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Rate of regional nodal metastases of cutaneous squamous cell carcinoma in the immunosuppressed patient

Eamon J. McLaughlin [a,*], Lauren Miller [a], Thuzar M. Shin [b], Joseph F. Sobanko [b], Steven B. Cannady [a], Christopher J. Miller [b], Jason G. Newman [a]

[a] Department of Otorhinolaryngology: Head and Neck Surgery, Hospital of the University of Pennsylvania, 3400 Spruce Street, Philadelphia, PA 19104, USA
[b] Department of Dermatology, Hospital of the University of Pennsylvania, 3400 Spruce Street, Philadelphia, PA 19104, USA

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ABSTRACT

Purpose: Immunosuppressed solid organ transplant recipients (SOTRs) have an increased risk of developing cutaneous squamous cell carcinomas (cSCCs) with metastatic potential. This study sought to determine the rate of regional lymph node involvement in a large cohort of solid organ transplant patients with cutaneous head and neck squamous cell carcinoma.
Materials and methods: A retrospective chart review was performed on solid organ transplant patients with head and neck cutaneous squamous cell carcinoma treated at a tertiary academic medical center from 2005 to 2015.
Results: 130 solid organ transplant patients underwent resection of 383 head and neck cutaneous squamous cell carcinomas. The average age of the patient was 63. Seven patients (5%) developed regional lymph node metastases (3 parotid, 4 cervical lymph nodes). The mean time from primary tumor resection to diagnosis of regional lymphatic disease was 6.7 months. Six of these patients underwent definitive surgical resection followed by adjuvant radiation; one patient underwent definitive chemoradiation. 6 of the 7 patients died of disease progression with a mean survival of 15 months. The average follow up time was 3 years (minimum 6 months).
Conclusions: Solid organ transplant recipients with cutaneous squamous cell carcinoma of the head and neck develop regional lymph node metastasis at a rate of 5%. Regional lymph node metastasis in this population has a poor prognosis and requires aggressive management and surveillance.

1. Introduction

Solid organ transplant recipients (SOTRs) have an increased risk for cutaneous squamous cell carcinoma (cSCC). For example, renal transplant recipients have up to an 82-fold increase increased risk of invasive cSCC compared to non-transplanted patients [1]. The risk of developing cSCC correlates with the degree and length of immunosuppression [2,3]. Compared to immunocompetent hosts, SOTRs develop cSCCs with higher rates of regional recurrence and a worse prognosis if metastases develop [4–7].

The overall rate of metastasis for cSCC is 2–5% [8–12]. Immunosuppression is an independent risk factor for regional lymph node involvement [9]. Other risk factors for metastasis include the maximum clinical diameter (>2 cm) and thickness of the primary tumor, poor differentiation, and location on the lip, ear, or posterior auricular area. In a large study of 615 patients, only tumors >2 mm in thickness were found to metastasize [9]. The rate of regional lymph node metastasis for immunocompromised patients has been previously reported as high as 12% [13].

Despite the increased risk and poor prognosis for of regional lymph node metastasis in SOTRs, there is a lack of consensus for strategies to manage clinically node negative patients. To determine the rate of regional lymph node metastases and the course of metastatic disease, we performed a retrospective chart review of all solid organ transplant patients with head and neck cutaneous SCC treated at our institution from 2005 to 2015.

2. Material and methods

This study was approved by the University of Pennsylvania Institutional Review Board. A retrospective chart review was performed for all SOTRs who underwent surgery between 2005 and 2015 for a cSCC of the head and neck at the Hospital of the University of Pennsylvania Department of Dermatology and/or Otorhinolaryngology. Patients were identified by searching the Penn Dermatology Oncology Center's operative database for SOTRs who had undergone Mohs surgery for cSCCs on the head and neck. A minimum of 6 months of follow up was required, which excluded 15 patients with 34 cancers. The charts

* Corresponding author at: Department of Otorhinolaryngology: Head and Neck Surgery, 3400 Spruce Street – 5 Silverstein Pavilion, Philadelphia, PA 19104, USA.
E-mail address: Eamon.McLaughlin@uphs.upenn.edu (E.J. McLaughlin).

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of all patients who met inclusion criteria were then reviewed for evidence of regional failure and subsequent treatment. Patient demographics, tumor characteristics, surgical details, and immunosuppressive regimens were recorded. Statistical analysis was performed using SAS 9.3 (SAS Institute Inc., Cary, North Carolina).

3. Results

130 solid organ transplant patients underwent Mohs resection of 383 head and neck cutaneous SCCs. The average age at the time of resection was 62 years (standard deviation ± 11). Patients underwent surgery for an average of 3.5 (range 1–13) additional head and neck cSCC during the mean follow up period of 3.36 years. The transplant type, immunosuppressive regimen, and primary lesion locations are shown in Tables 1 and 2.

Seven patients developed regional lymph node failure (4 cervical lymph nodes, 3 parotid). These patients' metastatic disease was detected on clinical exam by the physician or the patient themselves. Six of these patients underwent definitive surgical resection of their regional disease followed by adjuvant radiation (±) chemotherapy. One patient underwent primary chemoradiation due to medical comorbidities that prohibited surgery. The mean time from the resection of the primary lesion to presentation with regional lymph node involvement was 6 months (SD ± 4). Six of the seven patients died from locoregional disease progression or distant metastases. The mean time of regional lymph node treatment to death was 15 months (SD ± 6). These patients are discussed in Table 3.

4. Discussion

This is a retrospective review of 130 solid organ transplant patients treated for 383 cutaneous head and neck SCCs by the Hospital of the University of Pennsylvania Department of Dermatology and Otorhinolaryngology. This is the largest published review of cSCC in SOTR. Of this group, only 7 patients developed regional lymph node metastasis (1.8% rate of metastasis by cancer, 5.4% by patient). This is lower than the reported regional lymph node metastasis rate for all anatomic locations in immunocompetent hosts [8–14]. High risk cSCC occurred in all categories of SOTR, no one type of organ transplant was spared. All patients that developed metastatic disease were on a calcineurin inhibitor. In our patients the scalp was at least as high risk of a location as the ear or lip. Anatomic depth of invasion was critical for determining the risk of metastatic disease. 14% (6/44) of patients with primary tumor invasion beyond the dermis developed regional metastasis. (Table 2).

The current NCCN guidelines for cutaneous SCC includes immunosuppression as a high-risk feature, while the AJCC guidelines do not [14,15]. It has been well documented that an immunocompromised state is associated with an increased risk of local recurrence and poor survival [3–7]. However, the risk of regional lymph node involvement is more challenging to identify. In a study of 653 cutaneous SCCs, Branstch et al. found immunosuppression to be an independent risk factor for developing metastatic disease [9]. However, this study included only 31 patients who were immunocompromised. Carroll et al. followed 310 transplant patients in Australia over 18 months [16]. In this group 89 patients developed 373 invasive SCCs and 2 patients developed regional lymph node metastasis (2.2% rate of metastasis by patient, 0.5% rate of metastasis by cancer).

Rowe et al. performed a systematic review that analyzed 71 studies from 1940 to 1992 to develop prognostic factors for local recurrence, metastasis, and survival [13]. On the subject of immunocompromised patients the paper's conclusions are as follows: “Although the metastatic rate of an individual SCC in an immunosuppressed patient may be only 2% to 3%, each patient has so many aggressive SCCs that the overall metastatic rate per patient is 12.9%”.

There is an inherent bias in the way that we searched for patients for this study. We started by using a dermatology Mohs database and searched only for procedures performed on head and neck SCCs in immunocompromised patients. We then reviewed these patient's charts for any evidence of regional lymph node disease. Beginning our search with patients that had their primary tumor resection with dermatology leads to a potential selection bias for patients with smaller and less advanced tumors. This is evident by the majority of our patients being AJCC T2 or less. (Table 2) This is in contrast to a previous study from MD Anderson, which included patients referred directly to a Head and Neck Clinic and found a 21% regional lymph node involvement rate [17]. However, it could be also be argued that the patients included in this study represent the majority of patients presenting with cutaneous SCC who would first be referred to a dermatologist.

Table 1
Patient characteristics.

Transplant type	All patients N	%	Regional failures N
Heart	16	12%	2
Kidney	47	36%	3
Liver	18	14%	2
Lung	35	27%	
Liver/kidney	10	8%	
Heart/kidney	2	2%	
Kidney/pancreas	1	1%	
Heart/lung	1	1%	
Immunosuppressive regimen			
Tacrolimus, prednisone	29	22%	4
Tacrolimus, prednisone, mycophenolate mofetil	24	18%	2
Tacrolimus	19	15%	1
Azathioprine, tacrolimus, prednisone	12	9%	
Other single agent	4	3%	
Other double agent	24	18%	
Other triple agent	14	11%	
Other	4	3%	
Location of primary cSCC			
Scalp	60	16%	4
Forehead, brow	81	21%	
Periorbital	11	3%	
Ear, mastoid	54	14%	2
Preauricular, periparotid	52	14%	1
Nasal	18	5%	
Cheek	41	11%	
Labial	22	6%	
Cervical	42	11%	
Chin	2	1%	

Table 2
Patient tumor characteristics.

	All patients		Regional failures
Anatomic depth of tumor invasion			
Epidermis	12	3%	
Dermis	327	85%	1
Subcutaneous Fat	28	7%	3
Muscle	7	2%	
Cartilage	3	1%	1
Other	6	2%	2
T stage (AJCC)			
T1	281	73%	
T2	102	27%	7
T3	0	0%	
T4	0	0%	
T stage (Brigham and women's)			
T	265	69%	
T2a	91	24%	1
T2b	26	7%	6
T3	1	0%	
T4	0	0%	

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