurrent primary tumor.

PRESENTATION OF METASTASES

Sites involved by metastases throughout the course of metastatic skin cancer are listed in Table 3. All metastases within a given organ were counted as a single metastatic site. Thirty-nine patients had only 1 site involved, 16 had 2 sites, 8 had 3 sites, and 5 had 4 sites. Seventy-eight percent of patients had nodal metastases at some point during the course of
their disease. These data are summarized by involved nodal basins in Table 3. Twenty-six percent of patients had in-transit metastases. Systemic metastases to bone, central nervous system, lung, tongue, and liver were also reported but were less common.

In patients for whom details of the primary tumor were available (n=53), the mean±SD time from first transplantation to diagnosis of primary tumor was 8.8±6.3 years (range, 1.1-26.9 years), and the mean time from primary tumor to first diagnosis of metastasis (n=52) was 1.4±1.7 years (range, 0-8.3 years; median, 0.9 years). Overall (n=67), the mean time from first transplantation to first diagnosis of metastasis was 10.7±6.6 years (range, 1.7-28.4 years).

## TREATMENT OF METASTASES

Treatment of metastases varied widely and depended on the type of metastases. Initial treatments, along with the frequency of subsequent relapse, are listed by therapeutic modality in Table 4.

## RELAPSE OF METASTATIC DISEASE AFTER TREATMENT

Of 68 patients with 73 separate metastatic events, 23 patients had relapse of the metastatic disease after initial treatment for metastases; by 1 year, the cumulative incidence of relapse was 29% among the 61 patients known to have received treatment for their metastatic disease. The mean±SD time from first metastasis to first relapse was 0.7±0.5 year (range, 0.2-1.8 years). The treatments and outcomes of relapsed metastatic disease are listed in Table 5. After relapse, the disease-specific survival after 1 year was 44%. Only 1 patient was disease free and alive after relapse of metastatic disease at the time of analysis.

## COMPLICATIONS OF TREATMENT

Complications of treatment of metastases were reported in 27 of 68 cases. In addition to the expected adverse effects from radiation therapy, which most patients experienced, 1 patient each had exposure of bone within the radiation field, necrosis of a skin graft, pulmonary fibrosis, and neutropenia. In relation to surgical treatment, 1 patient each had lymphedema with recurrent cellulitis, chronic shoulder pain, and blood loss leading to respiratory arrest. Of the patients treated with chemotherapy, 1 had excessive bone marrow toxic effects, and 1 died from chemotherapy-induced postobstructive pneumonia.

## FINAL OUTCOME

The mean±SD length of follow-up after diagnosis of metastasis for all patients was 2.1±2.2 years (range, 0-9.4 years).
years). Among the 34 patients known to be alive (of whom 14 are alive with disease), the length of follow-up was 2.6 ± 2.6 years. Twenty-three patients died as a result of the disease (14 after a relapse), and 11 patients died from other (n=8) or unknown (n=3) causes. These data are summarized in Table 6.

As illustrated in the Kaplan-Meier curve in Figure 1, the overall and disease-specific survival rates at 3 years after the initial metastasis were 48% and 56%, respectively. The disease-specific survival curves for all patients with squamous cell carcinoma (n=58) vs non–squamous cell skin cancer (including Merkel cell carcinoma, melanoma, malignant fibrous histiocytoma, atypical fibroxanthoma, and spindle cell sarcoma; n=10) are illustrated in Figure 2. The differences were not statistically significant (P=.07), although a trend toward poorer survival with non–squamous cell tumors was apparent. Of the 2 patients with metastatic melanoma, 1 is still alive with advanced disease (1.6 years after initial metastasis) and the other died of complications of treatment.

### PROGNOSTIC FACTORS

At 1 year after the initial metastasis, the disease-specific survival was 39% and 89%, respectively, for patients with initial distant or systemic (n=13) vs in-transit or regional nodal metastases (n=55) (Figure 3). Patients whose initial metastases were distant or systemic were significantly more likely to die as a result of disease than patients whose initial metastases were in-transit or regional (RR, 6.5; 95% CI, 2.7-15.9; P<.001). The 1-year disease-specific survival was 87%, 67%, and 30% for patients who received surgical treatment (n=47), nonsurgical treatment (n=14), or no treatment (n=5), respectively, for their metastatic disease. (Treatment was unknown for 2 patients.) The disease-specific survival was not significantly different for surgical vs nonsurgical treatment (RR, 1.6; 95% CI, 0.6-4.1; P=.37). However, patients who were not treated at all were more likely to die as a result of disease than patients who received treatment for their metastatic disease, despite there being only 5 patients who were
not treated (RR, 4.2; 95% CI, 1.2-14.7; \( P = 0.02 \)). It should be noted that there was an association between site of initial metastasis and use of surgical treatment (\( P < 0.001 \)). Among the 66 patients with treatment information available, those with in-transit or regional nodal metastasis had surgical treatment more often (44/53; 83%) than patients with distant or systemic involvement (3/13; 23%). Number of metastatic sites involved initially (\( P = 0.54 \)), time from transplantation to diagnosis of first metastasis (\( P = 0.68 \)), history of primary tumor recurrence (\( P = 0.72 \)), and time from transplantation to diagnosis of primary tumor (\( P = 0.54 \)) were not significantly associated with disease-specific survival. Similar results were found when factors were evaluated for an association with survival free from death due to any cause.

**COMMENT**

The increased incidence of aggressive cutaneous malignancies in organ transplant recipients is well recognized, as is the more aggressive clinical course that these malignant tumors tend to follow.\(^{10-12}\) Studies have suggested that organ transplant recipients should receive frequent follow-up care from dermatologists and that any premalignant or malignant lesions should be treated early and aggressively.\(^{13,14}\) Recurrent skin cancer in this population should likewise be managed aggressively.

The results of this multicenter collaborative study provide clinically relevant insights into the demographic characteristics, timing, presentation, treatment, and outcome of metastatic skin cancer in organ transplant recipients. The primary tumors were predominantly squamous cell carcinoma, although uncommon cutaneous malignancies, including Merkel cell carcinoma, were recorded.

The number of nonmetastatic skin cancers that patients experienced before their metastatic tumors varied widely, with a maximum of 122. Subsequent to the appearance of metastatic skin cancer, a similar variety was noted, with some patients having relatively few new nonmetastatic skin cancers and others continuing to experience extensive neoplasia. The head and neck regions were the predominant sites of metastatic disease in the immunosuppressed population, as they are in immunocompetent patients, but multiple primary sites of the trunk and extremities were noted as well. The fact that many of the primary tumors in our series recurred locally after initial treatment highlights the importance of complete eradication of the primary tumor.

Although the mean time from transplantation to diagnosis of first metastasis was 10.7 years, metastases developed quickly after diagnosis of the primary tumor—in a mean of only 1.4 years. This finding emphasizes the need for close clinical follow-up after diagnosis of high-risk primary skin tumors in organ transplant recipients.

The primary site of metastasis of skin cancer in organ transplant recipients is the lymph nodes, as it is in immunocompetent patients. Therefore, regional nodes should routinely be palpated in all patients with a history of skin cancer other than basal cell carcinoma. Close inspection of the skin surrounding the primary treatment site is essential, as in-transit metastases developed in 26% of our patients (18/68). In our experience, in-transit metastases often appear as subtle, waxy, gray-white papules measuring 2 to 6 mm in diameter. Systemic metastases, primarily involving lungs and bone, were less common and portended a significantly worse prognosis.

Data regarding changes in immunosuppressive regimens before or after metastasis were not shown. Although decreasing immunosuppression after metastasis did not appear to have a clear beneficial effect in this population, a study by Dantal et al\(^{15}\) suggests that less intense immunosuppression may lower the incidence of cutaneous and internal malignancy in patients having long-term immunosuppression. Minimizing the use of immunosuppressants should be considered in patients who have numerous or high-risk skin cancers as well as in those experiencing metastasis.

In the population studied, most metastases were treated with surgery and adjuvant radiation therapy, surgery alone, or radiation therapy alone. However, because our study was retrospective and treatments were not randomized, we could not deduce which treatment modalities were superior for the treatment of metastases. The cumulative incidence of relapse was 29% within 1 year of diagnosis of metastasis. Relapse of metastatic disease was most commonly treated with chemotherapy alone, and disease-specific survival at 1 year after treatment of relapsed metastatic disease was 44%. Thus, although treatment of surgically resectable metastases was often successful, nonresectable metastatic disease and relapse of metastatic disease subsequent to treatment each carried a grave prognosis.

The overall 3-year survival for organ transplant recipients who had metastatic skin cancer was 48%. This survival rate was higher than expected, given that our series comprised immunosuppressed patients and that 5-year survival for metastatic squamous cell carcinoma in immunocompetent patients is approximately 25%.\(^{16}\) The 3-year disease-specific survival was 56%, indicating that almost half the patients would die from the disease within 3 years after experiencing metastasis if there was no other cause of death.

Squamous cell carcinoma and non–squamous cell tumors have different biological behavior, and although the overall and disease-specific survivals between these groups were not significantly different, a trend toward shorter survival was noted in the non–squamous cell tumors.
The data suggest, then, that metastatic skin cancer in organ transplant recipients must be observed closely and treated aggressively, regardless of tumor type. Univariate analysis of prognostic factors yielded several factors associated with disease-specific survival. Patients who received treatment had a better survival than those who did not. This finding may reflect the fact that patients with extensive metastatic disease were less likely to be treated with curative intent. The finding of improved survival for patients treated surgically rather than with nonsurgical modalities likewise highlights the poor outcomes of patients with unresectable disease. Lastly, patients who had in-transit or regional nodal metastases as their first site of metastasis had better survival than those whose first diagnosis of metastasis included a distant nodal or systemic site. Skin cancer metastatic to regional nodes, if limited, is a potentially curable disease. This fact supports the need for close follow-up of nodal basins to detect metastasis at a manageable stage.

Because of the low incidence of metastatic skin cancer in organ transplant recipients, a collaborative effort was required. Six collaborators joined the study after viewing our invitation at www.centerspan.org, a transplant Web site. Our experience with this Internet-initiated collaboration was positive and suggests that Web-based research collaboration is practical and beneficial for studies of this nature.

We acknowledge that the retrospective nature of our study is a limitation. Also, there is the possible selection bias that participating physicians had a specific interest in and expertise with transplantation. Finally, our findings do not allow for determination of relative therapeutic efficacy of treatment modalities, which were not randomized.

Our study reveals that metastatic skin cancer in organ transplant recipients is associated with substantial morbidity and high mortality. Emphasis should be placed on the prevention of skin cancer in these patients. They should be seen on a frequent and regular basis by dermatologists for a full skin and lymph node examination, even before they begin having multiple cutaneous malignancies. Similarly, early recognition of and intervention for particularly severe cutaneous malignancies are of the utmost importance, inasmuch as our series demonstrated a mean time of only 17 months from diagnosis of primary tumor to first metastasis. It is essential, therefore, that tumors that are at particularly high risk of recurrence and metastasis be managed aggressively and with great respect.

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REFERENCES


